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Published in:
Hematologic Malignancies

DOI:
10.1007/978-3-030-32482-7_11

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Contents

11.1 Introduction

Historically, Hodgkin lymphoma (HL) was the first malignant disease that could be cured. In the past century, the first successful outcomes of radiotherapy employing large radiation fields were reported, in particular, in patients with limited disease.

Further refinement of this initial treatment approach was achieved through carefully designed prospective randomized phase III

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_11

clinical trials. In this context, the step-by-step development of uniformly accepted staging procedures and clear definitions of stages and response criteria was a major achievement. This allowed direct comparison of study results performed in different consortia worldwide.

Focusing on stage-adapted treatment of HL, these trials allowed the definition of clinical prognostic factors. These, in turn, lead to risk-adapted treatment, which became more refined with subsequent studies. In line with these advances, treatment strategies changed from radiotherapy only using extended-field radiotherapy (EFRT) and later involved-field radiotherapy (IFRT) to combined modality treatment (CMT) with rather small radiotherapy fields and chemotherapy exposure.

Thanks to the long-term follow-up of thousands of patients treated within clinical trials over decades, significant late effects of treatment became apparent. The higher mortality rate in HL survivors turned out to be mainly due to secondary malignancies and damage to the cardiovascular and respiratory systems. Based on these unexpected findings, the ingredients of curative regimens were further adjusted. As far as possible, noncarcinogenic cytostatic agents were introduced in newly developed chemotherapy regimens, and radiation doses were further reduced. This has led to the current major challenges in the treatment of early-stage HL: maintaining the very high cure rates and at the same time reducing the incidence of early and late toxicity. To further improve on this strategy, it is strongly advocated to treat early-stage HL patients within clinical trials.

This chapter deals with past and recent developments in the treatment of stage I and II HL with favorable prognostic factors comprising about 40% of all early-stage HL patients.

11.2 Defining Favorable Early-Stage Disease

11.2.1 Staging

In HL patients, prognosis is distinctly worse with each progressive stage of disease, and the selection of appropriate treatment depends on accurate staging of the extent of disease. The Ann Arbor staging classification was formulated in 1971 and is still the most commonly used staging system for HL [1]. During the Cotswold meeting in 1989, some modifications were introduced to account for new imaging techniques such as computerized tomography (CT) scanning. In addition, clinical involvement of the liver and spleen was redefined, to formally introduce the concept of bulky disease and to draw the attention to the problem of equivocal complete remission [2]. Stage I indicates involvement of a single lymph node region or a single extranodal organ or site. In stage II disease, two or more lymph node regions on the same side of the diaphragm are involved, or there is localized involvement of an extranodal organ or site and of one or more lymph node regions on the same side of the diaphragm. The stage number is followed by the suffix A or B indicating the absence (A) or presence (B) of one or more of the following constitutional symptoms: (a) unexplained fever with temperatures above 38 °C during the previous month, (b) drenching night sweats during the previous months, and (c) unexplained weight loss of more than 10% of body weight in the previous 6 months. Mediastinal bulk was defined by the ratio of the maximum transverse tumor diameter to the internal thoracic diameter at the level of the T5–T6 vertebral interspace. A ratio exceeding one-third was considered bulky.

For the initial staging of HL, a detailed history, complete physical examination, and imaging studies with whole body positron emission tomography using [18F]-fluoro-2-deoxy-D-glucose (FDG-PET, here referred to as PET) scanning and CT scans of the neck, thorax, abdomen, and pelvis are generally recommended [3, 4]. In patients with PET-CT-assessed HL, bone marrow biopsy can be omitted [5]. See Chaps. 6 and 7 for a more comprehensive review of clinical evaluation and functional imaging.

About 8% of stage I–II HL patients present with infradiaphragmatic disease [6, 7]. Patients with infradiaphragmatic HL are generally older, more frequently male, have poorer performance status, and present less frequently with nodular

Table 11.1 Definition of early-stage favorable HL

EORTC–GELA	GHSG	NCI-C/ECOG
CS I–II without risk factors (supradiaphragmatic):	CS I–II without risk factors:	CS I–IIA without risk factors (supradiaphragmatic):
– No large mediastinal mass	– No large mediastinal mass	– No large mediastinal mass
– Age <50 years	– No extranodal disease	– Age <40 years
– No elevated ESR[a]	– No elevated ESR[a]	– ESR <50 mm/h
– 1–3 involved nodal regions	– 1–2 involved nodal regions	– 1–3 involved nodal regions
		– LPHL or NS histology

EORTC European Organization for Research and Treatment of Cancer, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *GHSG* German Hodgkin Study Group, *NCI-C* National Cancer Institute of Canada, *ECOG* Eastern Cooperative Oncology Group, *CS* clinical stage, *ESR* erythrocyte sedimentation rate, *LPHL* nodular lymphocyte-predominant Hodgkin lymphoma, *NS* nodular sclerosis

[a]ESR <50 mm/h without B symptoms or ESR <30 mm/h with B symptoms

sclerosis subtype compared to patients with supradiaphragmatic disease. Furthermore, these patients have a significantly poorer progression-free survival (PFS) and overall survival (OS) as compared to patients with supradiaphragmatic disease [7]. Therefore, these patients should be considered as early unfavorable HL which is further described in Chap. 12.

11.2.2 Prognostic Factors

Historically, several studies describing prognostic factors in early-stage HL have been performed [8, 9] to predict for occult disease in the abdomen and effectiveness of treatment. They were derived from long-term follow-up of patient cohorts treated in a variety of phase III prospective randomized trials. The prognostic significance of bulky disease particularly in the mediastinum, the presence of constitutional symptoms, the erythrocyte sedimentation rate (ESR), and the number of involved lymph node regions were uniformly included in clinically applied prognostic models (see Chap. 8 for prognostic factors). Different Lymphoma Collaborative Groups worldwide use varying combinations of prognostic factors to identify prognostic risk groups. These prognostic factors allow patients to be stratified into favorable or unfavorable prognostic groups. The current definitions of a favorable treatment group according to the different study groups in Europe and the United States are presented in Table 11.1. The Lymphoma Group of the European Organization for Research and Treatment of Cancer (EORTC) and the French–Belgian Groupe d'Etude des Lymphomes de l'Adulte (GELA) define clinical stage I–II patients as favorable if they present with the following characteristics: age <50 years and low ESR (<50 mm/h without and <30 mm/h with B symptoms), no more than three involved lymph node regions, and no large mediastinal mass [10]. All these criteria need to be met to be "favorable." The German Hodgkin Study Group (GHSG) criteria differ slightly in that they substituted age <50 years with no extranodal disease and specify no more than two involved nodal regions rather than ≤3 as in the EORTC [11]. In Canada and North America, it is common to define an early or limited stage risk group as stage I and IIA disease without bulky disease (see Table 11.1).

Many of these defined risk factors are reflective of or correlate with disease burden. Currently applied PET/CT imaging for staging of HL allows accurate measurement of total metabolic tumor volume (TMTV). The prognostic value of TMTV has been increasingly described in HL. In early-stage HL, a retrospective analyses of TMTV of staging PET/CT images from the EORTC/GELA/FIL H10 showed that TMTV outperforms the classical risk factors described above in terms of prediction of interim PET

positivity and PFS [12]. However, standardization of measurement of TMTV is the major challenge before clinical application.

11.3 Radiotherapy Alone

The use of radiation therapy, pioneered at Stanford University in the 1960s by Henry Kaplan and Saul Rosenberg, offered HL patients the first hope for cure. In the treatment of early stages, EFRT was considered the standard treatment modality for many years. With this technique, radiation was delivered not only to the clinically involved but also to the adjacent, clinically uninvolved sites. Because it was known that HL spreads to contiguous nodal sites, mantle field RT encompassed all nodal sites above the diaphragm. The combination of mantle field with inverted-Y field and spleen irradiation was termed "subtotal nodal irradiation" (STNI). See Chap. 9 for definitions of field size.

Significant advances in the treatment of HL were then derived from clinical trials. Investigators at Stanford demonstrated that radiation therapy alone using total lymphoid irradiation or STNI is an adequate treatment for nearly all patients with pathologic stages I–II. In a series of 109 patients, the freedom from relapse rate at 10 years was 77% [13].

A retrospective study from Canada studied the impact of patient selection and EFRT on outcome among patients with clinical stages I and II treated between 1978 and 1986. Patients with favorable prognostic features (age <50 years, ESR <40 mm/h, and lymphocyte-predominant or nodular sclerosing histology) treated with mantle and para-aortic-splenic irradiation had only 12.7% actuarial risk of relapse at 8 years [14].

Between 1964 and 1987, the EORTC performed four consecutive randomized clinical trials aiming to delineate the subsets of patients with stage I and II disease who could be safely treated with RT alone [15, 16] (Table 11.2).

Taken together, these four randomized trials demonstrated that staging laparotomy could be safely omitted in patients with favorable clinical characteristics in early favorable HL and that these patients could be treated by STNI (40 Gy) with a similar outcome as obtained by staging laparotomy followed by mantle field RT (40 Gy). Another important finding was that the overall outcome had gradually improved over the years (Fig. 11.1).

The total radiation dose in these EORTC trials was always 40 Gy. The GHSG HD4 trial showed that patients without risk factors had similar outcomes when treated with 40 Gy radiaton to the involved field and 30 Gy to the non-involved extended field [22]. The 7-year relapse-free and overall survival rates were 78% vs. 83% and 91% vs. 96%, respectively.

Radiation in mantle field technique was expected to cause less long-term toxicity compared with STNI. However, in clinically staged patients, results with mantle field irradiation alone have been disappointing. In the EORTC H7-VF and H8-VF trials, 40 female patients were treated with mantle field RT only. The respective prognostic factors were stage IA, age <40 years, nodular sclerosing or lymphocyte-predominant histology, and ESR <50 mm/h. These patients were expected to have a very low risk of occult abdominal involvement (5%). The relapse-free survival was however lower than expected: a total of 23% had relapsed at 6 years [21]. Because of this unacceptable rate, the very favorable subgroup has since been treated according to the EORTC strategy for the favorable subgroup.

Specht et al. reported on the influence of radiation field size on long-term outcome in early-stage disease in a meta-analysis of eight randomized trials evaluating larger vs. smaller radiation fields [23]. These trials included almost 2000 patients with both, favorable and unfavorable prognosis stage I–II disease. A definite and substantial reduction in the risk of treatment failure was demonstrated if more extensive radiotherapy was used. The 10-year risk of recurrence was 43% for patients treated with smaller-field irradiation compared to 31% for those treated with larger-field radiation therapy. Although the additional radiotherapy prevented a substantial proportion of recurrences, it did not significantly affect overall

Table 11.2 Early-stage favorable HL: selection of randomized studies of radiotherapy alone

Trial	Year	Study arms	Number of patients	Outcome	Overall survival	Reference
EORTC HI	1964–1971	A. Mantle field or inverted-Y RT	288	A. 38% DFS (15 years)	A. 58% OS (15 years)	Tubiana et al. [17]
		B. The same RT followed by vinblastine		B. 60% DFS (15 years)	B. 65% OS (15 years)	
				$p < 0.001$	$p = 0.15$ (NS)	
EORTC H2	1972–1976	A. Laparotomy and mantle field + Para-aortic lymph node RT	300	A. 76% DFS (12 years)	A. 79% OS (12 years)	Tubiana et al. [16, 18]
		B. STNI		B. 68% DFS (12 years)	B. 77% OS (12 years)	
				$p = 0.18$ (NS)	$p = 0.38$ (NS)	
EORTC H5F	1977–1982	Laparotomy negative patients	198	A. 69% DFS (9 years)	A. 94% OS (9 years)	Carde et al. [19]
		A. Mantle field RT		B. 70% DFS (9 years)	B. 91% OS (9 years)	
		B. STNI		$p > 0.50$ (NS)	$p > 0.50$ (NS)	
EORTC H6F	1982–1987	A. Laparotomy, if negative: Mantle field RT for LP or NSc histology	262	A. 84% RFS (6 years)	A. 89% OS (6 years)	Carde et al. [20]
		STNI for MC or LD histology		B. 80% RFS (6 years)	B. 93% OS (6 years)	
		B. STNI		$p = 0.25$ (NS)	$p = 0.24$ (NS)	
EORTC H7VF-H8VF	1988–1993	Mantle field RT	40	RFS 73% (6 years)	OS 95% (6 years)	Noordijk et al. [21]
GHSG HD4	1988–1994	A. STNI 40 Gy	376	A. 78% RFS (7 years)	A. 91% OS (7 years)	Dühmke et al. [22]
		B. STNI 30 Gy + IFRT 10 Gy		B. 83% RFS (7 years)	B. 96% OS (7 years)	
				$p = 0.093$ (NS)	$p = 0.16$ (NS)	

EORTC European Organization for Research and Treatment of Cancer, *GHSG* German Hodgkin Study Group, *DFS* disease-free survival, *OS* overall survival, *RFS* relapse-free survival, *STNI* subtotal nodal irradiation, *RT* radiotherapy, *IFRT* involved-field radiotherapy, *Gy* Gray, *NS* not significant, *LP* lymphocyte predominant, *NSc* nodular sclerosing, *MC* mixed cellularity, *LD* lymphocyte depleted

mortality. The lack of survival difference suggests that salvage chemotherapy for relapse after initial radiotherapy is effective enough to minimize the impact of any increase in relapse on survival.

To summarize, STNI was considered a standard treatment for early favorable HL until the 1990s. However, 25–30% of patients eventually relapsed with subsequent 10-year survival rates of only 63% [24].

11.4 Late Treatment Effects and Mortality

As the number of patients surviving HL increased and there was longer follow-up, it became evident that their life expectancy did not revert to that of the age-matched general population. The higher mortality of HL patients is largely a result of the long-term effects of treatment. Important late effects comprise secondary malignancies,

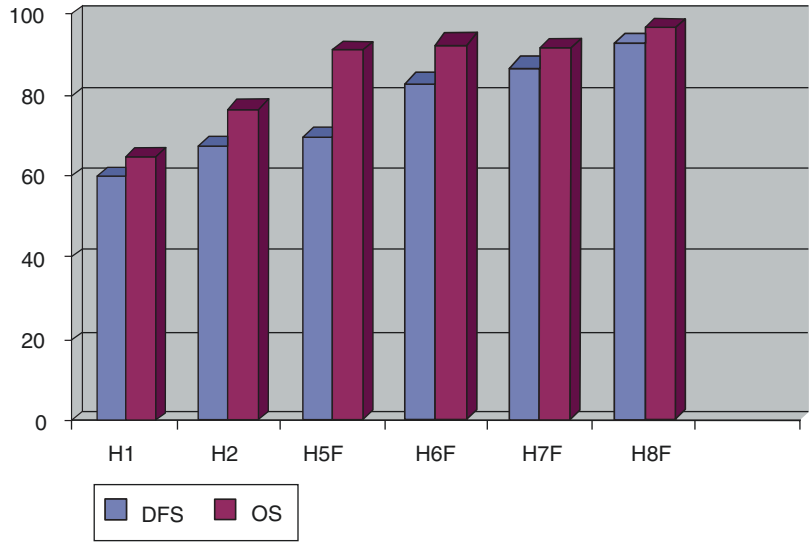

Fig. 11.1 Disease-free survival and overall survival in consecutive EORTC Lymphoma Group trials on early-stage favorable Hodgkin lymphoma (HL). *DFS* disease-free survival, *OS* overall survival

cardiovascular diseases, pulmonary problems, gonadal dysfunction, infectious complications, and fatigue. The incidence of the most life-threatening late side effects, i.e., secondary cancers and cardiovascular diseases, is significantly related to the radiation dose and field size, choice of cytostatic drugs, and total amount of drugs administered.

In patients with early favorable disease, mortality from causes other than HL has increased over time, exceeding HL-related mortality after 10–15 years [25, 26]. A large study with a median follow-up of more than 17 years examined case-specific mortality and absolute excess mortality, compared to population rates, in a cohort of 1261 Dutch patients [25]. These patients were younger than 40 years when treated between 1965 and 1987. HL was the most frequent cause of death (55%), followed by secondary malignancies (22%) and cardiovascular diseases (9%). In the first 10 years following initial treatment, the excess mortality rate was largely due to the primary disease, while after 10 years, causes other than HL contributed most to excess mortality. The actuarial risk of death is shown in Fig. 11.2. Even after 30 years of follow-up, there was no evidence of a decline in the relative risk of death from causes other than HL. In 30-year survivors, the annual excess mortality rate from all causes other than HL was nearly 3 per 100 patients. Solid tumors, especially in the digestive and respiratory tract, contributed most to this excess risk, followed by cardiovascular diseases [25]. In 2009, the EORTC and the GELA published their results of a study analyzing the cause-specific excess mortality in adult patients with respect to treatment modality [27]. The study population consisted of 4401 patients aged 15–69 in all stages, who were treated between 1964 and 2000. In patients with early-stage disease, the overall excess mortality was associated with age ≥40 years ($p = 0.007$), male gender ($p < 0.001$), unfavorable prognostic features ($p < 0.001$), treatment with EBVP (epirubicin, bleomycin, vinblastine, prednisone) plus IFRT ($p = 0.002$), and mantle field irradiation alone ($p = 0.003$). Therefore, excess mortality was linked to treatment modalities that were associated with poor failure-free survival resulting in a higher need for salvage treatment. Late treatment effects are covered in more detail in Chaps. 26–29.

11.5 Combined Modality Treatment

With the observation of high relapse rates and fatal long-term effects, most study groups abandoned STNI and EFRT from the treatment of early-stage HL. Studies were developed in an

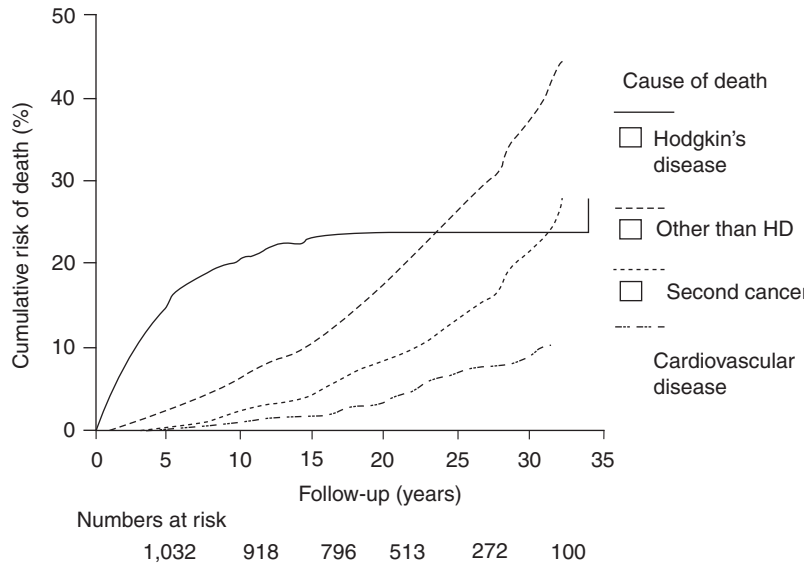

Fig. 11.2 The actuarial risks of death from major disease categories in 1261 Dutch HL patients. Data from Dutch database on Hodgkin lymphoma (Reprinted from Aleman et al. [25] with permission)

attempt to reduce long-term toxicity without increasing disease-specific mortality. Most randomized studies evaluated CMT in an attempt to define the optimal chemotherapy, number of cycles needed, as well as radiation field size and dose when combined with chemotherapy. Commonly used regimen and drug combinations are listed in Table 11.3.

11.5.1 Radiotherapy Alone Versus CMT

High relapse rates after treatment with radiotherapy alone prompted several groups to study CMT as induction therapy. An earlier meta-analysis of individual patient data showed that CMT reduced the relapse risk compared with radiotherapy alone, but did not improve overall survival [23]. Most of the trials included in this analysis were conducted between 1967 and 1988 using MOPP or MOPP-like regimens, which produced unacceptable hematologic toxicity, frequently induced secondary malignancies, and rendered most recipients infertile. These studies are therefore only of historical interest and will not be discussed further. Later, based mainly on results of studies in advanced HL, the ABVD regimen became the standard of care in early favorable HL. When compared with MOPP, ABVD had a better efficacy and produced less toxicity [28]. In particular, secondary leukemias and infertility were less frequently observed than after alkylating agent-containing regimens.

Table 11.3 Chemotherapy regimens used in early-stage favorable HL

Regimen	Drug combinations
ABVD	Doxorubicin, vinblastine, bleomycin, dacarbazine
EBVP	Epirubicin, bleomycin, vinblastine, prednisone
MOPP	Mechlorethamine, vincristine, procarbazine, prednisone
MOPP–ABV	Mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine
Stanford V	Vinblastine, doxorubicin, vincristine, bleomycin, mechlorethamine, etoposide, prednisone
VBM	Vinblastine, methotrexate, bleomycin

Two randomized studies, one in Germany and one in the United States, showed the benefit of adjuvant chemotherapy with a short course of ABVD or ABVD-like chemotherapy in early favorable patients: the GHSG HD7 trial compared EFRT alone with CMT consisting of two cycles of ABVD followed by EFRT in early favorable patients [11]. A significant advantage

in freedom from treatment failure (FFTF) was seen after CMT, mainly related to fewer relapses as compared with EFRT only (3% vs. 22%). There were no differences in overall survival between treatment arms. Importantly, CMT was not associated with significantly more acute or long-term toxicity. A trial from the United States confirmed the benefit of a short course of limited chemotherapy added to STNI in clinically staged IA and IIA patients [29]. The study showed that three cycles of doxorubicin and vinblastine (AV) followed by STNI were well tolerated and gave a superior failure-free survival compared with STNI alone. The conclusion from these two studies is that the number of relapses can be reduced by the addition of ABVD or ABVD-like chemotherapy to large radiation fields. However, long-term toxicity was still of concern due to the use of extensive radiation fields.

The Group Pierre-et-Marie-Curie showed that it was possible to replace the classic mantle field irradiation with a more limited radiotherapy to initially involved areas only. This novel approach termed IFRT involved the addition of chemotherapy to control occult disease in uninvolved areas [31]. IFRT reduced the irradiation of normal tissues, such as the breast, heart, and lungs.

Therefore, several groups performed randomized trials comparing STNI with a combined modality approach in which patients received smaller radiation fields and combination chemotherapy. The results of a selection of some of the largest trials are listed in Table 11.4.

Table 11.4 Early-stage favorable HL: selection of studies comparing STNI alone with combined modality treatment (CMT)

Trial	Year	Study arms	Number of patients	Outcome	Overall survival	Reference
SWOG/CALGB	1989–2000	A. STNI (36–40 Gy)	326	A. 81% FFS (3 years)	Follow-up too short	Press et al. [29]
		B. 3 AV + STNI (36–40 Gy)		B. 94% FFS (3 years)		
				$p < 0.001$		
Stanford–Kaiser Permanente	1988–1995	A. STNI (30–44 Gy)	78	A. 92% PFS (5 years)	A. 98% OS (5 years)	Horning et al. [30]
		B. 6 VBM + mantle field RT		B. 87% PFS (5 years)	B. 94% OS (5 years)	
				$p = 0.73$ (NS)	$p = 0.05$ (NS)	
EORTC H7F	1988–1993	A. STNI (36 Gy)	333	A. 78% EFS (10 years)	A. 92% OS (10 years)	Noordijk et al. [32]
		B. 6 EBVP + IFRT (36 Gy)		B. 88% EFS (10 years)	B. 92% OS (10 years)	
				$p = 0.0113$	$p = 0.79$ (NS)	
EORTC–GELA H8F	1993–1999	A. STNI (36 Gy)	542	A. 68% EFS (10 years)	A. 92% OS (10 years)	Fermé et al. [10]
		B. 3 MOPP–ABV + IFRT (36 Gy)		B. 93% EFS (10 years)	B. 97% OS (10 years)	
				$p < 0.001$	$p = 0.001$	
GHSG HD7	1994–1998	A. EFRT 30 Gy (IFRT 40 Gy)	627	A. 67% FFTF (7 years)	A. 92% OS (7 years)	Engert et al. [11]
		B. 2 ABVD + EFRT 30 Gy (IFRT 40 Gy)		B. 88% FFTF (7 years)	B. 94% OS (7 years)	
				$p < 0.0001$	$p = 0.43$ (NS)	

SWOG Southwest Oncology Group, *CALGB* Cancer and Leukemia, *EORTC* European Organization for Research and Treatment of Cancer, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *GHSG* German Hodgkin Study Group, *STNI* subtotal nodal irradiation, *IFRT* involved-field radiotherapy, *EFRT* extended-field radiotherapy, *Gy* Gray, *FFS* failure-free survival, *PFS* progression-free survival, *EFS* event-free survival, *FFTF* freedom from treatment failure, *OS* overall survival, *NS* not significant

In the EORTC H7F trial, patients with early favorable disease were treated with six cycles of EBVP followed by IFRT or STNI [32]. The 10-year event-free survival rate after EBVP and IFRT was 10% better than after STNI alone, whereas overall survival was 92% in both arms. This trial demonstrated that EFRT could be replaced by CMT including IFRT. However, in early unfavorable patients, EBVP was significantly less efficient than MOPP–ABV [32].

In the subsequent H8F trial by the EORTC–GELA, favorable HL patients were randomized between STNI or CMT consisting of three cycles of MOPP–ABV hybrid followed by IFRT [10]. Patients in the CMT arm had a lower relapse rate, which resulted in a significantly higher event-free survival rate than for patients in the STNI arm (93% vs. 68% at 10 years). Importantly, patients in the combined modality arm also had a significantly higher overall survival (97% vs. 92% at 10 years). The results of this study again demonstrated the superiority of CMT over EFRT alone and showed that IFRT is a sufficient treatment after chemotherapy for early favorable HL. However, due to its carcinogenic potential, MOPP–ABV was abandoned in favor of ABVD.

11.5.2 Optimal Number of Cycles of Chemotherapy

The use of fewer cycles of ABVD could potentially reduce late side effects of combined modality therapy. Between 1998 and 2003, the GHSG HD10 trial accrued more than 1300 favorable prognosis stage I–II HL patients. Patients were randomized to four arms in a 2 × 2 factorial design: two cycles of ABVD followed by 30 Gy IFRT, two cycles of ABVD followed by 20 Gy IFRT, four cycles of ABVD followed by 30 Gy IFRT, and four cycles of ABVD followed by 20 Gy IFRT. This trial tested a possible reduction in the number of ABVD cycles as well as reduction of radiation dose when using IFRT. With a median follow-up of 90 months, there were no significant differences in FFTF and overall survival at 5 years between four or two cycles of ABVD. In addition, there was also no difference between 30 and 20 Gy IFRT [33]. Importantly, there was also no significant difference in terms of overall survival, FFTF, and progression-free survival when all four arms were compared. The results were robust with longer follow-up (8 years). The treatment arms with four cycles of ABVD and 30 Gy IFRT showed significantly more acute toxicity in comparison with two cycles of ABVD and 20 Gy IFRT. Two cycles of ABVD followed by 20 Gy IFRT are thus GHSG standard of care for HL patients in early favorable stages.

11.5.3 Optimal Chemotherapy Combination

Reduction of chemotherapy-induced toxicity was pursued in the GHSG HD13 trial. This trial investigated whether drugs can be omitted from the ABVD regimen and randomized patients with early favorable HL to two cycles of either ABVD, AVD, ABV, or AV with all arms followed by 30 Gy IFRT. Compared with ABVD, the 5-year FFTF was reduced up to 11.7% (ABV) or 16% (AV) when dacarbazine and dacarbazine and bleomycin were deleted and reduced up to 3.9% (AVD) by the deletion of bleomycin. The reduction in FFTF did not translate into poorer OS [34]. Therefore, it seems that particularly dacarbazine and to a lesser extent bleomycin are relevant therapeutic agents in ABVD. The Stanford group has reported good results in 87 patients with stage I or IIA non-bulky HL treated with an abbreviated Stanford V regimen administered weekly for 8 weeks followed by 30 Gy modified IFRT [35]. At a median follow-up of 10 years, the FFP was 94%.

11.5.4 Optimal Radiation Dose

Apart from the choice of cytostatic agents and the number of courses, the question of radiation field size and dose has also been evaluated (for a selection of randomized trials, see Table 11.5). A decline in late complications is expected with lower radiation doses as their incidence is directly

Table 11.5 Early-stage favorable HL: selection of studies of RT field size and dose in CMT

Trial	Year	Study arms	Number of patients	Outcome	Overall survival	Reference
Milan	1990–1997	A. 4 ABVD + STNI 36–40 Gy	133	A. FFP 93% (12 years)	A. OS 96% (12 years)	Bonadonna et al. [36]
		B. 4 ABVD + IFRT 36–40 Gy		B. FFP 94% (12 years)	B. OS 94% (12 years)	
EORTC–GELA H9F	1998–2004	A. 6 EBVP + IFRT 36 Gy	783	A. EFS 87% (4 years)	A. OS 98% (4 years)	Noordijk et al. [37]
		B. 6 EBVP + IFRT20 Gy		B. EFS 84% (4 years)	B. OS 98% (4 years)	
		C. 6 EBVP (no RT)		C. EFS 70% (4 years)	C. OS 98% (4 years)	
		Median follow-up 33 months		No RT arm closed because of excess failure rate ($p < 0.001$)		
GHSGHD10	1998–2003	A. 2 ABVD + IFRT 30 Gy	1.370	No differences in FFTF between patients given two or four cycles of ABVD or 20 or 30 Gy IFRT (FFTF 91–93%)	No survival differences between patients given two or four cycles of ABVD or 20 or 30 Gy IFRT (OS 96–97%)	Engert et al. [33]
		B. 2 ABVD + IFRT 20 Gy				
		C. 4 ABVD + IFRT 30 Gy				
		D. 4 ABVD + IFRT 20 Gy				
		Median follow-up 91 months				

EORTC European Organization for Research and Treatment of Cancer, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *GHSG* German Hodgkin Study Group, *STNI* subtotal nodal irradiation, *IFRT* involved-field radiotherapy, *RT* radiotherapy, *Gy* Gray, *FFP* freedom from progression, *OS* overall survival, *EFS* event-free survival, *FFTF* freedom from treatment failure

correlated with the dose of radiation administered.

Two randomized trials have investigated radiation doses in early favorable HL patients treated with CMT. In the EORTC–GELA H9F trial, 783 patients with stage I–II disease and favorable characteristics received six cycles of EBVP. Patients in complete remission after chemotherapy were randomized to receive standard dose IFRT (36 Gy), low-dose IFRT (20 Gy), or no RT at all. The experimental arm without RT was closed early due to an excess failure rate compared with the two RT arms, but there were no differences in outcome reported between the two radiation dose levels.

As discussed in Sect. 11.5.2, the GHSG HD10 trial compared doses of 30 and 20 Gy IFRT after two or four cycles of ABVD. No significant differences were observed between patients receiving 30 Gy IFRT and 20 Gy IFRT in terms of overall survival (97.7 vs. 97.5%), FFTF (93.4 vs. 92.9%), and progression-free survival (93.7 vs. 93.2%), respectively [33]. Therefore, IFRT with a dose of 20 Gy seems to be sufficient after two cycles of ABVD.

11.5.5 Optimal Radiation Field Size

The rationale for reduced radiation therapy field size is to decrease potential late complications such as cardiovascular and secondary cancers as the amount of irradiated normal tissue is reduced. Several randomized trials in early unfavorable HL have shown that after effective chemotherapy, IFRT is as effective as EFRT in terms of overall survival and FFTF [10, 38]. However, data from

randomized trials in patients with early favorable HL are scarce.

Bonadonna et al. reported the long-term follow-up of 133 patients with early HL randomly assigned to IFRT or STNI after four cycles of ABVD and found no significant differences in overall survival (94 vs. 96%) or freedom from progression (94 vs. 93%) at 12 years [36] (see Table 11.5). The limited size of the patient sample, however, had no adequate statistical power to test for non-inferiority of IFRT vs. STNI.

The EORTC–GELA group introduced the concept of involved-node radiotherapy (INRT) to further decrease the radiotherapy fields [39, 40]. INRT only includes the initially involved lymph nodes with a small isotropic margin. Identifying and contouring involved lymph nodes is of outmost importance. Therefore, it is recommended that all patients have cervical and thoracic CT scans pre- and post-chemotherapy, preferably in the radiotherapy position, and must be examined by the radiation oncologist before the start of the chemotherapy [39, 41]. Better sparing of normal tissues such as the salivary glands, heart, coronary arteries, and breast in female patients is expected with the use of INRT compared to IFRT (Fig. 11.3). The new INRT concept was applied in the EORTC–GELA–FIL H10 randomized trial for patients with early-stage HL. As is shown later in this chapter, INRT was associated with higher PFS rates compared to no radiotherapy.

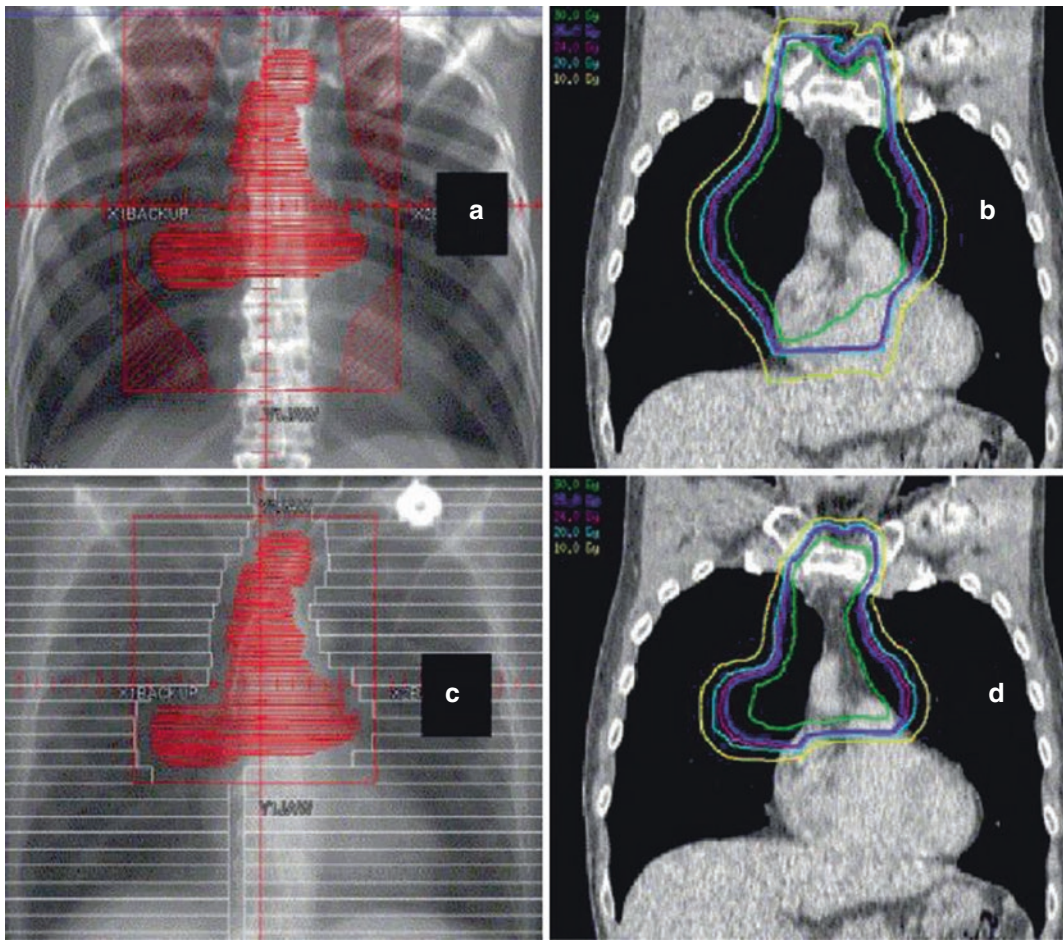

Fig. 11.3 Comparison between radiation field sizes and the volume of heart irradiation using either IFRT (**a**, **b**) or INRT (**c**, **d**) for a mediastinal tumor mass (PTV in red color) (Reprinted from Girinsky et al. [39] with permission)

Canadian researchers reported promising results with INRT in a retrospective study, although a greater radiation margin was applied as in the EORTC–GELA–FIL H10 trial [42]. In British Columbia, the extent of the radiation therapy field size underwent serial changes during the last decades, from EFRT to IFRT and eventually since 2001 to INRT with margins from 1.5 to 5 cm. There were no statistically significant differences among the three groups for PFS and overall survival. There were also no marginal recurrences in the INRT patient group [42]. Although the exact definition of INRT needs further standardization, the concept of INRT seems feasible.

11.6 Chemotherapy Alone

The potentially life-threatening late side effects of radiotherapy for HL patients have raised the question whether those in early-stage disease can be treated with chemotherapy alone. This question is particularly relevant for patients in whom the risk of RT-induced toxicity is deemed less acceptable. Chemotherapy-only protocols have been successfully used in children and adolescents (see Chap. 14 on pediatric HL). However, few data exist on their role in adults. Table 11.6 shows a selection of randomized trials performed in adult patients with early favorable HL dealing with the issue of chemotherapy alone. These trials encountered a number of problems with design, patient accrual, as well as variations in the type of chemotherapy and field size of radiation therapy utilized.

The use of chemotherapy alone is not a new concept. In the early 1990s, two trials comparing MOPP with radiotherapy as first-line therapy in early-stage HL were published [43, 44]. Long relapse-free survival varied from 70% to 80%, with varying outcomes of salvage chemotherapy.

The National Cancer Institute of Canada (NCI-C) and the Eastern Cooperative Oncology Group (ECOG) conducted a randomized phase III trial addressing the role of ABVD alone for early favorable and unfavorable HL. The experimental arm consisted of four cycles of ABVD alone if a complete remission was achieved after two cycles. Otherwise, patients received six cycles. The standard arm was STNI with 36 Gy. Among the favorable-risk patients, there was no difference between the two arms for event-free survival, freedom from disease progression, and overall survival after a median follow-up of 11.3 years [45]. However, even longer follow-up is still needed to determine late toxicities.

Only two randomized trials comparing CMT with chemotherapy alone in early favorable patients have been published. As discussed in Sect. 11.5.4, one was the EORTC–GELA H9F trial in which IFRT in 36 Gy was compared with 20 Gy or no radiotherapy in CR patients after six cycles of EBVP. The chemotherapy-only arm was prematurely closed due to an excessive number of relapses [37].

The Memorial Sloan Kettering Cancer Center randomized early non-bulky HL patients between six cycles of ABVD alone and six cycles of ABVD plus 36 Gy radiotherapy. Due to the poor accrual rate, the trial was closed before completion, and only 152 patients were randomized. No significant differences were observed between CMT and chemotherapy alone, but the sample size was insufficient [46].

11.7 Treatment Adaptation Based on PET Scan Response

Functional imaging with PET scanning has become the standard tool for staging and response assessment in HL (see Chap. 7). Interim PET scanning enables evaluation of early metabolic changes rather than the morphologic changes occurring later during and after treatment. Several studies using PET after two or three cycles of ABVD have shown that early metabolic changes are predictive of the final treatment response and PFS [47–51]. Based on these studies which were mainly performed among advanced stage patients, several cooperative groups incorporated interim PET imaging in their early-stage trials to reduce treatment exposure in responding patients to prevent overtreatment and/or intensify treatment in case of nonresponsiveness [52–54]. A

Table 11.6 Early-stage favorable HL: selection of randomized studies of chemotherapy alone in adult patients

Trial	Year	Study arms	Number of patients	Outcome	Overall survival	Reference
NCI-US	1978–1989	A. 6–8 MOPP	84	A. DFS 82% (10 years)	A. OS 90% (10 years)	Longo et al. [43]
		B. Radiotherapy		B. DFS 67% (10 years)	B. OS 85% (10 years)	
				p = NS	p = NS	
Rome–Florence	1979–1982	A. Mantle field + Para-aortic RT (36–44 Gy)	89	A. RFS 70% (8 years)	A. OS 93% (8 years)	Biti et al. [44]
		B. 6 MOPP		B. RFS 71% (8 years)	B. OS 56% (8 years)	
				p = NS	$p < 0.001$	
NCI-C/ECOG HD6	1994–2002	A. 4–6 ABVD	123	A. EFS 87% (5 years)	A. OS 97% (5 years)	Meyer et al. [45]
		B. STNI		B. EFS 88% (5 years)	B. OS 100% (5 years)	
				p = 0.6 (NS)	p = 0.3 (NS)	
EORTC–GELA H9F	1998–2004	A. 6 EBVP + IFRT 36 Gy	783	A. EFS 87% (4 years)	A. OS 98% (4 years)	Noordijk et al. [37]
		B. 6 EBVP + IFRT 20 Gy		B. EFS 84% (4 years)	B. OS 98% (4 years)	
		C. 6 EBVP (no RT)		C. EFS 70% (4 years)	C. OS 98% (4 years)	
		Median follow-up 33 months		No RT arm closed because of excess failure rate ($p < 0.001$)		
Memorial Sloan Kettering Cancer center	1990–2000	A. 6 × ABVD	152	A. FFP 81% (5 years)	A. OS 90% (5 years)	Strauss et al. [46]
		B. 6 × ABVD + RT		B. FFP 86% (5 years)	B. OS 97% (5 years)	
				p = 0.61 (NS)	p = 0.08 (NS)	

NCI-US National Cancer Institute United States, *EORTC* European Organization for Research and Treatment of Cancer, *NCI-C* National Cancer Institute of Canada, *ECOG* Eastern Cooperative Oncology Group, GELA Groupe d'Etude des Lymphomes de l'Adulte, *STNI* subtotal nodal irradiation, *IFRT* involved-field radiotherapy, *RT* radiotherapy, *Gy* Gray, *NS* not significant, *FFP* freedom from progression, *OS* overall survival, *DFS* disease-free survival, *RFS* relapse-free survival, *EFS* event-free survival

summary of the results of these large randomized trials are displayed in Table 11.7 and Fig. 11.4.

In the NCI rapid trial, patients with stage IA or IIA non-bulky HL were treated with three cycles of ABVD after which PET scanning was performed. The PET scan was negative in 426 out of 602 patients (75%). These 426 patients were randomized between no further treatment and IFRT. In the intention-to-treat analysis, the PFS after 3 years in the no further treatment arm was 90.8% versus 94.6% in the IFRT arm. Because of the large numbers of cross-overs in this trial, the per protocol analysis is also of interest. In this analysis, PFS was 90.8% versus 97.1% in the arm including IFRT [52].

The EORTC/GELA/FIL H10 trial with a total of 1950 randomized patients also investigated chemotherapy-only strategies in case of interim PET negativity. In this trial, patients with early favorable disease were treated in the standard arm with three cycles of ABVD and 30 Gy INRT. An interim PET scan was performed after two cycles, but no treatment change was performed on the basis of this scan. In the experimental arm, there was both a de-escalation non-inferiority question in case of a negative interim PET scan and an escalating superiority question in case of a positive interim PET scan. In patients with negative PET findings, INRT was substituted by a single extra cycle of ABVD in

Table 11.7 Results of PET response-adapted early favorable Hodgkin lymphoma trials focusing at de-escalation by leaving out radiotherapy: EORTC H10-F, UK RAPID and GHSG HD16trials

Trial	Year	Study arms	Number of patients	Outcome	Overall survival	Reference
UK RAPID trial	2003–2010	3 ABVD if PET negative followed by: A. 30 Gy IF-RT B. No further treatment	426	PFS at 3 years (per protocol analysis) A. 97.1% B. 90.8%.	At 3 years A. 97.1% B. 99%.	Radford et al. [52]
EORTC H10-F	2006–2011	2 ABVD if PET negative followed by: A. 3×ABVD + IN-RT B. 4×ABVD (no radiotherapy).	1950	PFS at 5 years: A. 99% B. 87.1%	At 5 years: A. 100 B. 99.6%.	Andre et al. [53]
GHSG HD16	2009–2015	2 ABVD if PET negative followed by: A. 20 Gy IF-RT B. No further treatment	1150	PFS at 5 years: A. 93.4% B. 86.1%.	At 5 years: A. 98.1% B. 98.4%	Fuchs et al. [54]

PFS progression-free survival, *OS* overall survival, *INRT* involved-node radiotherapy, *IFRT* involved-field radiotherapy, *n.a.* not available

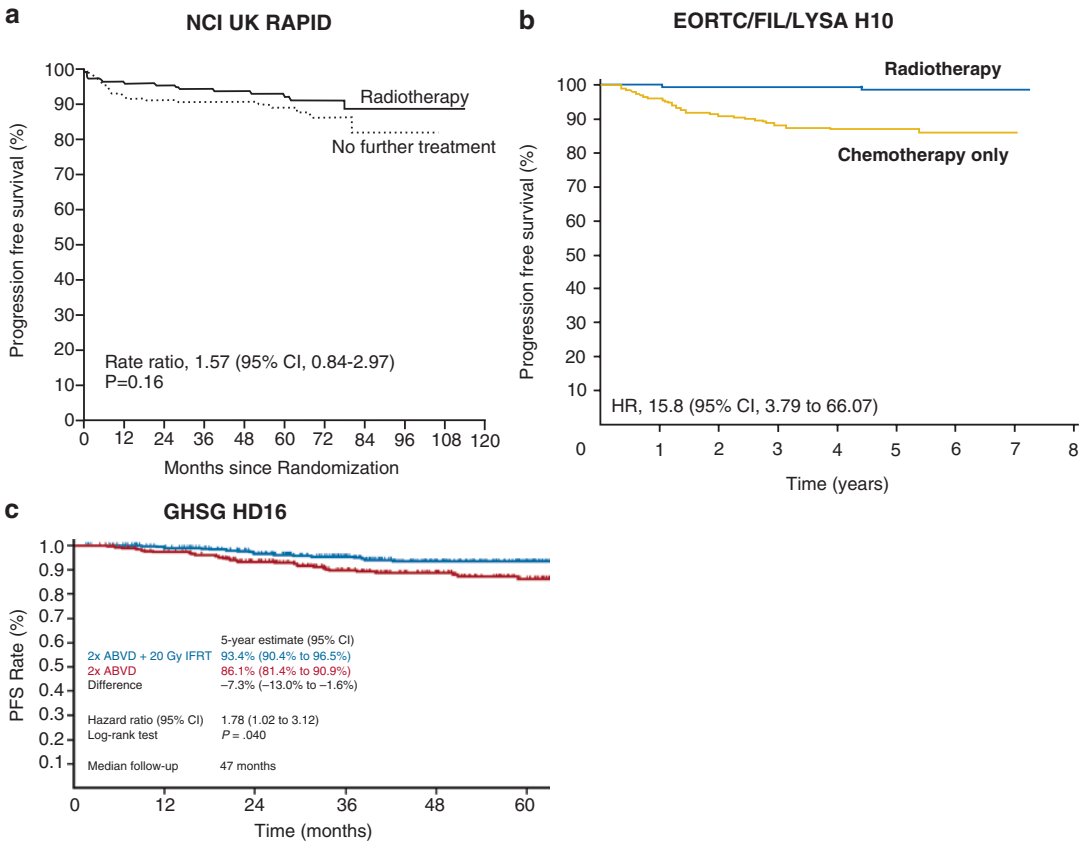

Fig. 11.4 Results of the recently published trials of PET adapted trials in early favorable Hodgkin lymphoma. Shown are progression-free survival curves for the UK RAPID trial (**a**), EORTC/LYSA/FIL H10 favorable (**b**) and GHSG HD16 (**c**)

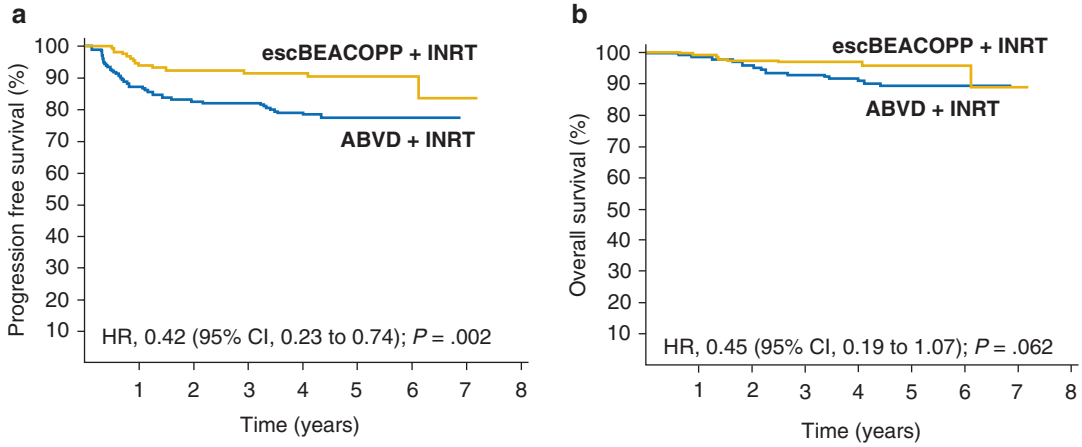

Fig. 11.5 Results of the EORTC/LYSA/FIL H10 trial in case of a positive FDG-PET scan after 2 ABVD among patients with both favorable and unfavorable early-stage HL. Shown are progression-free survival (**a**) and overall survival (**b**)

favorable subgroup patients and two extra cycles in patients with unfavorable disease. The de-escalation arm with the substitution of radiotherapy by extra chemotherapy was closed prematurely due to futility based on 33 events. In line with the results of the RAPID trial, final results at 5-year follow-up showed that early favorable patients with a negative PET after two cycles of ABVD have an excellent outcome when treated with CMT (5-year PFS 99%). Substituting radiotherapy by a single extra course of ABVD resulted in a decrease of about 12% PFS [53].

Similar were reported from GHSG HD16 trial which was recently published. In this large trial involving 1150 patients with early favorable HL, patients with a negative PET scan after two cycles of ABVD were randomized between standard 30 Gy IFRT and no further treatment. Again omission of radiotherapy resulted in a decrease of tumor control with PFS of 93.4% at 5 years in the CMT arm versus 86.1% in the chemotherapy-only arm [54]. There were no differences in overall survival at 5 years.

Taken together, these three trials demonstrated that omission of radiotherapy among patients with early-stage HL and a negative PET scan after two or three cycles of ABVD resulted in a clinically relevant decrease in PFS. Although it must be mentioned that chemotherapy-only strategies based on interim PET scanning also resulted in excellent treatment outcomes and can be seen as a treatment option for patients in whom radiotherapy is expected to result in excessive short- and/or long-term toxicity. Overall survival in all trials was not different between treatment arms meaning that almost all patients not receiving radiotherapy could successfully be salvaged. Long-term effects on overall survival of the omission of radiotherapy and the impact of salvage treatments need to be awaited.

The EORTC H10 study was the only study that also investigated escalation of treatment based on a positive interim PET scan. Patients with both early favorable and early unfavorable HL and a positive interim PET scan after two cycles of ABVD subsequently received two cycles of escBEACOPP. In this joint group, escalation to escBEACOPP + INRT resulted in improved 5-year PFS of 90.6% compared to 77.4% for standard three cycles (early favorable) or four cycles (early unfavorable) of ABVD + INRT (Fig. 11.5) [53].

In conclusion, interim PET-guided treatment results in improved tumor control in patients with positive findings by escalating chemotherapy on one hand, and it gives the possibility to relatively safely omit radiotherapy where needed in patients with a complete response on ABVD chemotherapy on the other hand.

11.8 Recommendations and Future Directions

In most parts of the world, CMT strategies including 2–3 cycles of ABVD followed by 20–30 Gy IFRT will remain standard treatment for patients with early favorable HL. Incorporation of an interim PET-guided approach with escalation to escBEACOPP in case of positive findings might further improve the already excellent treatment results. In patients at increased risk of RT-related toxicity because of age, sex, and disease localization, PET-guided treatment might aid the selection of patients in whom radiotherapy can be relatively safely omitted. Although, in such cases, omission of radiotherapy will result in a decrease of local tumor control of about 7–12%, outcomes with chemotherapy only are still excellent. Therefore, balancing the risk of RT-related toxicity to the possible decrease in local tumor control is the main challenge when planning treatment upfront. When balancing this risk, it is important to realize that data on toxicity of radiotherapy are mainly based on past radiotherapy techniques, fields, and doses, and all have been massively improved last decades. It is therefore of outmost importance to collect long-term follow-up outcomes of current treatment modalities.

With this approach, PFS rates exceeding 90% and OS rates exceeding 95% can be achieved. At present, the goal in early favorable HL is to maintain the excellent efficacy while further reducing acute and late toxicity. Incorporation or replacing current chemotherapy regimens by successful new drugs in HL like brentuximab vedotin or checkpoint inhibitors might be a further improvement and a possible route to chemotherapy free treatment in HL. However, it might be difficult to improve on current excellent treatment results with only short courses of limited chemotherapy or radiotherapy. Other opportunities to improve outcome of early favorable HL are the introduction of proton beam radiotherapy, better selection of patients for certain treatments based on biomarkers, or better methods for detection of minimal residual disease (MRD) in HL. These efforts are currently being made and are further discussed in Chap. 13.

References

1. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M (1971) Report of the committee on Hodgkin's disease staging classification. Cancer Res 31:1860–1861
2. Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC et al (1989) Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 7:1630–1636
3. Juweid ME, Stroobants S, Hoekstra OS, Mottaghy FM, Dietlein M, Guermazi A et al (2007) Use of positron emission tomography for response assessment of lymphoma: consensus of the imaging Subcommittee of International Harmonization Project in lymphoma. J Clin Oncol 25:571–578
4. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ et al (2007) Revised response criteria for malignant lymphoma. J Clin Oncol 25:579–586
5. El-Galaly TC, d'Amore F, Mylam KJ, de Nully Brown P, Bøgsted M, Bukh A et al (2012) Routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography-staged treatment naïve patients with Hodgkin lymphoma. J Clin Oncol 30:4508–4514
6. Specht L, Nissen NI (1988) Hodgkin's disease stages I and II with infradiaphragmatic presentation: a rare and prognostically unfavourable combination. Eur J Haematol 40:396–402
7. Sasse S, Goergen H, Plütschow A, Böll B, Eichenauer DA, Fuchs M et al (2018) Outcome of patients with early-stage infradiaphragmatic Hodgkin lymphoma: a comprehensive analysis from the German Hodgkin study group. J Clin Oncol 36:2603–2611
8. Specht L (1996) Prognostic factors in Hodgkin's disease. Semin Radiat Oncol 6:146–161
9. Tubiana M, Henry-Amar M, van der Werf-Messing B, Henry J, Abbatucci J, Burgers M et al (1985) A multivariate analysis of prognostic factors in early stage Hodgkin's disease. Int J Radiat Oncol Biol Phys 11:23–30
10. Ferme C, Eghbali H, Meerwaldt JH, Rieux C, Bosq J, Berger F et al (2007) Chemotherapy plus involved-field radiation in early stage Hodgkin's disease. N Engl J Med 357:1916–1927
11. Engert A, Franklin J, Eich HT, Brillant C, Sehlen S, Cartoni C et al (2007) 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 25:3495–3502
12. Cottereau AS, Versari A, Loft A, Casasnovas O, Bellei M, Ricci R et al (2018) Prognostic value of baseline metabolic tumor volume in early-stage Hodgkin lymphoma in the standard arm of the H10 trial. Blood 131:1456–1463

13. Hoppe RT, Coleman CN, Cox RS, Rosenberg SA, Kaplan HS (1982) The management of stage I–II Hodgkin's disease with irradiation alone or combined modality therapy: the Stanford experience. Blood 59:455–465
14. Gospodarowicz MK, Sutcliffe SB, Clark RM, Dembo AJ, Fitzpatrick PJ, Munro AJ et al (1992) Analysis of supradiaphragmatic clinical stage I and II Hodgkin's disease treated with radiation alone. Int J Radiat Oncol Biol Phys 22:859–865
15. Raemaekers J, Kluin-Nelemans H, Teodorovic I, Meerwaldt C, Noordijk E, Thomas J et al (2002) The achievements of the EORTC lymphoma group. European Organisation for Research and Treatment of Cancer. Eur J Cancer 38(Suppl 4):S107–S113
16. Tubiana M, Henry-Amar M, Carde P, Burgers JM, Hayat M, Van der Schueren E et al (1989) Toward comprehensive management tailored to prognostic factors of patients with clinical stages I and II in Hodgkin's disease. The EORTC lymphoma group controlled clinical trials: 1964–1987. Blood 73:47–56
17. Tubiana M, Henry-Amar M, Hayat M, Breur K, van der Werf-Messing B, Burgers M (1979) Long-term results of the E.O.R.T.C. randomized study of irradiation and vinblastine in clinical stages I and II of Hodgkin's disease. Eur J Cancer 15:645–657
18. Tubiana M, Hayat M, Henry-Amar M, Breur K, van der Werf MB, Burgers M (1981) Five-year results of the E.O.R.T.C. randomized study of splenectomy and spleen irradiation in clinical stages I and II of Hodgkin's disease. Eur J Cancer 17:355–363
19. Carde P, Burgers JM, Henry-Amar M, Hayat M, Sizoo W, Van der Schueren E et al (1988) Clinical stages I and II Hodgkin's disease: a specifically tailored therapy according to prognostic factors. J Clin Oncol 6:239–252
20. Carde P, Hagenbeek A, Hayat M, Monconduit M, Thomas J, Burgers MJ et al (1993) Clinical staging versus laparotomy and combined modality with MOPP versus ABVD in early stage Hodgkin's disease: the H6 twin randomized trials from the European Organization for Research and Treatment of Cancer lymphoma cooperative group. J Clin Oncol 11:2258–2272
21. Noordijk EM, Carde P, Dupouy N, Hagenbeek A, Krol AD, Kluin-Nelemans JC et al (2006) Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. J Clin Oncol 24:3128–3135
22. Duhmke E, Franklin J, Pfreundschuh M, Sehlen S, Willich N, Ruhl U et al (2001) Low-dose radiation is sufficient for the noninvolved extended-field treatment in favorable early stage Hodgkin's disease: long-term results of a randomized trial of radiotherapy alone. J Clin Oncol 19:2905–2914
23. Specht L, Gray RG, Clarke MJ, Peto R (1998) International Hodgkin's disease collaborative group. Influence of more extensive radiotherapy and adjuvant chemotherapy on long-term outcome of early stage Hodgkin's disease: a meta-analysis of 23 randomized trials involving 3,888 patients. J Clin Oncol 16:830–843
24. Horwich A, Specht L, Ashley S (1997) Survival analysis of patients with clinical stages I or II Hodgkin's disease who have relapsed after initial treatment with radiotherapy alone. Eur J Cancer 33:848–853
25. Aleman BM, van den Belt-Dusebout AW, Klokman WJ, Van't Veer MB, Bartelink H, van Leeuwen FE (2003) Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 21:3431–3439
26. Ng AK, Bernardo MP, Weller E, Backstrand KH, Silver B, Marcus KC et al (2002) Long-term survival and competing causes of death in patients with early stage Hodgkin's disease treated at age 50 or younger. J Clin Oncol 20:2101–2108
27. Favier O, Heutte N, Stamatoullas-Bastard A, Carde P, Van't Veer MB, Aleman BM et al (2009) Survival after HL: causes of death and excess mortality in patients treated in 8 consecutive trials. Cancer 115: 1680–1691
28. Canellos GP, Anderson JR, Propert KJ, Nissen N, Cooper MR, Henderson ES et al (1992) Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 327:1478–1484
29. Press OW, LeBlanc M, Lichter AS, Grogan TM, Unger JM, Wasserman TH et al (2001) Phase III randomized intergroup trial of subtotal lymphoid irradiation versus doxorubicin, vinblastine, and subtotal lymphoid irradiation for stage IA to IIA Hodgkin's disease. J Clin Oncol 19:4238–4244
30. Horning SJ, Hoppe RT, Mason J, Brown BW, Hancock SL, Baer D et al (1997) Stanford-Kaiser Permanente G1 study for clinical stage I to IIA Hodgkin's disease: subtotal lymphoid irradiation versus vinblastine, methotrexate, and bleomycin chemotherapy and regional irradiation. J Clin Oncol 15:1736–1744
31. Zittoun R, Audebert A, Hoerni B, Bernadou A, Krulik M, Rojouan J et al (1985) Extended versus involved fields irradiation combined with MOPP chemotherapy in early clinical stages of Hodgkin's disease. J Clin Oncol 3:207–214
32. Noordijk EM, Carde P, Dupouy N, Hagenbeek A, Krol AD, Kluin-Nelemans JC et al (2006) Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. J Clin Oncol 24:3128–3135
33. Engert A, Plütschow A, Eich HT, Lohri A, Dörken B, Borchmann P et al (2010) Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med 363:640–652
34. Behringer K, Görgen H, Hitz F, Zijlstra JM, Greil R, Markova J et al (2015) Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin's lymphoma

(GHSG HD13): an open-label, randomised, non-inferiority trial. Lancet 11;385:1418–1427
35. Advani RH, Hoppe RT, Baer D, Mason J, Warnke R, Allen J et al (2013) Efficacy of abbreviated Stanford V chemotherapy and involved-field radiotherapy in early-stage Hodgkin lymphoma: mature results of the G4 trial. Ann Oncol 24:1044–1048
36. Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P (2004) ABVD plus subtotal nodal versus involved-field radiotherapy in early stage Hodgkin's disease: long-term results. J Clin Oncol 22:2835–2841
37. Thomas J, Fermé C, Noordijk EM, Morschhauser F, Girinsky T, Gaillard I et al (2018) Comparison of 36 Gy, 20 Gy, or no radiation therapy after 6 cycles of EBVP chemotherapy and complete remission in early-stage Hodgkin lymphoma without risk factors: results of the EORT-GELA H9-F intergroup randomized trial. Int J Radiat Oncol Biol Phys 100:1133–1145
38. Engert A, Schiller P, Josting A, Herrmann R, Koch P, Sieber M et al (2003) Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's lymphoma study group. J Clin Oncol 21:3601–3608
39. Girinsky T, van der Maazen R, Specht L, Aleman B, Poortmans P, Lievens Y et al (2006) Involved-node radiotherapy (INRT) in patients with early HL: concepts and guidelines. Radiother Oncol 79:270–277
40. Shahidi M, Kamangari N, Ashley S, Cunningham D, Horwich A (2006) Site of relapse after chemotherapy alone for stage I and II Hodgkin's disease. Radiother Oncol 78:1–5
41. Girinsky T, Specht L, Ghalibafian M, Edeline V, Bonniaud G, Van Der Maazen R et al (2008) The conundrum of HL nodes: to be or not to be included in the involved node radiation fields. The EORTC-GELA lymphoma group guidelines. Radiother Oncol 88:202–210
42. Campbell BA, Voss N, Pickles T, Morris J, Gascoyne RD, Savage KJ et al (2008) Involved-nodal radiation therapy as a component of combination therapy for limited-stage Hodgkin's lymphoma: a question of field size. J Clin Oncol 26:5170–5174
43. Longo DL, Glatstein E, Duffey PL, Young RC, Hubbard SM, Urba WJ et al (1991) Radiation therapy versus combination chemotherapy in the treatment of early stage Hodgkin's disease: seven-year results of a prospective randomized trial. J Clin Oncol 9:906–917
44. Biti GP, Cimino G, Cartoni C, Magrini SM, Anselmo AP, Enrici RM et al (1992) Extended-field radiotherapy is superior to MOPP chemotherapy for the treatment of pathologic stage I–IIA Hodgkin's disease: eight-year update of an Italian prospective randomized study. J Clin Oncol 10:378–382
45. Meyer RM, Gospodarowicz MK, Connors JM, Pearcey RG, Wells WA, Winter JN et al (2012) ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med 366:399–408
46. Straus DJ, Portlock CS, Qin J, Myers J, Zelenetz AD, Moskowitz C et al (2004) Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. Blood 104:3483–3489
47. Gallamini A, Hutchings M, Rigacci L, Specht L, Merli F, Hansen M et al (2007) Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. J Clin Oncol 25:3746–3752
48. Hutchings M, Mikhaeel NG, Fields PA, Nunan T, Timothy AR (2005) Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in HL. Ann Oncol 16:1160–1168
49. Hutchings M, Loft A, Hansen M, Pedersen LM, Buhl T, Jurlander J et al (2006) FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in HL. Blood 107:52–59
50. Oki Y, Chuang H, Chasen B, Jessop A, Pan T, Fanale M et al (2014) The prognostic value of interim positron emission tomography scan in patients with classical Hodgkin lymphoma. Br J Haematol 165:112–116
51. Gallamini A, Barrington SF, Biggi A, Chauvie S, Kostakoglu L, Gregianin M (2014) The predictive role of interim positron emission tomography for Hodgkin lymphoma treatment outcome is confirmed using the interpretation criteria of the Deauville five-point scale. Haematologica 99:1107–1113
52. Radford J, Illidge T, Counsell N, Hancock B, Pettengell R, Johnson P (2015) Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med 372:1598–1607
53. André MPE, Girinsky T, Federico M, Reman O, Fortpied C, Gotti M (2017) 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 35:1786–1794
54. Fuchs M, Goergen H, Kobe C, Kuhnert G, Lohri A, Greil R et al (2019) Positron emission tomography-guided treatment in early-stage favorable Hodgkin lymphoma: final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. J Clin Oncol 37:2835–2845