Treatment of Early Unfavorable Hodgkin Lymphoma

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12.1 Prognostic Factors

12.1.1 Definition

The Ann Arbor staging system with the 1989 Cotswolds modifications is still being used worldwide in patients with Hodgkin lymphoma (HL) [1]. Modern staging procedures recommend

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the routine use of [^{18}F] fluoro-2-deoxy-D-glucose positron emission tomography-CT scanning (PET-CT) at diagnosis [2]. With the introduction of PET-CT scanning at diagnosis, up to 30% of patients will be upstaged mainly from early to advanced stages. In addition, the extent of radiation fields in CS I/II disease can be influenced by identifying additional lesions by PET-CT scanning [2, 3]. Interestingly, when a PET-CT is performed for initial staging, a bone marrow biopsy is no longer required [4, 5]. In the study by El-Galaly et al. [5], 18% of patients showed focal skeletal lesions on PET-CT, but only 6% had positive bone marrow biopsies. None of the patients would have been allocated to other treatments based on bone marrow biopsy results. Patients with early-stage disease rarely have bone marrow involvement in the absence of a suggestive PET finding, confirming that, if a PET-CT is performed, a bone marrow aspirate/biopsy is no longer required for the routine evaluation.

Even in stage I/II, the extent of disease varies substantially requiring a risk-adapted treatment. In many early-stage patients, mediastinal bulky disease is present, which has been demonstrated as prognostically unfavorable. Other poor prognostic clinical factors include higher age, increased number of involved nodes, and elevated erythrocyte sedimentation rate (ESR), accompanied by B symptoms. Though slight differences in definition exist between major cooperative groups, clinical stage I/II HL patients in Europe are generally divided into an early favorable and an early unfavorable (intermediate) subgroup. Patients in North America presenting with adverse factors (mainly the presence of bulky disease) are treated like those having stage III–IV disease; thus, these patients are not included in clinical trials for stage I/II disease.

The factors used by the European Organization for Research and Treatment of Cancer (EORTC) Lymphoma Group/Lymphoma Study Association (LYSA), the German Hodgkin Study Group (GHSG), the National Cancer Institute of Canada (NCIC), and the Eastern Cooperative Oncology Group (ECOG) are shown in Table 12.1. These risk factors and the resulting prognostic groups were originally defined in the context of treatment with extended-field radiotherapy (RT). In a combined modality setting, the differences in prognosis between favorable and unfavorable disease are likely to be smaller. In more recent series, the treatment was mainly tailored according to the prognostic group. Thus, one would have anticipated that these prognostic factors today have less independent prognostic significance. Klimm et al. analyzed the impact of the three different staging and prognostic subgroup definitions on the outcome of 1173 early-stage patients treated homogeneously in the HD10 and HD11 trials of the GHSG [6]. Figure 12.1 shows the PFS of these patients related to the GHSG, EORTC/LYSA, and NCCN prognostic risk factor score, respectively: all three staging systems identified the unfavorable risk group. Especially tumor-specific risk factors rather than patient-specific risk factors such as mediastinal bulk and high tumor activity were predictive for poor outcome.

Table 12.1 Risk factors according to cooperative treatment groups

	EORTC/LYSA	GHSG	NCIC/ECOG
Risk factors (RF)	A: Mediastinal mass	A: Mediastinal mass	A: Histology other than LP/NS
	B: Age ≥ 50 years	B: Extranodal disease	B: age > 40
	C: ESR ≥ 50 or ESR ≥ 30 with B symptoms	C: ESR ≥ 50	C: ESR > 50
	D: ≥ 4 nodal areas	D: ≥ 3 nodal areas	D: ≥ 3 sites
Stages			
Favorable	I–II without RF	I–II without RF	I–II without RF
Unfavorable or intermediate	I–II with ≥1 RF	I–II with ≥1 RF and IIB with C/D without AB	I–II with ≥1 RF

EORTC European Organization for Research and Treatment of Cancer, *LYSA* Lymphoma Study Association, *GHSG* German Hodgkin Study Group, *NCIC* National Cancer Institute of Canada, *ECOG* Eastern Cooperative Oncology group, *ESR* erythrocyte sedimentation rate, *LP* lymphocyte predominance, *NS* nodular sclerosis

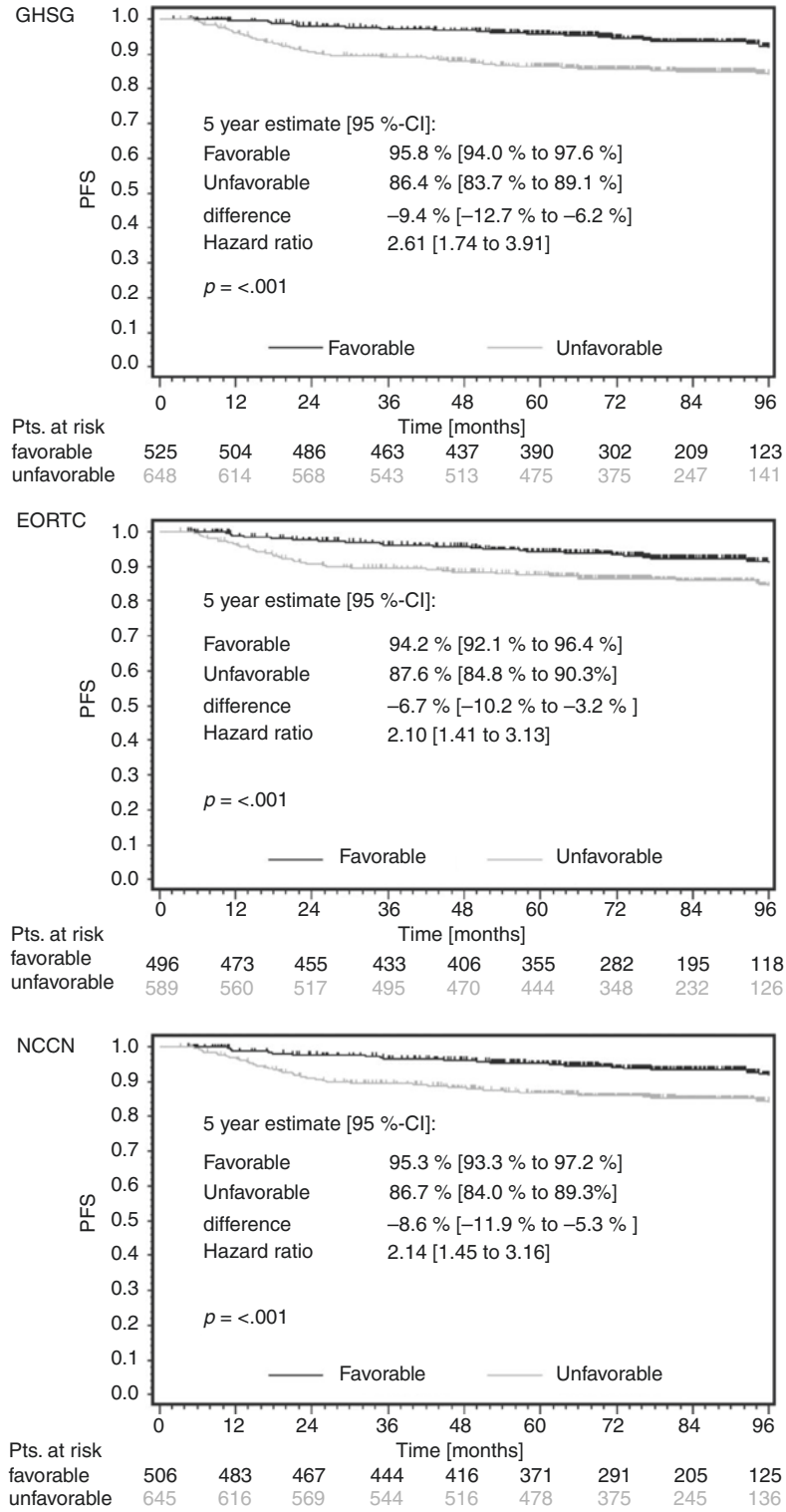

Fig. 12.1 Estimated progression-free survival using staging definitions of the German Hodgkin Study Group, the European Organization for Research and Treatment of Cancer (*EORTC*), or National Comprehensive Cancer Network (*NCCN*) [6]

Table 12.2 Multivariate analysis testing total metabolic tumor volume (TMTV), with interim PET response after two cycles (iPET2) and individual baseline factors, EORTC, GHSG, NCCN staging systems

	PFS[a]			PFS (final model)		
TMTV tested with:	HR	95% CI	*P*	HR	95% CI	*P*
A. Individual factors						
TMTV > 147 cm^3	3.9	1.6–9.5	0.0032	4.4	2.0–9.5	0.0002
IPET 2	11.0	4.8–25.1	<0.0001	10.9	4.9–24.4	<0.0001
B symptoms	2.1	0.9–4.8	0.076			
≥ 4 involved sites	2.0	0.8–5.2	0.16			
M/T ≥ 0.35	0.8	0.3–2.0	0.65			
B.EORTC						
TMTV > 147 cm^3	3.5	1.6–7.8	0.0016	4.4	2.0–9.5	0.0002
IPET2	9.2	4.1–20.6	<0.0001	10.9	4.9–24.4	<0.0001
Unfavorable EORTC	3.2	0.9–11.1	0.067			
C.GHSG						
TMTV > 147 cm^3	4.1	1.8–9.3	0.0006	4.4	2.0–9.5	0.0002
IPET2	10.6	4.7–23.9	<0.0001	10.9	4.9–24.4	<0.0001
Unfavorable GHSG	1.3	0.4–4.0	0.69			
D.NCCN						
TMTV > 147 cm^3	3.7	1.7–8.4	0.00014	4.4	2.0–9.5	0.0002
IPET2	10.2	4.5–22.8	<0.0001	10.9	4.9–24.4	<0.0001
Unfavorable NCCN	1.8	0.6–5.7	0.30			

[a]All variables integrated in the Cox model; final model: with significant factors after performing the backward stepwise Cox model (Adapted from Cottereau, Blood 2018 with permission)

In terms of overall survival, the scores reflected the unfavorable risk profile as well. These data underline the continued need for identifying a poor-risk group within the group of stage I/II disease though new risk factors with a higher specificity might be useful.

12.1.2 New Prognostic Factors

Several different prognostic factors adopted so far are surrogates of the tumor burden. Specht et al. [7] were the first to demonstrate the strong prognostic impact of tumor burden attempting to estimate tumor volume. This was based on the categorization of lesion size by physical examination as well as mediastinal and hilar involvement (chest X-rays) as well as adding grades of all involved sites. The superiority of tumor burden over other prognostic factors was further confirmed by Gobbi et al. [8]. More recently, PET-CT scanning has been used to define the functionally active tumor volume using total metabolic tumor volume (TMTV). Cottereau et al. conducted an analysis on 294 early-stage HL including interim PET and TMTV in the different prognostic models (EORTC/LYSA, GHSG and NCC) [9]. In this analysis, only TMTV and interim PET remained significant (Table 12.2). Although PET-CT is a tool that allows to refine prognosis and treatment strategies if there is a certain degree of inaccuracy in its application. An area of growing interest is combing PET-CT and biomarkers such as circulating tumor-free DNA. Spina et al. recently demonstrated that this biomarker could identify residual disease during treatment of disease after two courses of treatment [10]. Incorporation of both, PET-CT and cell-free tumor DNA, in our decision algorithm will possibly profoundly modify the way we use prognostic factors in the future.

12.2 Long-Term Side Effects

The present management of early-stage HL aims at curing the disease with a specific attention to the reduction of late effects. The most severe late effect due to the treatment of HL is secondary cancer. In a recent large study [11] with a median follow-up of 19.1 years, the standardized incidence

ratio was 4.6 (95% confidence interval (CI), 4.3–4.9) in the study cohort when compared with the general population. The risk was still elevated 35 years or more after treatment (SIR, 3.9; 95% CI, 2.8–5.4), and the cumulative incidence of a second cancer in the study cohort at 40 years was 48.5% (95% CI, 45.4–51.5). Unfortunately, the cumulative incidence of second solid cancers did not differ between study periods (1965–1976, 1977–1988, or 1989–2000) ($P = 0.71$ for heterogeneity), suggesting that the efforts made to reduce the burden of treatment did not translate into a reduction of second cancers. However, the impact of treatment modifications in the last 20 years is not well known. Also, as the risk is better known, it might be suggested that well-conducted cancer screening programs could also reduce the severity of late malignancies. However, in the study of Baxstrom et al. [12], many women did not get the appropriate dual screening for breast cancer despite their increased risk, with only 36.6% of the study sample receiving dual screening. Proper screening allows detection of secondary breast cancer at earlier stages where treatment can be local, but this study raised the issue of compliance of this population to cancer screening programs. Finally, cancer screening is not yet possible for thyroid, lung, and soft tissue cancers.

Cardiovascular and valvular diseases represent another important late effect occurring in patients receiving mediastinal radiotherapy [13, 14]. The reduction in dose and volume of radiotherapy led to a reduction in these complications. Nevertheless, radiotherapy may still result in substantial incidental cardiac exposure if the disease affects the mediastinum.

12.3 Non-PET-Adapted Treatment Strategies

12.3.1 Fields and Dose of Radiotherapy

The use of large radiation fields was abandoned after both, the GHSG HD8 trial [15] and the H8U trial conducted by the EORTC/LYSA [16]. In HD8, long-term noninferiority of involved-field radiotherapy (IF-RT) was compared with extended-field RT. With regard to treatment-associated long-term toxicity, a non-significant trend towards less secondary neoplasia was observed with IF-RT in the most recent follow-up analysis (15-year cumulative, 14% vs. 17%; $p = 0.3$) [17]. This trend was more pronounced when examining only the incidence of acute myeloid leukemia or myelodysplastic syndromes (2.4% vs. 0.8%; $p = 0.1$), but not in non-Hodgkin lymphoma (2.6% vs. 2.9%; $p = 1.0$). In solid second neoplasia, the trend became more pronounced with longer follow-up but did not meet statistical significance (12% vs. 10.4%; $p = 0.7$). Due to the long latency period of second solid neoplasia, prolonged follow-up is crucial to finally assess the risk of secondary malignancies with more limited RT fields.

In the H8U trial, 42 of 766 (5%) patients relapsed who had a confirmed or unconfirmed complete remission after radiotherapy: 15 of 253 patients (6%) in the group received six cycles of MOPP-ABV plus IF-RT, 14 of 259 patients (5%) in the group received four cycles of MOPP-ABV plus IF-RT, and 13 of 254 patients (5%) in the group received MOPP-ABV plus subtotal nodal RT [16]. There were no significant differences in the 5-year event-free survival estimates among the three groups.

The GHSG used a two-by-two factorial design in the HD11 trial aimed at comparing unfavorable early-stage HL using two different chemotherapy regimen: 4xABVD vs. 4xBEACOPPbaseline (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristin, procarbazin, prednisone) as well as 30 Gy IF-RT vs. 20 Gy [18]. Concerning RT, the 20 Gy arm was inferior to 30 Gy when ABVD was used, but when BEACOPP was used, this difference disappeared and 20 Gy was equivalent to 30 Gy.

Taken together, 4xABVD and 30 Gy IF-RT were considered as standard of care for early unfavorable HL.

12.3.2 Chemotherapy

Besides the objective of reducing long-term toxicity with dose and field reductions, investigators aimed at improving disease control further by modifying chemotherapy schemes.

The GHSG HD11 study was based on a two-by-two factorial design with the aim of comparing patients between two different regimen in unfavorable early-stage HL: 4xABVD vs. 4xBEACOPPbaseline (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristin, procarbazin, prednisone) and 30 Gy IF-RT vs. 20 Gy [18]. No improvement was demonstrated using four cycles of BEACOPPbaseline compared with four cycles of ABVD.

Similarly, the EORTC/LYSA H9U [19] study compared 6 cycles of ABVD and 30 Gy IF-RT (standard arm) with 4xABVD and 30 Gy IF-RT and 4xBEACOPPbaseline followed by 30 Gy IF-RT. Results in the 4xABVD and IF-RT (5-year EFS, 85.9%) and the 4xBEACOPPbaseline and IF-RT (5-year EFS, 88.8%) were not inferior to 6xABVD and IF-RT (5-year EFS, 89.9%) differences of 4.0% (90% CI, −0.7% to 8.8%) and of 1.1% (90% CI, −3.5% to 5.6%), respectively. The 5-year OS estimates were 94%, 93%, and 93%, respectively. Because four cycles of BEACOPPbaseline were more toxic but equally efficient than four cycles of ABVD, it was not considered as a new standard.

In their HD14 follow-up trial, the GHSG compared four cycles of ABVD and 30 Gy IF-RT with two BEACOPPesc plus two ABVD and 30 Gy IF-RT. With a total of 1528 patients included, a significant PFS advantage for « 2+2 » compared with 4xABVD was detected with a 5-year PFS difference of 6.2% (95.4% vs. 89.1%; HR, 0.45; 95% CI, 0.3–0.69) [20]. The « 2+2 » approach, however, is associated with more hematologic toxicity, but no difference in long-term toxicity or OS has been documented so far. A longer follow-up will be needed to assess potential risks and long-term benefits with intensive upfront therapy in patients with early-stage unfavorable disease.

12.3.3 Chemotherapy Alone

Based on randomized trials performed in advanced Hodgkin lymphoma patients and the risk of late complications after radiotherapy, the question arose whether RT can also be omitted in unfavorable early stages. A number of trials conducted had important limitations: some trials included pediatric patients, all stages of disease used divergent definitions of unfavorable prognostic features, or there was a lack of statistical power to detect clinically relevant differences in PFS between RT and no-RT arms. The NCIC/ECOG study on early stages had 12-year overall survival as primary endpoint; patients with bulky disease were excluded from entry [21]. This study showed a significant 11% survival benefit for treatment with ABVD alone as compared to ABVD+STNI, notwithstanding a significant 8% advantage in PFS for those who received combined modality treatment. The remarkable conversion of an inferior PFS to a superior long-term OS for the ABVD-alone treatment arm was mainly due to an excess of late toxic deaths in the combined modality treatment (CMT): 23 vs. 11 in the former. These deaths were mainly due to second cancers and intercurrent disease. Admittedly, STNI has become outdated, but the results corroborate the difficulties in interpreting different treatment approaches with divergent short-term (control of disease) and long-term (toxicity) effects.

12.4 PET-Adapted Treatment Strategies

12.4.1 Interim PET

In the publication of Gallamini et al., 260 newly diagnosed HL patients were consecutively enrolled in order to evaluate the prognostic role of an interim PET-CT (iPET). Most of the patients were advanced HL, and the study showed that iPET overshadows the prognostic value of the International Prognostic Score and emerges as the single most important tool for planning of risk-adapted treatment in advanced HL [22]. A similar evaluation conducted in 257 stage I to IIA patients treated with chemotherapy plus radiation therapy led to similar conclusions showing that iPET was a strong prognostic factor for both, progression free and OS [23].

The standardization of iPET is critical for the appropriate incorporation of this imaging modal-

ity into routine clinical practice. For this purpose, successive international interpretation criteria have been proposed and are regularly updated according to improvement of diagnosis, treatment, and follow-up modalities. The current recommendation is to use the 2014 Lugano Classification for response assessment but also for staging of HL [24]. The Deauville 5-point scale criteria (D5PS) allow for more accurate measurement of response by using a categorical scoring system designed for the visual interpretation of PET-CT. This score is now well validated and reproducible [25].

However, it should be emphasized that the definition of PET-CT negativity to escalate or de-escalate therapy has been highly variable between studies changing with the evolution of interpretation criteria. The actual recommendation is to classify PET-CT with a D5SP <4 as negative and D5SP >3 as positive. This categorization is also in agreement with the PET-CT results of the phase III H10 trial in early-stage HL recently reanalyzed using the D5PS criteria showing that patients with an interim PET-CT having a D5SP <4 have a prognosis similar to those with D5PS of 1 or 2 [9].

Subsequently, several trials were launched with the aim to evaluate early treatment adaptation according to iPET results after 2 or 3 cycles of ABVD.

12.4.2 Clinical Trials

12.4.2.1 Rapid Study

In the UK RAPID trial, 602 patients with newly diagnosed stage IA or stage IIA HL received 3 cycles of ABVD and then underwent iPET [26]. RAPID included both, favorable (2/3) and unfavorable (1/3) early-stage HL in the same trial according to GHSG or EORTC/LYSA risk classification. Patients with negative iPET (Deauville score of 1 or 2) were randomly assigned to receive IF-RT or no further treatment; patients with positive iPET (Deauville score 3–5) received a fourth cycle of ABVD and RT. The 3-year progression-free survival rate was 94.6% (95% CI, 91.5–97.7) in the RT group and 90.8% (95% CI, 86.9–94.8) in the group receiving no further therapy, with an absolute risk difference of −3.8 percentage points (95% CI, −8.8–1.3). As the upper confidence interval limit exceeded the predefined non-inferiority margin of 7%, the study did not show non-inferiority of the strategy of no further treatment. Nevertheless, patients in this study with early-stage HL and negative iPET findings after three cycles of ABVD had a very good prognosis either with or without consolidation radiotherapy. The impact on overall survival and late effects needs additional follow-up.

12.4.2.2 H10 Study

Actually, the only published study to evaluate an iPET approach in the specific group of unfavorable patients is H10 [27]. Unfavorable patients were defined as age ≥50 years, large mediastinal mass (M/T ratio >0.35), elevated erythrocyte sedimentation rate (with B symptoms, ≥30 mm/h; without B symptoms, ≥50 mm/h), and >3 nodal areas. Patients with a negative iPET were randomized between 4xABVD followed by IN-RT (n = 292) or 6 cycles of ABVD (n = 302). After a median follow-up of 5.1 years, a total of 54 PFS events have occurred: 16 patients experienced relapsed disease and 6 died from causes not related to HL in the ABVD + IN-RT arm. In contrast, 30 patients experienced relapse and 2 died from causes not related to HL in the ABVD-only arm. Intention-to-treat 5-year PFS rates were 92.1% (95% CI, 88.0–94.8) and 89.6% (95% CI, 85.5–92.6) in the ABVD + IN-RT and ABVD-only arms, respectively, with HR 1.45 (95% CI, 0.8–2.5) favoring ABVD + IN-RT. Non-inferiority could not be demonstrated as the upper bound of the 95% CI for the estimated HR (2.50) exceeded the prespecified non-inferiority margin (2.10). However, the difference for the 5-year PFS was only 2.5% (95% CI: −6.6% −0.5%) fitting in the range of the 10% prespecified non-inferiority margin. Therefore, in this group of unfavorable patients, the benefit of combined modality treatment seems to be less clinically relevant than in the favorable group.

In the 594 unfavorable patients, 30/302 developed relapse after chemotherapy alone vs. 16/292 after CMT. Relapses after chemotherapy alone

occurred <2 years in 27/30 patients and in 3 patients after 2 years. Relapses after CMT occurred <2 years in 8/16 patients, and in 8 patients after 2 years. Relapses after chemotherapy occurred mostly in initially involved areas in 26/30. After CMT, relapses in involved areas were observed in 9/16 patients (Table 12.3).

12.4.2.3 Other Studies

In the 50604 phase 2 trial, patients with non-bulky stage I/II disease with a negative iPET after 2xABVD (135 of 149 patients, Deauville score (DS), 1–3) were treated with an additional 2xABVD without consolidative RT, whereas patients with a positive iPET (14 of 149 patients) received 2xBEACOPPesc and 30 Gy IF-RT. Estimated 3 years PFS rates of 91% and 66%, respectively, for the iPET-negative and PET-positive cohorts were reported (p = 0.011), HR 3.84 (95% CI, 1.50–9.84) [28]. These data suggest that four cycles of ABVD result in durable remissions for the majority of patients with early-stage non-bulky HL and negative iPET.

The GHSG HD17 study evaluating iPET-adapted treatment in unfavorable patients has completed recruitment, but results are pending. The trial compares 2xBEACOPPesc + 2xABVD, and RT vs. 2xBEACOPPesc + 2xABVD in iPET-negative patients. Major difference comparing the different studies are reported in (Table 12.3).

Table 12.3 Comparison of RAPID, H10, and HD17 trials

	H10	RAPID	HD17
PET baseline	95%	0%	0%
Interim PET	2xABVD	3xABVD	2xABVD
PET review	75%	100%	100%
Noninferiority margin	10%	7%	
Stage	I–IIB (bulky)	I–IIA	I–IIB (bulky without RF)
Radiotherapy	IN RT 30Gy	IF RT 30Gy	IF RT 30Gy
PET interpretation	International Harmonization Project [38]	5-point scale	5-point Deauville score

12.4.2.4 Management of iPET-Positive Patients

In the RAPID [26] and HD17 trial, patients with a positive iPET received the standard arm of treatment. So far, only the data from RAPID are published. Among the 571 patients enrolled in the study having an iPET after 3 ABVD, 145 were iPET positive (D5PS 3–5). So far, 127 of the 145 patients (87.6%) in the group with positive PET findings were alive without disease progression. There had been 18 events in this group: 10 events of disease progression (6.9% of the patients), 5 deaths with disease progression (3.4% of the patients), and 3 deaths without disease progression (2.1% of the patients). A total of 8 of the 14 patients (57.1%) in this group who required second-line treatment received high-dose chemotherapy followed by autologous transplant.

In the H10 study, iPET-positive patients from both favorable and unfavorable groups were included together, because of their presumed shared poor prognosis, in a randomized trial comparing 3-4xABVD and RT vs. 2xABVD + 2xBEACOPPesc and IN-RT. In the overall iPET-positive group (n = 361) and a median follow-up of 4.5 years, a total of 57 events for PFS occurred: 41 (36 relapses and 5 deaths not related to HL) in the ABVD + IN-RT arm and 16 (13 relapses and 3 deaths not related to HL) in the BEACOPPesc + IN-RT arm. Intent-to-treat 5-year PFS rates were 77.4% (95% CI, 70.4–82.9) and 90.6% (95% CI, 84.7–94.3) in the ABVD + INRT and BEACOPPesc + IN-RT arms, respectively, with an HR of 0.42 (95% CI, 0.23–0.74; P = 0.002) in favor of BEACOPPesc + IN-RT. The 5-year OS rates were 89.3% vs. 96.0% for ABVD + IN-RT and BEACOPPesc + IN-RT, respectively, with an HR of 0.45 (95% CI, 0.19–1.07; P = 0.062) (Fig. 12.2).

12.5 ESMO and NCCN Recommendations

The recently published ESMO guidelines recommend for intermediate stage: 4xABVD or 2xBEACOPPesc + 2xABVD and 30 Gy IS-RT or 2xABVD and an iPET, if the iPET is negative: 2

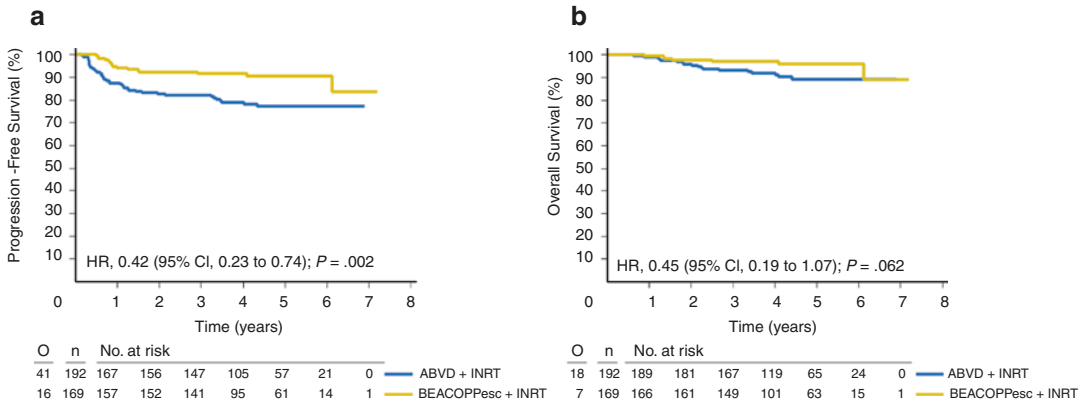

Fig. 12.2 PFS (**a**) and OS (**b**) of patients iPET positive patients included in the H10 trial. After 2xABVD patients were randomized between 2xABVD and 30 Gy INRT vs. 2xBEACOPPesc and 30 Gy INRT. Reprinted from André et al. with permission

additional ABVD and 30 Gy IS-RT and if iPET is positive: 2 additional BEACOPPesc and 30 Gy IS-RT [4].

The 2017 NCCN guidelines recommend a PET-guided approach. For intermediate or unfavorable disease and bulky mediastinum, several options are discussed including the HD14, H10 approaches but also Stanford V [29].

12.6 New Drugs

12.6.1 Brentuximab Vedotin

Brentuximab vedotin (BV) is an antibody–drug conjugate composed of a CD30-targeted chimeric monoclonal antibody covalently linked to the microtubule disrupting agent monomethyl auristatin E via a protease-cleavable linker. In a phase 2 single-arm study, patients with relapsed or refractory HL treated with BV after failure of high-dose chemotherapy and post-autologous stem-cell transplant, 76 (75%) of 102 patients achieved an objective response, and 35 patients (34%) achieved complete remission. Adverse events were manageable with dose reduction or delay. BV was also tested in combination with AVD chemotherapy (BV-AVD) demonstrating promising efficacy with a favorable safety profile in a phase I trial for treatment-naive patients [30]. Based on these results, Fornecker et al. conducted a randomized multicenter, phase II trial in order to improve the PET response rate after 2 cycles with BV-AVD for previously untreated, early-stage unfavorable HL [31]. In total, 170 patients were included, 113 were randomized in the BV-AVD arm and 57 in the ABVD arm. After 2 cycles of treatment, 93/113 patients (82.3%, 95% CI 75.3–88.0) and 43/57 (75.4%, 95% CI 64.3–84.5) achieved a negative PET (Deauville score 1–3) based on central review in the experimental and standard arms, respectively. With the lower bound of the 90% confidence interval superior to 75% in the experimental arm, the primary objective can be considered to be met. An increased toxicity with BV-AVD regimen compared to ABVD was observed with a higher rate of grade 3–4 AEs and SAEs during treatment. In another trial, Kumar et al. treated 29 early-stage unfavorable patients with 4 cycles of BV-AVD followed by 20 Gy involved-site radiotherapy, and 90% of patients achieved a negative PET after two cycles [32].

12.6.2 Checkpoint Inhibitors

Nivolumab and Pembrolizumab are immune checkpoint inhibitors targeting the programmed death-1 receptor [33, 34]. These checkpoint inhibitors augment T-cell activation and restore antitumor T-cell function. In the phase 2 CheckMate 205 study, nivolumab demonstrated

frequent (65–73%) and durable objective responses across 3 cohorts of patients with relapsed/refractory HL after failure of autologous hematopoietic cell transplantation. Cohort D of CheckMate 205 enrolled untreated patients with advanced-stage newly diagnosed HL (stage III, IV, or II with B symptoms and extranodal or bulky disease). Nivolumab monotherapy followed by N-AVD combination therapy was well-tolerated and active in patients with newly diagnosed, untreated, advanced-stage HL. This combination of nivolumab and AVD is actually being evaluated in phase II in early-stage unfavorable HL (NIVAHL, NCT03004833). Pembrolizumab is also being evaluated in combination with AVD (NCT03226249).

12.7 Conclusions and Future Strategies

The reduction of dose and size of RT and more recently, PET-adapted strategies have reduced the burden of treatment used to treat early-stage HL and also defined a subpopulation that can benefit from early intensification. Unfortunately, there is no evidences that this could reduce long-term toxicities. Recently, three new drugs (brentuximab vedotin, nivolumab, and pembrolizumab) showed interesting results in the setting of relapsing patients [35–37]. These drugs are now also being actively evaluated in first-line for early-stage HL, either alone (i.e., in elderly patients) or in combination with AVD. Phase II data are promising, but only randomized phase III trial can change the standard of care in this highly curable group of patients. Finally, circulating cell-free DNA could emerge as a very interesting tool to refine response evaluation and better define cure [10].

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