Hematologic Malignancies
Series Editor: Martin Dreyling

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Anas Younes *Editors*

Hodgkin Lymphoma

A Comprehensive Overview

Third Edition

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ISSN 2197-9766 ISSN 2197-9774 (electronic)
Hematologic Malignancies
ISBN 978-3-030-32481-0 ISBN 978-3-030-32482-7 (eBook)
https://doi.org/10.1007/978-3-030-32482-7

Preface

Hodgkin lymphoma has become one of the best curable malignancies in both adult and pediatric patients. More than 80% of all patients can be cured with risk-adapted treatment including chemotherapy and radiotherapy. This progress is largely due to the development of multi-agent chemotherapy and the improvements in radiotherapy.

Due to the high cure rate and the young age of most patients affected, Hodgkin lymphoma has also become a model for studying long-term toxicity of radiotherapy and chemotherapy that may impact quality of life and/or survival. Future treatment should continue to balance the need for improving the cure rate while reducing treatment-related side effects. In addition, there are a number of relevant physical and psychosocial issues including infertility and fatigue that need to be further exploited.

Monoclonal antibodies against this antigen were successfully used for diagnostic immunophenotyping and exploited therapeutically. This strategy has come full circle with the advent of the anti-CD30 antibody drug conjugate Brentuximab Vedotin. This drug has shown remarkable responses in relapsed and refractory classical Hodgkin lymphoma and is also being used in combination with chemotherapy.

The development of targeted treatment for patients with Hodgkin lymphoma is rapidly evolving. The recent approval of checkpoint inhibitors has added an additional treatment option for patients with relapsed cHL, opening the door for new developments including new combinations of chemotherapy or radiotherapy being evaluated in first line.

This book should give you a comprehensive overview of the most relevant biology, diagnostic and clinical aspects of Hodgkin lymphoma. We would like to express our sincere gratitude to all those who have contributed to this project.

Cologne, Germany — Andreas Engert
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Part I

Epidemiology and Pathogenesis

Epidemiology of Hodgkin Lymphoma

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_1

1.1 Introduction

The treatment of Hodgkin lymphoma has become one of the great successes in modern oncology with cure rates exceeding 90% for patients with early-stage disease and approaching the same level for patients with advanced disease [1, 2] (see also elsewhere in this book).

Although Hodgkin lymphoma was among the first haematological malignancies described in the literature in 1832 [3], the advances made in the understanding of the natural history of Hodgkin lymphoma and its causes are less impressive.

It might be ventured that the impressive treatment results leave this to be of little consequence; however, efforts in this regard are continuously worthwhile. Accordingly, the good prognosis for Hodgkin lymphoma is entirely dependent on modern care which is inaccessible in many parts of the world, where the disease still carries considerable mortality. Moreover, as highlighted by a growing literature, the high cure rates have been achieved at the cost of a high frequency of late and often severe adverse treatment effects among Hodgkin lymphoma survivors [4]. Consequently, if better understanding of Hodgkin lymphoma aetiology could help identify means to its prevention, e.g. through vaccination [5], much could be gained.

The present chapter gives an overview of the epidemiology of Hodgkin lymphoma and summarizes current understanding of its risk factors. For a more detailed review, please be referred to [6].

1.2 Definition and Histological Classification (WHO)

Hodgkin lymphoma is a malignancy which in the vast majority of cases is derived from germinal centre B-lymphocytes, with odd cases (possibly) being of T-cell origin [7].

The current WHO classification recognizes two main variants of Hodgkin lymphoma, specifically classic Hodgkin lymphoma and nodular lymphocytic predominant Hodgkin lymphoma [8, 9].

The two variants of Hodgkin lymphoma display different clinical, morphological, immunological and molecular characteristics, allowing them to be distinguished with reasonable precision [10, 11]. Because the two variants are also believed to have different natural histories, they are conventionally considered separately in epidemiological investigations whenever possible. This is also the case in the present chapter, which for all practical purposes will focus on classic Hodgkin lymphoma.

Classic Hodgkin lymphomas make up around 95% of all cases and are further divided into four subtypes referred to as nodular sclerosis (70% of all classic Hodgkin lymphomas), mixed cellularity (20–25% of classic Hodgkin lymphomas), lymphocyte-rich, and lymphocyte-depleted classic Hodgkin lymphoma, respectively [12, 13].

Because the distinction between the classic Hodgkin lymphoma subtypes relies entirely on a subjective interpretation of the histological presentation of the tumour lesion, it is subject to

both inter- and intra-observer variation [10, 11]. While classic Hodgkin lymphoma subtype may previously have had clinical relevance, this is no longer the case with modern imaging tools aiding diagnosis [14].

Importantly, because of the distribution of the Hodgkin lymphoma variants and classic Hodgkin lymphoma subtypes, investigations reporting associations of one kind or another for Hodgkin lymphoma overall will still be epidemiologically informative.

1.3 Hodgkin Lymphoma Occurrence

1.3.1 Overall Incidence

The International Agency for Research on Cancer estimates that world-wide close to 80,000 individuals (33,431 women and 46,559 men) were diagnosed with Hodgkin lymphoma in 2018 and that slightly more than 26,000 individuals (10,397 women and 15,770 men) succumbed to the disease the same year [15].

This places Hodgkin lymphoma as the 27th commonest cancer diagnosed and the 27th commonest cancer-specific cause of death [15].

Both Hodgkin lymphoma incidence and mortality display considerable geographic variation. Overall, Hodgkin lymphoma incidence is higher in Western world industrialized countries than in Asian and developing countries (Fig. 1.1).

In the USA, for instance, age-standardized (world population) incidence rates were of the order 2.8 and 2.2 per 100,000 per year in men and women, respectively, whereas the corresponding figures for Indian men and women were 0.79 and 0.58 per 100,000 per year, respectively [15].

Hodgkin lymphoma mortality, conversely, is higher in some developing countries than in industrialized countries (Fig. 1.2). Accordingly, age-standardized mortality rates (world) were 0.25 and 0.14 per 100,000 per year for US men and women, respectively, and 0.53 and 0.35 per 100,000 per year for Indian men and women, respectively [15].

As already alluded to the discordant incidence and mortality patterns reflect that modern therapy can cure most Hodgkin lymphoma patients and that access to such therapy is dependent on the level of socio-economic development [16]. Of note, similar socio-economically dependent variation in Hodgkin lymphoma mortality can also be observed in affluent countries [17] and underscores the continued need for epidemiological investigations to promote preventive interventions.

1.3.2 Age-Specific Incidence Patterns Vary Geographically

1.3.2.1 Historical Patterns

Hodgkin lymphoma occurs at all ages, but among populations, age-specific incidence distributions tend to vary with their ethnic and socio-economic make-up. This variation was summarized into four prototypical incidence patterns (numbered I through IV) in studies in the 1950s, 1960s and 1970s [18–20]. Because they have permeated Hodgkin lymphoma epidemiological thinking for decades, the four patterns are briefly described for the sake of completeness.

Pattern I was observed in developing countries and comprised an accumulation of Hodgkin lymphoma cases—predominantly mixed cellularity—among young boys, low incidence throughout the second and third decades of life and increasing incidence with age among older adults.

Pattern III was seen in affluent Western countries and demonstrated low incidence in childhood, a marked accumulation of cases—typically nodular sclerosis—in adolescents and younger adults (AYA), a lower incidence in middle-aged adults and an increasing incidence with age among older adults.

Pattern II was observed in rural areas of affluent countries and perceived as an intermediate between patterns I and III.

Finally, a pattern IV prevailed in Asian countries and featured low incidence rates throughout the first four decades of life followed by increasing incidence with age among older adults.

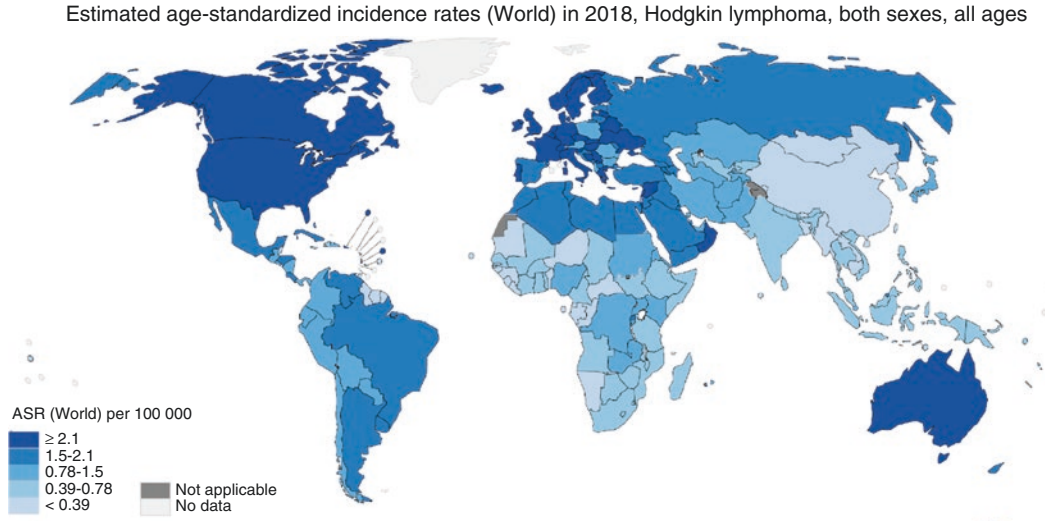

Fig. 1.1 Estimated age-standardized incidence rates of Hodgkin lymphoma for both sexes combined (Data from [15])

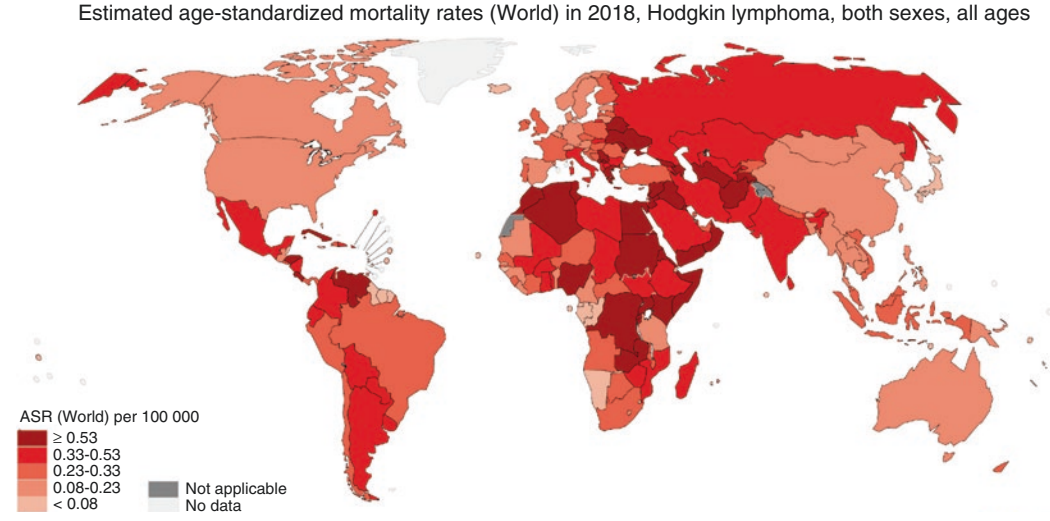

Fig. 1.2 Estimated age-standardized mortality rates of Hodgkin lymphoma for both sexes combined (Data from [15])

1.3.2.2 Modern Age-Specific Incidence Patterns

The main features of the prototypical Hodgkin lymphoma incidence patterns, i.e. incidence peaks in boys, AYAs and older adults, are still recognizable.

In Chennai, India, for instance, the age-specific Hodgkin lymphoma incidence pattern for the period 1993–2012 displayed a type I-like pattern with a peak in boys less than 10 years of age, no incidence peak among adolescents and younger adults and increasing incidence with age among older adults (Fig. 1.3), even if a transition towards a type II-like pattern can be observed in the more recent of these data [15].

Of note, an incidence peak among boys can also be demonstrated within European populations when more granular data are available for analysis [21, 22].

In the USA, conversely, Hodgkin lymphoma incidence follows a type III-like pattern with incidence peaks among AYAs and older adults, respectively (Figs. 1.3 and 1.4).

Even within the US age-specific incidence patterns adhere to the correlation with socio-economic level. In California, a survey of cases diagnosed 1988–1992 showed higher Hodgkin lymphoma incidence among adolescents and younger adults in the highest compared with the lowest tertile of socio-economic status (Fig. 1.4) [23].

1.3.2.3 Age-Specific Incidence Patterns for Hodgkin Lymphoma Subtypes

The bimodal age distribution of Hodgkin lymphoma incidence overall in affluent populations is largely mirrored by the corresponding distribution of the classic Hodgkin lymphoma variants (Fig. 1.5).

Both nodular sclerosis and mixed cellularity classic Hodgkin lymphoma display bimodal age distributions with incidence peaks in AYA and older adult age groups, respectively (Fig. 1.5). Mixed cellularity classic Hodgkin lymphoma may be the most common subtype among the youngest children [21], but otherwise nodular sclerosis classic Hodgkin lymphoma is the most common subtype in all age groups.

While the age-specific incidence patterns for nodular sclerosis and mixed cellularity Hodgkin lymphoma overall are similar for the two sexes and Hodgkin lymphoma incidence overall is higher in men than in women, the incidence of classic Hodgkin lymphoma—in effect the nodular sclerosis subtype—may be higher in women than in men in adolescence and early adulthood (Fig. 1.3).

For lymphocyte-depleted and lymphocyte-rich classic Hodgkin lymphoma, incidence rates generally increase with age (Fig. 1.5).

Although it correlates with the level of socio-economic development, the geographical variation in Hodgkin lymphoma incidence likely also reflects an association with ethnicity (Fig. 1.6). Thus, in a Californian survey, variation in Hodgkin lymphoma incidence rates between ethnic/racial groups was apparent even within strata of socio-economic status [23].

1.3.3 Incidence Trends

Changes to Hodgkin lymphoma classification systems have not been substantial in principle allowing analyses of incidence over longer time periods. However, considerable misclassification between Hodgkin and non-Hodgkin lymphomas in the older age groups (see [10, 11, 24] and references therein) resulted in inflated Hodgkin lymphoma incidence rates in these age groups in earlier studies. Improvement of diagnostic precision may, therefore, contribute to the decreasing Hodgkin lymphoma incidence rates that have been reported in older age groups (e.g. [24–26]).

The misclassification vis-à-vis non-Hodgkin lymphoma has been less for Hodgkin lymphoma among younger patients, rendering incidence trend analyses more meaningful. The correlation between age-specific incidence patterns and level of socio-economic development in the underlying population strongly suggests that Hodgkin lymphoma occurrence (and risk) is influenced by environmental factors. More specifically, it indicates that Hodgkin lymphoma incidence in childhood and in adolescence and early adulthood is determined by correlates of socio-economic status or, alternatively, Westernized living.

Therefore, it is perhaps of little surprise that increasing incidence of Hodgkin lymphoma has been described among adolescents and younger adults in conjunction with continued improvements in living standards in both industrialized and developing countries (e.g. [25–29]). Interestingly, the rate of increase appears to have

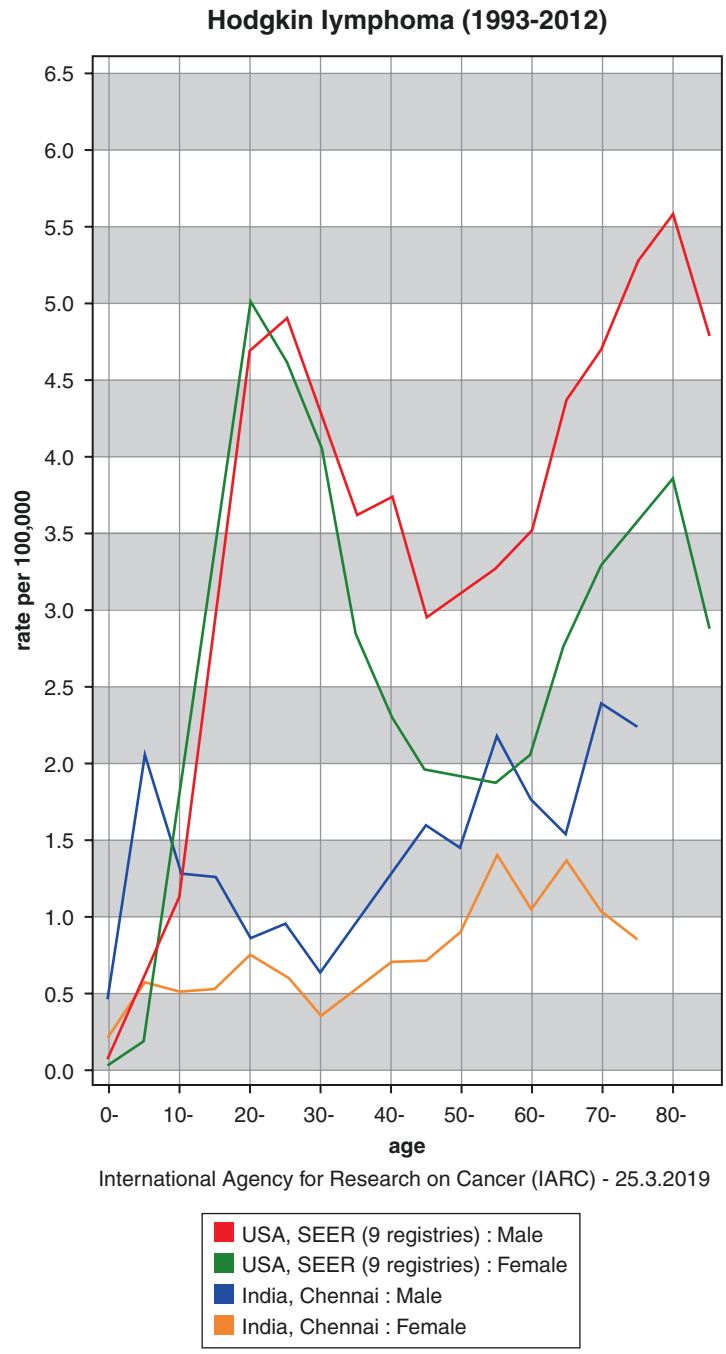

Fig. 1.3 Age-specific incidence rates for Hodgkin lymphoma in Chennai, India, and in the USA in the period 1993–2012 (Data from Bray F, Colombet M, Mery L, Piñeros M, Znaor A, Zanetti R and Ferlay J, editors (2017) Cancer Incidence in Five Continents, Vol. XI (electronic version) Lyon, IARC. http://ci5.iarc.fr last accessed on [25 March 2019])

been more pronounced among AYA women than among AYA men.

Because diagnostic misclassification also extends to subtypes of classic Hodgkin lymphoma [10, 11] and because the increasing use of non-excisional biopsies for lymphoma diagnosis limits the tumour material available for diagnostic purposes [30], changes in classic Hodgkin lymphoma subtype-specific trends are also difficult to interpret.

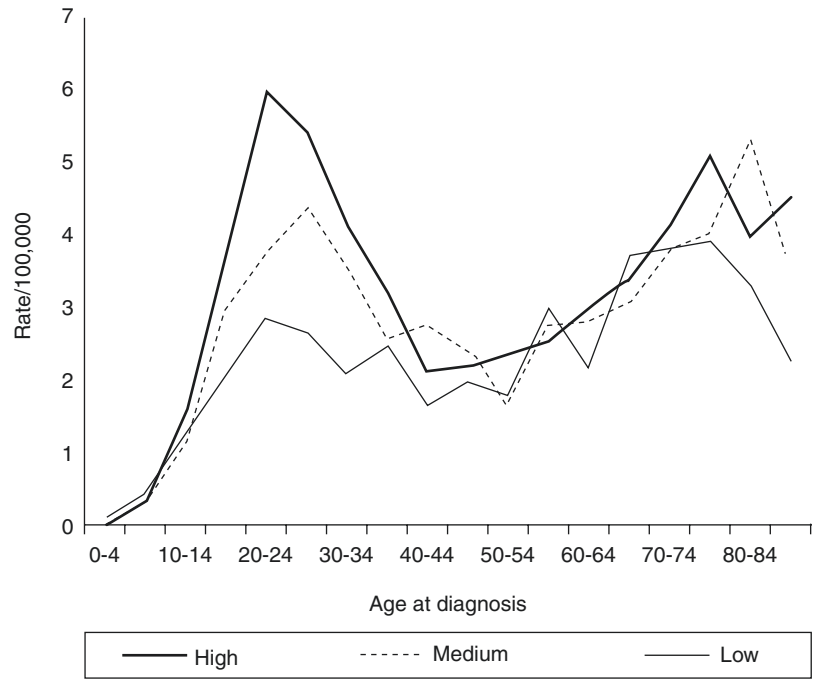

Fig. 1.4 Age-specific incidence rates of Hodgkin lymphoma by tertile of neighbourhood socio-economic status, California, 1988–1992 (Figure reproduced from [23])

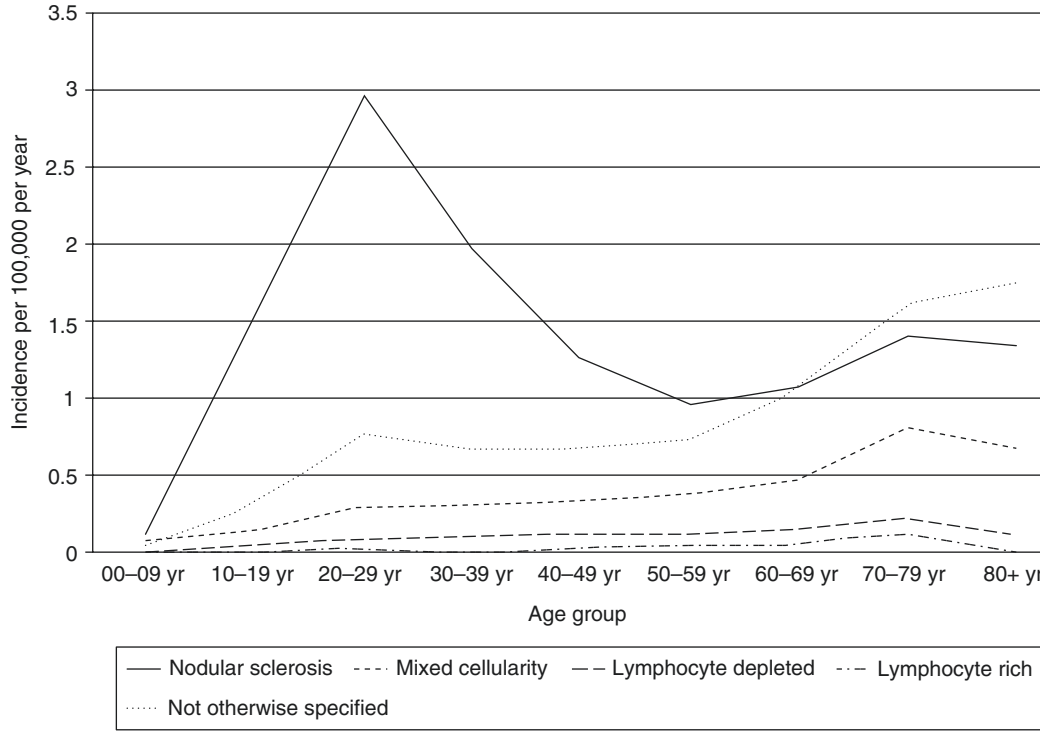

Fig. 1.5 Age-specific incidence rates of classic Hodgkin lymphoma in both sexes combined by histological subtype in the USA (2000–2011) (Data from US SEER 18. This Figure was reproduced from [6])

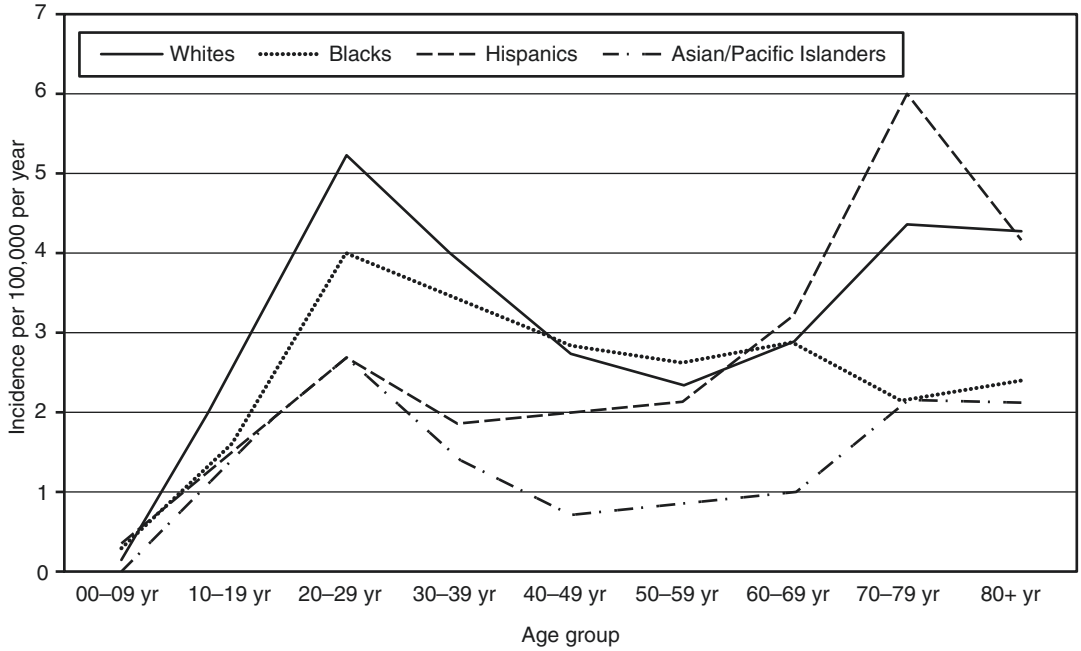

Fig. 1.6 Age-specific incidence rates of classic Hodgkin lymphoma overall in both sexes combined by race/ethnicity in the USA (2008–2012) (Data from US SEER 18. Figure reproduced from [6])

1.3.4 Classifications for Epidemiological Studies: Multi-disease Models

Efforts to unravel causes of Hodgkin lymphoma have been complicated by the strong suspicion that several epidemiologically and etiologically distinct Hodgkin lymphoma variants exist and because efforts to define these have proven exceedingly difficult.

1.3.5 Classifications by Age at Diagnosis, Histology and Tumour Epstein-Barr Virus Status

Intrigued by the bimodal age distribution and by corresponding epidemiological and clinical variation between cases within the age-specific incidence peaks, MacMahon in 1966 [19] proposed that three etiologically heterogeneous Hodgkin lymphoma types existed and that age at diagnosis, specifically 0–14 years, 15–34 years and 50+ years, could be used as a proxy to distinguish between them.

MacMahon, moreover, suggested that Hodgkin lymphoma in young adults had an infectious aetiology [19].

As information on Hodgkin lymphoma subtypes, classified using modern criteria, became available for larger patient series, the composition of cases within the incidence peaks (Fig. 1.6) led to the proposal that nodular sclerosis and mixed cellularity Hodgkin lymphoma each captured one of the supposedly etiologically distinct variants.

In 1985, Poppema and colleagues were the first to report the presence of Epstein-Barr virus genome products in the malignant Hodgkin/Reed-Sternberg cells in a patient with Hodgkin lymphoma [31]. Nearly 35 years later, we now know that some 30% of Hodgkin lymphomas among adults in affluent Western populations and even more in African and Asian countries are positive for Epstein-Barr virus [32]. We also know that epidemiologically Epstein-Barr virus-positive and Epstein-Barr virus-negative Hodgkin lymphomas differ (reviewed in [33], and further discussed in Chap. 2). Consequently, tumour Epstein-Barr

virus status offers itself as a third way to group classic Hodgkin lymphoma into epidemiologically distinct entities.

1.3.6 Overlap Between Epidemiological Classifications of Hodgkin Lymphoma

Each of the three proposed means to stratify Hodgkin lymphoma into etiologically and epidemiologically specific entities has empirical merit, as will be discussed in the sections below. However, they are sufficiently incongruent to reflect the same phenomenon or subtype.

Age at diagnosis displays some overlap with both histology (Fig. 1.5) and tumour Epstein-Barr virus status (Fig. 1.7). However, there is less overlap between tumour Epstein-Barr virus status and histological subtype. While most mixed cellularity classic Hodgkin lymphomas are Epstein-Barr virus-positive and most nodular

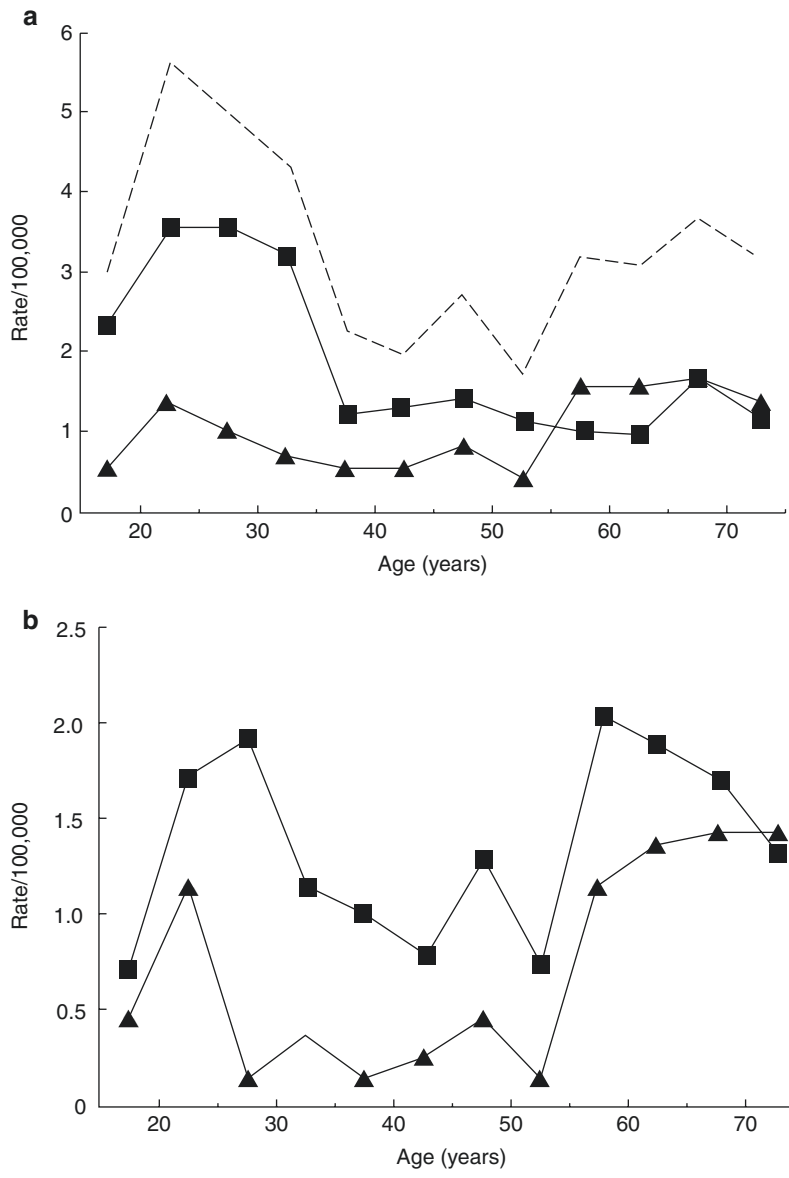

Fig. 1.7 Age-specific incidence rates for classic Hodgkin lymphoma overall (dotted line), Epstein-Barr virus-negative (squares) and virus-positive (triangles) classic Hodgkin lymphomas. Panel b: Age-specific Epstein-Barr virus-positive classic Hodgkin lymphoma among men (squares) and women (triangles) (Figure reproduced from [10])

sclerosis classic Hodgkin lymphomas are Epstein-Barr virus-negative, nodular sclerosis classic Hodgkin lymphomas still make up more than half of all Epstein-Barr virus-positive cases [33].

Because Epstein-Barr virus remains the most plausible causal candidate for Hodgkin lymphoma, its incongruence with the tumour histology classification is insufficient grounds for its dismissal. Therefore, age at diagnosis, tumour histology and tumour Epstein-Barr virus status likely represent different elements of Hodgkin lymphoma natural history, emphasizing its complexity.

1.4 Familial Accumulation of Hodgkin Lymphoma: Genetic Predisposition

It has been known for more than half a century that Hodgkin lymphomas cluster within families, the earliest investigation indicating an approximately threefold increased risk among Hodgkin lymphoma patients' first-degree relatives [34].

Subsequent studies with access to larger and even register-based data have largely confirmed this association. The hitherto largest investigation, a Nordic register-based investigation of 57,475 first-degree relatives of 13,922 classic Hodgkin lymphoma patients, yielded an overall standardized incidence ratio of 3.3 (95% confidence interval 2.8–3.9) for familial recurrence, corresponding to a 0.6% lifetime risk of classic Hodgkin lymphoma among patient relatives [35].

Owing to its magnitude, the Nordic study allowed for stratification of analyses by type of family relation and found a standardized incidence ratio of 2.1 (95% confidence interval 1.6–2.6) for the combined group of patient parents and offspring, but 6.0 (95% confidence interval 4.8–7.4) among patient siblings [35]. Even more extremely increased risks were observed for same-sex twins (standardized incidence ratio 57 (95% confidence interval 21–125)), consistent with the results of a previous American twin study [36].

Hodgkin lymphoma also clusters with other haematological malignancies, notably chronic lymphocytic leukaemia [37] and diffuse large B-cell lymphoma [38], with relative risks for these malignancies being slightly less increased—twofold—than for classic Hodgkin lymphoma.

1.4.1 Genetic Studies: Genome-Wide Association Studies

The accumulation of Hodgkin lymphomas among relatives must reflect shared environmental and constitutional risk factors. Both candidate gene investigations and genome-wide association studies confirm the suspicion that genetic predisposition is important to Hodgkin lymphoma risk.

The histological presentation of Hodgkin lymphoma is dominated by admixture of accessory and inflammatory cells indicating that immune function is important to the disease. Early research, therefore, focused on the association between tissue type, i.e. HLA, and Hodgkin lymphoma risk. Indeed, Hodgkin lymphoma was among the first diseases linked with markers of specific HLA types [39, 40].

Genotyping of more than 5000 patients with Hodgkin lymphoma has identified a total of 18 genetic loci associated with Hodgkin lymphoma risk. Based on these loci, Sud and colleagues point to three key biological processes underlying Hodgkin lymphoma susceptibility. These are (1) the germinal centre reaction (2p16.1, REL; 3q28, BCL6 and mir-28; 6p21, HLA; 6q23.3, MYB; 8q24.21, MYC; 11q23.1, POU2AF1; 16p11.2, MAPK3; 19p13.3, TCF3; 20q13.12, CD40), (2) T-cell differentiation and function (3p24.1, EOMES; 5q31,1, IL13; 6q22.33, PTPRK and THEMIS; 6q23.3, MYB; 6q23.3, AHI1; 10p14, GATA3; 16p13.1, SOCS1 and CLEC16A; 16p11.2, MAPK3 and CORO1A) and (3) constitutive NF-kB activation (2p16.1, REL; 3p24.1, AZI2; 6q23.3, TNFAIP3; 20q13.12, CD40) [41].

1.4.1.1 Hodgkin Lymphoma Subtype-Specific Associations in Genetic Analyses

In addition to shedding light on possible mechanisms underpinning Hodgkin lymphoma pathogenesis in general (discussed in the following

chapter (The Role of Viruses in the Genesis of Hodgkin Lymphoma)), the genetic investigations also add further credence to the notion of etiological heterogeneity between classic Hodgkin lymphoma subtypes.

Accordingly, as discussed in the following chapter, evidence is mounting that risk of Epstein-Barr virus-positive Hodgkin lymphoma is strongly associated with alleles in the HLA class I region (e.g. rs2734986, HLA-A; rs6904029, HCG9), whereas risk of Epstein-Barr virus-negative disease is more strongly associated with alleles within the HLA class II region (e.g. rs6903608, HLA-DRA) [42].

The variation in genetic associations underscores the importance of detailed phenotyping in genome-wide association as well as other types of studies of Hodgkin lymphoma. Thus, in the absence of information on either tumour histology or tumour Epstein-Barr virus status, neither the presence nor absence of associations can be fully interpreted.

This is illustrated by an extended analysis of the HLA region in the first GWAS to stratify cases by EBV status [42, 43]. This study revealed a single nucleotide polymorphism near the *HLA-DPB1* gene (rs6457715) which was associated with Epstein-Barr virus-positive (odds ratio 2.33 (95% confidence interval 1.83–2.97; P 10–12)), but not with Epstein-Barr virus-negative Hodgkin lymphoma risk (odds ratio 1.06 (95% confidence interval 0.92–1.21); $P_{hom} = 10^{-8}$), a difference that was present even within strata defined by classic Hodgkin lymphoma histology [43].

With that reservation, the association with class I alleles for Epstein-Barr virus-positive Hodgkin lymphomas or with mixed cellularity Hodgkin lymphoma suggests that cytotoxic T-cells' control of virally infected lymphocytes whether before or after malignant transformation is significant to the risk of the lymphoma.

Epstein-Barr virus-negative Hodgkin lymphoma's association with HLA class II alleles may reflect a similar role of immune control of an infectious agent in the pathogenesis of this Hodgkin lymphoma subtype. Alternatively, it may also be indicative of the involvement of CD4-positive T follicular helper cells in Hodgkin lymphoma pathogenesis [44].

For further discussion, please be referred to Chap. 2.

1.5 Risk Factors

1.5.1 Prevailing Hypotheses in Hodgkin Lymphoma Epidemiology

As already mentioned, for more than half a century, it has been assumed that Hodgkin lymphomas in children, AYA and older adults differ epidemiologically—possibly aetiologically—from one another [19]. Therefore, epidemiological investigations have conventionally considered risk factors for Hodgkin lymphoma for the three age groups separately, when practically possible.

Owing to the bimodal age distribution of Hodgkin lymphoma in affluent populations, the epidemiology of AYA Hodgkin lymphoma has been the most studied.

1.5.1.1 Childhood Socio-Economic Environment

The correlation between age-specific Hodgkin lymphoma incidence patterns and level of socio-economic development in the underlying population led to the formulation of the so-called late infection model for Hodgkin lymphoma [45, 46].

This model suggests that Hodgkin lymphoma among children, adolescents and younger adults is caused by an infectious agent and that lymphoma risk increases with increasing age at primary infection [45, 46].

Early studies supported this understanding of AYA Hodgkin lymphoma indirectly by reporting that correlates of childhood socio-economic affluence, which are thought to be associated with low childhood infectious disease pressure, such as length of maternal education, home ownership and being a member of a small sibship, were associated with increased risk of AYA Hodgkin lymphoma [47]. Moreover, within sib-

ships, Hodgkin lymphoma risk correlated inversely with number of older siblings, i.e. birth order [47].

Mack and colleagues recently (2015) reported the results of a register-based case-control study nested in a cohort of US army conscripts in the period 1950–1968. The study included 656 men diagnosed with Hodgkin lymphoma at ages 17–32 years and individually matched controls. In univariate analyses, they found increased Hodgkin lymphoma risk with small sibship size (odds ratio 1.4 (95% confidence interval 1.1–1.9) for 2–3 vs. >3 children), birth order (odds ratio 1.9 (95% confidence interval 1.4–2.6) for first vs. middle born) and short age gap to nearest sibling (odds ratio 2.1 (95% confidence interval 1.5–3.1) for more vs. less than 5 years) [48].

Information on histological subtype was available for a subset of the cases in the study of US conscripts, but analyses did not point to different associations for nodular sclerosis and mixed cellularity Hodgkin lymphoma. No information on tumour Epstein-Barr virus status was available for analyses [48].

In later investigations—that is, studies of patients diagnosed in more recent years—the association between traditional measures of childhood socio-economic affluence and AYA Hodgkin lymphoma risk in Western countries has been less compelling or even absent [49–54].

This change in the epidemiology of Hodgkin lymphoma in AYA may suggest that family or rather sibship structure no longer reflects the early life exposures associated with the disease [51]. Of note in this regard, in two case-control investigations, one American and one Scandinavian, kindergarten attendance was associated with reduced Hodgkin lymphoma risk in AYAs (odds ratio 0.64 (95% confidence interval 0.45–0.92) and odds ratio = 0.78 (95% confidence interval 0.56–1.09)) [49, 52].

Information on tumour Epstein-Barr virus status was available in both investigations, and while no differences in association with nursery school attendance were observed in the American investigation, it tended to be stronger for virus-negative Hodgkin lymphoma in the Scandinavian study [49, 52]. This contrast highlights that varying associations may simply result from the subtype composition of the studied Hodgkin lymphomas.

The evidence supporting the idea that childhood socio-economic environment influences Hodgkin lymphoma risk in childhood is also insubstantial. One Danish register cohort study found that risk of Hodgkin lymphoma before age 15 years increased with sibship size and birth order [55]. This association was reproduced in neither Swedish [56] nor American data [57]. However, a large North American case-control investigation reported findings similar to the Danish study: increasing sibship size was positively and increasing maternal education and household income inversely associated with Hodgkin lymphoma risk before age 15 years [58].

1.5.2 Anthropometry

Hodgkin lymphoma risk up to the age of early adulthood in some investigations (though not all) associates with increasing birth weight (e.g. [53, 54]). In a Californian register-based investigation, Hodgkin lymphoma risk in the age group 0–19 years was found to increase by 16% (95% confidence interval 1.03–1.30) per kilogram increase in birth weight [54]. While in this investigation the association appeared specific to nodular sclerosis classic Hodgkin lymphoma [54], it applied to both nodular sclerosis and mixed cellularity classic Hodgkin lymphoma in the other [53].

Like reports of association between stature late in childhood/in early adolescence and subsequent risk of Hodgkin lymphoma [59, 60], the association with birth weight may at least in part reflect Hodgkin lymphomas association with childhood socio-economic affluence.

A number of prospective investigations have pointed to an association between obesity and Hodgkin lymphoma risk [61–63]. For example, in the UK Million Women Study, body mass index correlated with Hodgkin lymphoma risk (hazard ratio 1.64 (95% confidence interval 1.21–2.21) per 10 kg per square meter increase)) [63]. If true, the association between obesity and Hodgkin lymphoma risk could reflect obesity-related inflammation references.

1.5.3 Medical History

1.5.3.1 Infections

The *late infection model* fostered much interest in the search for infectious agents that might cause Hodgkin lymphoma. Among suspected organisms, the human herpesvirus Epstein-Barr virus, first isolated from Burkitt lymphoma tissue [64] and soon after established as the cause of infectious mononucleosis [65], has long been the centre of attention.

Epstein-Barr Virus Infection: Infectious Mononucleosis

Epidemiological, serological and molecular-biological (i.e. the presence of Epstein-Barr virus genome products in the malignant cells) evidence link Epstein-Barr virus infection to Hodgkin lymphoma development. Here, only the epidemiological and serological evidence will be presented; for the presence and role of Epstein-Barr virus in the malignant cells, please see Chap. 2.

Infectious mononucleosis is rarely seen among children but is a common presentation of primary infection with the Epstein-Barr virus when it is delayed until adolescence [66]. Numerous investigations have assessed the association between infectious mononucleosis and Hodgkin lymphoma, and most have reported increased Hodgkin lymphoma risk in the wake of infectious mononucleosis (reviewed in [33]).

The largest of these was a Scandinavian register-based cohort study of more than 40,000 patients with infectious mononucleosis followed for the occurrence of Hodgkin lymphoma. Compared with the general population, the infectious mononucleosis patients were at a 2.55 (95% confidence interval 1.87–3.40)-fold increased Hodgkin lymphoma risk. The risk increase was particularly high shortly after the Epstein-Barr virus infection but remained increased for up to 20 years of follow-up [67]. Because infectious mononucleosis typically occurs in adolescence, the increased Hodgkin lymphoma risk tended to present in younger adults.

In a few investigations, information on Hodgkin lymphoma Epstein-Barr virus status has been available for analyses. One such was an extension of the Scandinavian cohort study mentioned above, according to which infectious mononucleosis was associated with an increased risk of Epstein-Barr virus-positive classic Hodgkin lymphomas (standardized incidence ratio 4.0 (95% confidence interval 3.4–4.5)) and not Epstein-Barr virus-negative classic Hodgkin lymphoma (standardized incidence ratio 1.5 (95% confidence interval 0.9–2.5)) [68].

While similar subtype-specific observations were also made in British and Scandinavian case-control investigations [49, 69], other studies have reported increased risks for both Epstein-Barr virus-positive and Epstein-Barr virus-negative Hodgkin lymphomas [70] or no associations at all [50, 52].

Epstein-Barr Virus Infection: Serological Evidence

Support for the association between Epstein-Barr virus infection and Hodgkin lymphoma risk also comes from serological investigations [71, 72].

In 1989 Nancy Mueller and colleagues in a prospective nested case-control study found that aberrant patterns of anti-Epstein-Barr virus antibodies were associated with overall Hodgkin lymphoma risk [73].

Three decades later this study was replicated only this time with information on tumour Epstein-Barr virus status. Comparing pre-diagnostic antibody patterns in 40 and 88 patients with Epstein-Barr virus-positive and Epstein-Barr virus-negative classic Hodgkin lymphomas with those in matched controls, Levin and colleagues showed that an inverted anti-EBNA1/anti-EBNA2 antibody level ratio (≤ 1) consistent with impaired control of Epstein-Barr virus infection was associated with a 4.7 (95% confidence interval 1.6–13.8)-fold increased risk of Epstein-Barr virus-positive Hodgkin lymphoma, whereas no association was observed for Epstein-Barr virus-negative Hodgkin lymphoma [74].

Epstein-Barr Virus Infection: Variation in Tumour Prevalence

Epstein-Barr virus can, as already mentioned, be demonstrated in the malignant cells in a proportion

of classic Hodgkin lymphomas [32]. Importantly, however, its presence is non-randomly distributed between cases and tends to reflect ethnic, socio-demographic, age, sex and disease-specific circumstances, adding further support to the suspicion of a causal relation.

This variation was most eloquently demonstrated by Glaser and colleagues in a pooled analysis of 1546 patients [75]. The analysis showed that irrespective of age at diagnosis, Epstein-Barr virus could more often be demonstrated in mixed cellularity than in nodular sclerosis Hodgkin lymphoma, in children from deprived rather than affluent settings and in male than in female patients, except among older adults. At the same time, compared with adolescents and younger adults, Hodgkin lymphomas in children and older adults were more often Epstein-Barr virus-positive [75].

The seminal paper by Glaser and colleagues once again underscores the importance of information on histological subtype and tumour Epstein-Barr virus status in epidemiological investigations.

A Four-Disease Model for Hodgkin Lymphoma

The age-dependent variation in prevalence of Epstein-Barr virus-positive Hodgkin lymphomas along with its association with infectious mononucleosis has given rise to the four-disease model, according to which Epstein-Barr virus-positive and Epstein-Barr virus-negative Hodgkin lymphomas are etiologically separate entities [76]. The model is further discussed in Chap. 2, but in summary suggests that Epstein-Barr virus-positive Hodgkin lymphoma develops in conjunction to primary infection with the virus (children and adolescents) or because of subsequent loss of control with the viral infection in its chronic phase owing to immune impairment for a variety of reasons, while no causes for Epstein-Barr virus-negative Hodgkin lymphoma are suggested.

Other Childhood Infections

The search for other specific childhood infections causally associated with classic Hodgkin lymphoma has so far been in vain (see also Chap. 2). Indeed, direct support for the decreased infectious disease load in early childhood among adolescent and younger adult Hodgkin lymphoma patients implied by the *late infection* hypothesis is scarce.

Even if in interview-based case-control studies self-reported history of infections such as measles, mumps and rubella have been associated with reduced risk of Hodgkin lymphoma in adolescence and early adulthood [50, 69, 77, 78], the validity of such recalled childhood health history may be questioned. Still, in Mack and colleagues' prospective study of army conscripts, history of mumps ascertained at the start of follow-up also was associated with reduced Hodgkin lymphoma risk [48].

Cozen and colleagues retrospectively assessed childhood exposures likely to produce oral exposure to microbes among 188 sets of twins discordant for Hodgkin lymphoma diagnosed at ages 13–50 years. Most interestingly, their study showed that Hodgkin lymphoma risk was lower for the twins whose behaviour mostly likely led to oral microbial exposure [79].

1.5.3.2 Primary and Secondary Immune Deficiencies

Similar to non-Hodgkin lymphomas, Hodgkin lymphomas also occur excessively among patients suffering from (certain) primary and secondary immune deficiencies (reviewed in [80]).

Risk of Hodgkin lymphoma is between 4- and 16-fold increase in cohort studies of HIV-infected people and between 2- and 7-fold increase in cohort studies of solid organ transplant recipients (reviewed in [80]).

Most Hodgkin lymphoma occurring in the setting of immune deficiency is Epstein-Barr virus-positive [80]. Correspondingly, in one cohort study of people with AIDS-related immune deficiency, risk was more increased for mixed cellularity (rate ratio 18.3 (95% confidence interval 15.9–20.9)) and lymphocyte-depleted (rate ratio 35.3 (95% confidence interval 24.7–48.8)) Hodgkin lymphoma subtypes than for nodular sclerosis Hodgkin lymphoma [81].

There is (some) evidence that Hodgkin lymphoma risk correlates inversely with degree of

immune suppression as measured by CD4-lymphocyte count among HIV-infected people, but the correlation is less strong than for non-Hodgkin lymphoma and, in contrast to the latter, risk does not correlate with measures of HIV load [82, 83].

These differences between Hodgkin and non-Hodgkin lymphoma may explain why the overall incidence of Hodgkin lymphoma has not decreased to the same extent as non-Hodgkin lymphoma following the introduction of highly active antiviral therapy (see [82] and references therein).

1.5.3.3 Autoimmune and Allergic Disorders

Autoimmune and Allergic/Atopic Diseases

Several studies have reported an increased risk of Hodgkin lymphoma among patients with autoimmune diseases (see reviews [80, 84]). A large Swedish investigation reported a twofold increased risk of Hodgkin lymphoma risk among 878,000 patients registered with any of 33 autoimmune conditions in the Swedish inpatient register [85].

Temporal variation in relative risk of Hodgkin lymphoma suggested that the increased risk was partially explained by reversed causality; specifically, that incipient (undiagnosed) Hodgkin lymphoma led to autoimmune disease diagnosis. Thus, the standardized incidence ratio (SIR) for Hodgkin lymphoma decreased with time since autoimmune disease diagnosis from 5.2 (95% confidence interval 4.2–6.3) in the first year of follow-up to 2.0 (95% confidence interval 1.7–2.4) in the period 1–4 years after autoimmune disease diagnosis and to 1.5 (1.2–1.7) at 5 or more years after autoimmune disease diagnosis [85].

Accordingly, when the first 5 years after autoimmune diagnosis was disregarded, statistically significantly increased risk of Hodgkin lymphoma was observed for patients with rheumatoid arthritis (SIR = 2.0 (95% confidence interval 2.1–3.7)), autoimmune haemolytic anaemia (SIR = 16.6 (95% confidence interval 3.1–49.2)), Behcet disease (SIR = 4.0 (95% confidence interval 1.3–9.3)) and systemic lupus erythematosus (SIR = 4.1 (95% confidence interval 1.5–9.0)). Elevated risk estimates, albeit not statistically significant, were still observed for various other autoimmune diseases [85].

The mechanisms underlying the association between Hodgkin lymphoma and autoimmune diseases have remained elusive. Interestingly, in another register-based study from Sweden, reduced risk of Hodgkin lymphoma was observed in families of patients with acute glomerular nephritis, ankylosing spondylitis and Graves disease and increased in family members of patients with pemphigus. In first-degree relatives of Hodgkin lymphoma patients, several autoimmune diseases occurred in excess (Behcet disease, dermatitis herpetiformis, multiple sclerosis, primary biliary cirrhosis and rheumatoid arthritis) or in deficit (celiac disease and psoriasis) pointing to some form of shared risk between the two disease groups [86], which to some extent could be genetic in nature [87].

Multiple sclerosis stands out from other autoimmune diseases in this regard. Thus, studies have shown that Hodgkin lymphoma in young adults and multiple sclerosis clusters mutually within individuals [88] and within families [86, 89]. Moreover, the two conditions have also been found to share genetic risk profiles to the extent that polygenic risk scores for either of the two diseases are associated with risk of the other [87]. Interestingly, these two disparate conditions both share the association with infectious mononucleosis, raising the possibility that the three conditions are somehow immunologically related.

Few studies have examined the association between allergic/atopic diseases and Hodgkin lymphoma risk ([90], review in [91]). Methodological issues aside, the results of the analyses are too heterogeneous to preclude conclusions other than that the current evidence does not support any association between the two. In agreement with this, Levin and colleagues found no evidence of an association between prediagnostic titres of IgE and Hodgkin lymphoma risk in a prospective serological investigation [92].

1.5.3.4 Medications

Regular use of aspirin has been suggested to be associated with reduced Hodgkin lymphoma risk in one American [93] and in two partly

overlapping Danish studies [94]. Combining the two sets of results in a meta-analysis, long-term use of aspirin was associated with an odds ratio of 0.62 (95% confidence interval 0.46–0.82) for Hodgkin lymphoma [94]. Aspirin's interference with inhibition of NF-κB which is constitutively active in the malignant Hodgkin/Reed-Sternberg cells and its binding to cyclooxygenase (COX)-1 and cyclooxygenase-2, which are overexpressed in Hodgkin lymphoma, both lend biological plausibility to the observed association [93, 94].

Of note, the same investigations also reported increased Hodgkin lymphoma risk among users of other nonsteroidal anti-inflammatory drugs such as selective Cox-2 inhibitors or acetaminophen. However, temporal variation in the risk increase suggested that reverse causality—confounding by indication—most likely accounted for the observed association [93, 94].

1.5.4 Environmental Exposures

1.5.4.1 Ultraviolet Light

Recent decades have witnessed considerable epidemiological interest in the possible association between vitamin D and cancer because of the vitamin's potential anticarcinogenic effects [95]. Because ultraviolet light radiation is critical to vitamin D production, studies have typically focused on this exposure, as is also the case for Hodgkin lymphoma investigations.

An association between ultraviolet radiation exposure and Hodgkin lymphoma risk is supported by two types of evidence. Firstly, according to ecological studies, Hodgkin lymphoma incidence rates and ambient levels of ambient ultraviolet radiation correlate inversely [96, 97].

Secondly, according to a pooled analysis of data from four case-control studies including a total of 1320 patients with Hodgkin lymphoma and 6381 controls, history of sunburn (odds ratio = 0.77 (95% confidence interval 0.63–0.95)) and sunlamp use (odds ratio = 0.81 (95% confidence interval 0.69–0.96)) and cumulative lifetime exposure to ultraviolet radiation were each associated with statistically significantly decreased risk of Hodgkin lymphoma [98]. The observed associations tended to be stronger for Epstein-Barr virus-positive than for Epstein-Barr virus-negative Hodgkin lymphomas [98].

Both the ecological and the analytical epidemiological data are compatible with ultraviolet radiation exposure in some way or other preventing Hodgkin lymphoma pathogenesis.

1.5.4.2 Tobacco

Considering tobacco's many effects on the human immune system, it is conceivable that it is also associated with Hodgkin lymphoma risk [99]. Support for this notion comes from two meta-analyses and a pooled analysis of several large datasets.

The meta-analyses both conclude that current smoking carries a statistically significant 30–40% increased risk of Hodgkin lymphoma [100, 101], whereas the pooled analyses suggest a statistically nonsignificant 16% increased risk [102].

Both meta-analyses also find evidence of dose-response associations between Hodgkin lymphoma risk and current cigarette smoking measured as number of cigarettes smoked, years smoked and pack-years [100, 101]. The pooled analysis, in contrast, found no evidence of a dose-response pattern in the association between Hodgkin lymphoma risk and cigarette smoking [102].

In stratified analyses, the association with current smoking was stronger for mixed cellularity than for nodular sclerosis Hodgkin lymphoma [100] and correspondingly also stronger for Epstein-Barr virus-positive than for Epstein-Barr virus-negative Hodgkin lymphoma [101, 102].

1.5.4.3 Alcohol

A reduced Hodgkin lymphoma risk with alcohol intake has been suggested by most investigations of the topic, even if observed associations do not always reach statistical significance and rarely display dose-response patterns [103–112].

In a recent meta-analysis of available cohort studies, ever drinking alcohol was associated with a statistically nonsignificant reduced Hodgkin lymphoma risk (relative risk = 0.74 (95% confidence interval 0.52–1.05)) [113].

Although results vary between studies, the reported inverse association has been reported for

all Hodgkin lymphoma subgroups, i.e. for both younger and older adult patients, for Epstein-Barr virus-positive and Epstein-Barr virus-negative Hodgkin lymphoma, as well as for nodular sclerosis and mixed cellularity Hodgkin lymphoma alike.

One caveat to the interpretation of the observed reduced Hodgkin lymphoma risk is that the lymphoma may be accompanied by alcohol intolerance [114]. Consequently, reduced alcohol intake could result from early Hodgkin lymphoma manifestations. An attempt to mitigate this problem was introduced in the UK Million Study in which an increased risk of Hodgkin lymphoma among never drinkers (hazard rate ratio = 1.70 (95% confidence interval 1.27–2.26)) compared with occasional drinkers (0.5–3 drinks weekly) was unaffected when the first 3 years of follow-up was disregarded [112]. Still, this study also showed no dose-response pattern between alcohol consumption and Hodgkin lymphoma risk.

1.6 Conclusion

Studies have demonstrated that Hodgkin lymphomas occurring at different ages have different epidemiologic profiles. This variation is commonly interpreted as evidence that Hodgkin lymphoma comprises two or more aetiologically heterogeneous conditions.

Age, histological presentation and tumour Epstein-Barr virus status have been suggested to identify unique classic Hodgkin lymphoma entities. Evidence is strong that Epstein-Barr virus-positive Hodgkin lymphomas are aetiologically different from their Epstein-Barr virus-negative counterparts. There is also good evidence that the risk of Epstein-Barr virus-positive Hodgkin lymphoma at different ages to a large extent is influenced by circumstances influencing age at primary infection and immunological response to or control of the infection, whether in its acute or chronic phases. Meanwhile, the causes of Epstein-Barr virus-negative Hodgkin lymphoma have remained elusive and call for continued research.

Both Epstein-Barr virus-positive and Epstein-Barr virus-negative Hodgkin lymphoma can have different histopathological presentations. From the perspective of the understanding of what drives Hodgkin lymphoma development, this represents a field of research that has only been little explored in Epstein-Barr virus status-specific contexts.

The favourable prognosis of Hodgkin lymphoma achievable with modern therapy is unlikely to foster clinical interest into the clinical significance of tumour Epstein-Barr virus status or other (potential) markers of baseline treatment needs. Accordingly, though it could further access to large dataset amenable for research, the motivation to determine epidemiologically relevant markers in clinical trials is modest.

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The Role of Viruses in the Genesis of Hodgkin Lymphoma

2

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Contents

Abbreviations

BARTs	BamHI fragment A rightward transcripts
BHRF1	BamHI-H rightward open reading frame 1
cHL	Classic Hodgkin lymphoma
DDR1	Discoidin domain receptor 1
EBER	EBV-encoded small RNAs
EBNA	EBV nuclear antigen
EBV	Epstein-Barr virus
HHV	Human herpesvirus
HL	Hodgkin lymphoma
HLA	Human leukocyte antigen
HPyV	Human polyomavirus
HRS	Hodgkin and Reed-Sternberg

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_2

IHC	Immunohistochemistry
LMP	Latent membrane protein
MCHL	Mixed cellularity Hodgkin lymphoma
MCPyV	Merkel cell polyomavirus
miRNAs	MicroRNAs
MV	Measles virus
NSHL	Nodular sclerosis Hodgkin lymphoma
ORF	Open reading frame
PyV	Polyomavirus
SNP	Single nucleotide polymorphism
TSPyV	Trichodysplasia spinulosa polyomavirus
TTMDV	Torque teno midi virus
TTMV	Torque teno mini virus
TTV	Torque teno virus

2.1 Introduction

Hodgkin lymphoma (HL) is a heterogeneous condition. Seminal papers published in 1957 and 1966 suggested that HL in younger and older adults had different etiologies and further suggested an infectious etiology for young adult HL [1, 2]. Subsequent epidemiological studies provide broad support for these hypotheses [3, 4]. Data linking young adult HL with a high standard of living in early childhood and lack of child-child contact suggest that delayed exposure to common childhood infections may be involved in the etiology of these cases [5, 6]. There is now compelling evidence that a proportion of cases of HL are associated with the Epstein-Barr virus (EBV). Paradoxically, older adult and childhood cases of HL are more likely to be EBV-associated than young adult cases [7–9]. In this article, we review studies on viral involvement in HL with a focus on classic HL (cHL), since nodular lymphocyte-predominant HL is considered a separate disease entity. The association with EBV will be discussed with an emphasis on findings that support a causal role for EBV in this malignancy. Studies investigating the direct involvement of other exogenous viruses will be summarized.

2.2 Hodgkin Lymphoma and Epstein-Barr Virus

EBV is a herpesvirus with a worldwide distribution [10–13]. Over 90% of healthy adults are infected by EBV, and, following primary infection, the virus establishes a persistent infection with a reservoir in memory B-cells [14]. Although EBV is an extremely efficient transforming agent, the virus is kept under tight control by cell-mediated immune responses, and both primary and persistent infections are usually asymptomatic [10, 15].

EBV infection can be lytic or latent. Lytic infection is associated with expression of a large number of viral genes, production of progeny virus, and death of the infected cell; in contrast, latent infection is associated with expression of a small number of EBV genes, persistent infection, and growth transformation [10]. In B-cells transformed by EBV in vitro, six EBV nuclear antigens (EBNA1, 2, 3A, 3B, 3C, and LP, also called EBNA1–6) and three latent membrane proteins (LMP1, LMP2A, and LMP2B) are expressed [10]. In addition, noncoding viral RNAs are transcribed in latently infected cells [16]. These include two small non-polyadenylated transcripts, the EBERs, and over 44 viral microRNAs (miRNAs) located within introns of the BARTs (BamHI fragment A rightward transcripts) or around the coding region of the BHRF1 (BamHI-H rightward open reading frame 1) gene [16–22]. Expression of the full set of latent genes is known as latency III [10, 13]. EBV gene expression in EBV-positive lymphomas occurring in the context of immunosuppression frequently follows this pattern, but more restricted patterns of EBV gene expression are observed in other malignancies, including cHL [10, 12, 13]. The EBNA3 family proteins are immunodominant, and the other latent antigens elicit only subdominant or weak cell-mediated immune responses [23, 24]. The pattern of gene expression in EBV-associated malignancies most probably depends on both the lineage and stage of differentiation of the infected tumor cells and the host EBV-specific immune response.

In EBV-associated cHL (also referred to as EBV-positive cHL), all of the tumor cells, the Hodgkin and Reed-Sternberg (HRS) cells, are infected by EBV [25–27]. The EBV infection within tumors is also clonal suggesting that all of the tumor cells are derived from a single infected cell [28, 29]. The HRS cells express EBNA1, LMP1, LMP2A, and 2B, but the remaining EBNAs are downregulated (Fig. 2.1); the non-coding EBER RNAs and BART miRNAs are also expressed [25, 26, 30–33]. This pattern of gene expression is referred to as latency type II [10]. EBV infection of HRS cells can be readily demonstrated in sections of routinely fixed, paraffin-embedded material using either EBER in situ hybridization or LMP1 immunohistochemistry (IHC) (Fig. 2.1) [25, 26]. Reagents for both assays are commercially available.

2.2.1 Epstein-Barr Virus and the Pathogenesis of Hodgkin Lymphoma

The molecular pathogenesis of cHL and the origin of the HRS cell are described in detail in Chap. 3. Briefly, HRS cells have clonally rearranged immunoglobulin genes with evidence of somatic hypermutation, indicating a derivation from B-cells that have participated in a germinal center reaction [34, 35]. A pathognomonic feature of these cells is the global suppression of B-cell signature genes and inappropriate expression of genes associated with other hematopoietic lineages [36, 37]. Importantly, HRS cells do not express B-cell receptors (BCRs). Survival of germinal center B-cells normally requires signaling through both BCRs and CD40; HRS cells must, therefore, have acquired a non-physiological survival mechanism(s). Functional studies of EBV, and LMP1 and LMP2A, support a role for the virus in HRS cell survival, transcriptional reprogramming, and immune evasion, as summarized below (Fig. 2.2).

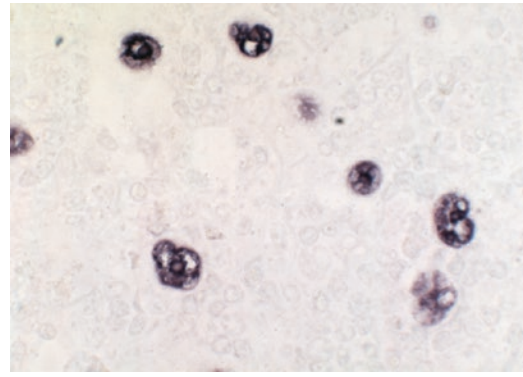

Fig. 2.2 EBV EBER in situ hybridization staining of EBV-positive Hodgkin and Reed-Sternberg cells. The characteristic staining pattern is observed in the nuclei of Hodgkin and Reed-Sternberg cells

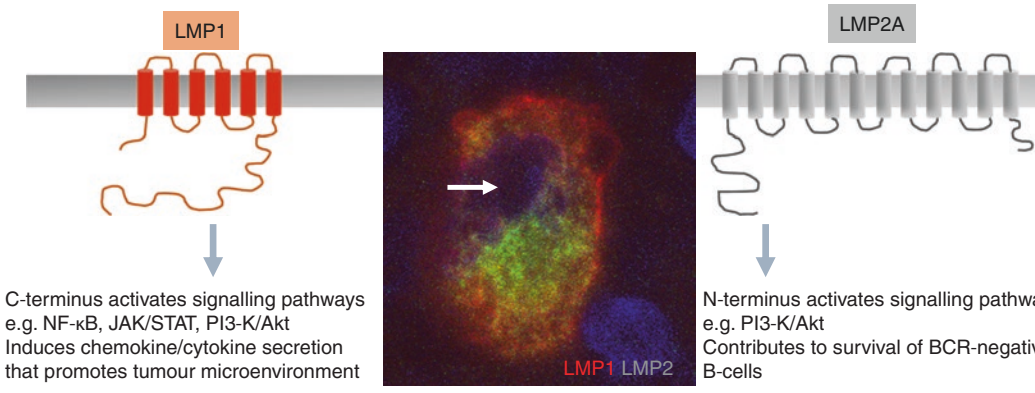

Fig. 2.1 The latent membrane proteins of EBV contribute to the pathogenesis of classic Hodgkin lymphoma. Schematic diagram of LMP1 (left) and LMP2A (right) proteins in the cell membrane (gray bar). Both are transmembrane proteins that signal constitutively through the C-terminus in the case of LMP1 and the N-terminus in the case of LMP2A. The photomicrograph in the center shows the co-expression of LMP1 (red) and LMP2A (green) in the same Hodgkin and Reed-Sternberg cell in a tissue section of classic Hodgkin lymphoma. The nucleus of the Hodgkin and Reed-Sternberg cell stained blue with DAPI is arrowed

In 2005, three independent groups published data showing that germinal center B-cells lacking BCRs could survive and be immortalized by EBV [38–40]. In elegant experiments, Mancao and Hammerschmidt later showed that this survival function was dependent on LMP2A expression [41]. A series of in vivo and in vitro studies from the Longnecker laboratory further defined LMP2A function and showed that this viral protein could mimic an activated BCR and provide a survival signal to BCR-negative B-cells [42–44]. LMP2A expression in B-cells also results in downregulation of B-cell-specific genes and induction of genes associated with proliferation and inhibition of apoptosis, a gene expression profile similar to that seen in cHL-derived cell lines [45]. Constitutive activation of Notch1 by LMP2A, and subsequent inhibition of E2A and downregulation of EBF, two transcription factors that regulate B-cell development, appears to be involved in both survival signaling and transcriptional regulation [44]. Although these data suggest a role for LMP2A in the survival and reprogramming of HRS cells, many of the intracellular molecules involved in BCR signaling are downregulated in HRS cells, and therefore the precise contribution of LMP2A in cHL is not clear.

CD40 signaling plays a critical role in the positive selection of germinal center B-cells expressing high-affinity immunoglobulin and their subsequent exit from the germinal center [46]. EBV LMP1 is an integral membrane protein which interacts with several signal transduction pathways to activate NF-κB, Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase [47–51]. In this way, LMP1 mimics a constitutively active CD40 molecule, although it provides a more potent and sustained signal. Many of the genes that are transcriptionally regulated by LMP1 in germinal center B-cells are also CD40 and NF-κB targets [52]. Activation of the NF-κB pathway, which is a feature of both EBV-positive and EBV-negative HRS cells, leads to upregulation of anti-apoptotic genes and is thought to play a key role in HRS cell survival [53–55]. LMP1 expression in germinal center B-cells also leads to increased expression of Id2, an inhibitor of the E2A transcription factor mentioned above, and repression of B-cell signature genes [52]; therefore, LMP1 may also contribute to transcriptional reprogramming.

The EBV genome is maintained as an episome in infected cells; i.e., it does not normally integrate. The EBNA1 protein is responsible for maintenance of the genome in episomal form, genome replication, and genome partitioning during mitosis [10, 56]. EBNA1 can also influence both viral and cellular gene expression and appears to confer a B-cell survival advantage, although the impact of EBNA1 on oncogenesis in vivo is controversial [10, 57–60]. Interestingly, in the context of cHL, overexpression of EBNA1 in vitro leads to the appearance of multinucleated cells [57].

The EBV EBER RNAs are two small, non-polyadenylated RNA pol III transcripts that are stably expressed in the nuclei of all latently infected cells, including HRS cells. The precise function of the EBERs remains unclear, and, although not essential for transformation, expression of these small RNAs is required for efficient EBV-induced B-cell growth and transformation [16, 61–63].

EBV-encoded miRNAs were identified first in 2004, and their important role in EBV biology and oncogenesis is an area of intense study [16, 17, 22, 64, 65]. Functional analysis of the BHRF1 and BART miRNAs suggests roles in evading the immune response, promoting cell survival and proliferation, inhibiting viral reactivation, and fine-tuning gene expression [16, 22, 64, 65]. EBV-associated malignancies, including cHL, express BART miRNAs, but the BHRF1 miRNAs, which are associated with latency type III, are not expressed [33]. In vitro studies of knockout viruses lacking some or all of the miRNAs suggest that they have an important role in the initial stages of B-cell transformation by EBV; BHRF1 miRNAs play the predominant role with some contribution from BART miRNAs at low multiplicity of infection [22]. In contrast, in vivo studies in a murine huNSG model suggest that the main function of these miRNAs is to attenuate the antiviral T-cell-mediated immune response, leading to increased numbers of EBV-

infected B-cells at later time points [66]. Again, these effects appear to be mediated by the BHRF1 miRNAs, as viruses deficient in only the BART miRNAs produced similar results to wild-type virus in this model system [66]. Ross et al. reported that miRNA BART11-5p downregulates the B-cell transcription factor EBF1, suggesting a plausible role for this miRNA in cHL [67]. EBV also regulates the expression of host miRNAs; infection of primary B-cells leads to a conspicuous downregulation of many miRNAs with the notable exception of mIR-155, which is highly expressed by both EBV-positive and EBV-negative HRS cells [68, 69]. Analysis of host miRNAs in cHL is described in more detail in Chap. 4, but it has been reported that EBV status of tumors is associated with differences in expression pattern [70].

While most studies have investigated the effects of the latent genes in isolation, there is evidence that co-expression of the EBV latent genes is important. For example, it has been shown that LMP1 is transforming when expressed alone in transgenic mouse B-cells [71]. However, when LMP2A is expressed together with LMP1, the resulting mouse B-cells are normal [71]. Comparison of LMP1 and LMP2A in B-cells confirms they have both synergistic and counteracting transcriptional effects [72]. Furthermore, in another study it was shown that LMP1 and LMP2A co-expression in mouse B-cells resulted in tumors, but only if the animals were immunosuppressed suggesting that the combined expression of these latent genes is immunogenic in vivo [73].

There is evidence that the tumor microenvironment in EBV-positive and EBV-negative cHL is different. Thus, the T-helper cells present in EBV-positive cHL are enriched for functional Th1 cells [74]. EBV-positive cHL is also preferentially infiltrated by regulatory Type 1 cells (Tr1), which express ITGA2, ITGB2, and LAG3 and secrete IL-10 [75]. This Th1-biased infiltrate is consistent with previous reports of higher numbers of activated CD8+ T-cells in EBV-positive cHL [76] and is also associated with the presence of predominantly M1-polarized macrophages [77]. There is evidence that the EBV latent genes are responsible, at least in part, for the recruitment and modification of this tumor microenvironment. LMP1, in particular, has been shown to induce expression of many of the chemokines and cytokines secreted by EBV-infected HRS cells [78, 79]. The cHL tumor microenvironment also contributes to the suppression of host anti-EBV-specific immunity. Thus, while LMP1 and LMP2A proteins are targets of CD8+ cytotoxic T lymphocytes, it is clear that immune effectors present in the tumor tissues of EBV-positive cHL cannot kill the virus-infected cells [80, 81]. LMP1 probably also contributes to the suppression of EBV-specific immunity through its ability to induce expression of the immunosuppressive cytokines, including IL-10, and upregulate the immune checkpoint ligand, PD-L1 [82, 83]. LMP1 also upregulates the collagen receptor, discoidin domain receptor 1 (DDR1), a receptor tyrosine kinase expressed by HRS cells [84]. Engagement of DDR1 by collagen leads to the increased survival of lymphoma cells, thus providing a link between the expression of LMP1 and pro-survival signaling from the tumor microenvironment.

2.2.2 Risk Factors for Epstein-Barr Virus-Associated Hodgkin Lymphoma

It is clear that EBV is associated with only a proportion of cHL cases. In industrialized countries around one third of cases are EBV-associated, whereas in Africa and Central and South America, this proportion is significantly higher [8, 9, 85, 86]. EBV-associated cHL cases are not randomly distributed among all cHL cases, and the demographic features and risk factors for the development of EBV-positive and EBV-negative cHL show distinctive features [8, 9, 86]. Childhood (<10 years) and older adult (50+ years) cases are more likely to be EBV-associated than young adult cases (15–34 years) [7, 8, 86]. Among EBV-associated cases, males outnumber females by approximately 2:1, whereas males and females are more evenly represented among EBV-negative cases [9, 86]. In developing countries, childhood cHL is more com-

mon than in industrialized countries, resulting in a higher proportion of EBV-associated cases [9, 86, 87]. Material deprivation is associated with an increased proportion of EBV-positive childhood cHL cases in industrialized countries, and there is some evidence that this also holds for older adult cases [85, 88].

EBV infection usually occurs in childhood, and in many parts of the world, there is almost universal infection by the age of 5 years [11, 89]. If infection is delayed until adolescence, as is increasingly observed in industrialized countries, primary EBV infection manifests as infectious mononucleosis in around 25% of individuals [90]. Infectious mononucleosis has been associated with an increased risk of EBV-associated cHL in some, although not all, studies [6, 91–93]. The increased risk appears relatively short-lived with a median time interval between infectious mononucleosis and cHL of approximately 3–4 years (see Chap. 1: Epidemiology of Hodgkin Lymphoma) [92, 93]. Thus, in both developing and developed countries, there appears to be a period following primary EBV infection, probably lasting several years, in which risk of EBV-associated cHL is increased. cHL occurring in the context of immunosuppression is almost always EBV-associated (see Chap. 1: Epidemiology of Hodgkin Lymphoma) [94, 95], and it is likely that the increased incidence of EBV-associated cHL that occurs in older adults is related to immune senescence. Based on these data, we have proposed an extension of MacMahon's model of HL that divides cHL into four subgroups on the basis of tumor EBV status, age at diagnosis, and age at infection by EBV (Fig. 2.3) [2, 96].

Recent data also suggest that humoral and cell-mediated responses to EBV modulate risk of EBV-associated cHL. Levin and colleagues examined anti-EBV antibody profiles in serum samples from military personnel (mainly young men) that had been collected several years before the diagnosis of cHL [97]. Individuals who subsequently developed EBV-positive, but not EBV-negative, cHL were more likely to have elevated

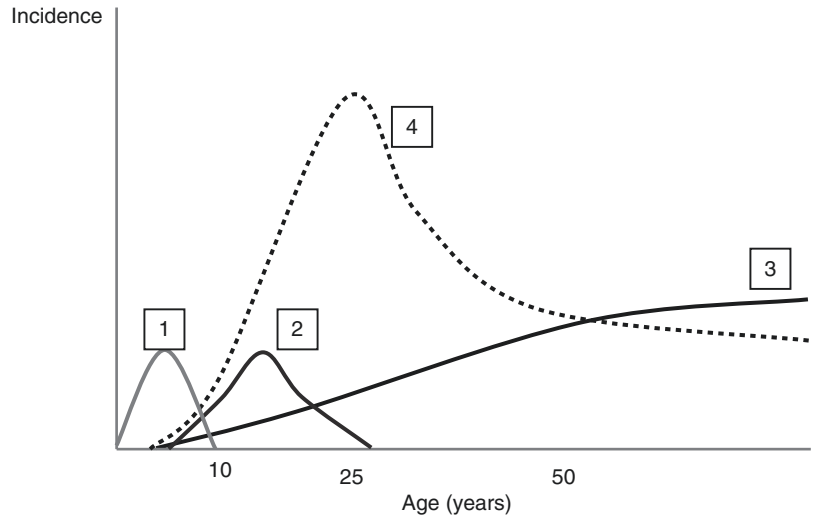

Fig. 2.3 The four-disease model of classic Hodgkin lymphoma. This model divides classic Hodgkin lymphoma into four subgroups based on EBV tumor status, age at diagnosis, and age at EBV infection. Three groups of EBV-associated disease are recognized: (1) a childhood disease, usually occurring below the age of 10 years, which is commoner in developing countries; (2) a disease, most commonly seen in young adults, which occurs following infectious mononucleosis; and (3) a disease associated with poor control of EBV infection, which is typified by the older adult cases but can occur at other ages, particularly in the context of immunosuppression. (4) Superimposed on these is a single group of EBV-negative classic Hodgkin lymphoma cases, which account for the young adult age-specific incidence peak seen in industrialized countries. The relative incidence of each of these four disease subgroups will determine the overall shape of the age-specific incidence curve in any geographical locale

antibody titers to EBV viral capsid and early antigens and an anti-EBNA-1/anti-EBNA2 antibody ratio ≤1.0 when compared to controls. Decreased anti-EBNA-1/anti-EBNA2 antibody ratios have been previously associated with EBV-associated cHL [98], and it has been suggested that a ratio ≤ 1.0, which persists for more than 2 years after infectious mononucleosis, indicates defective control of persistent EBV infection [99]. Variations in EBNA-1 titer are significantly associated with polymorphisms in the human leukocyte antigen (HLA) region [100], suggesting that titers may, in part, be genetically determined and relate to the findings described below.

Data from HLA association studies and genome-wide association studies (GWAS) show clear associations between cHL risk and both HLA alleles and single nucleotide polymorphisms (SNPs) in this region. Although some SNPs appear to be associated with all cHL, independent of EBV status, most HLA associations differ between EBV-positive and EBV-negative subgroups [101–108]. Both HLA class I and II alleles are associated with EBV-positive cHL, whereas EBV-negative cHL is largely associated with class II alleles [102, 103, 105, 107]. Since class I and II alleles present peptides from pathogens to CD8- and CD4-positive T-cells, respectively, this suggests that genetically determined differences in the cell-mediated response to EBV influence disease risk. HLA-A∗01 is associated with an increased risk of EBV-associated cHL, whereas HLA-A∗02, specifically A∗02:01, is associated with decreased risk [102, 103]. Associations with these alleles are independent, i.e., the increased risk associated with A∗01 is not simply due to lack of A∗02, and effects are dependent on the copy number of each of the alleles [103] (Fig. 2.4). As a result, there is an almost tenfold variation in odds of EBV-associated cHL between HLA-A∗01 homozygotes and HLA-A∗02 homozygotes [103]. More recent data suggest that B∗37:01 is also associated with an increased risk of EBV-positive cHL [105, 107]. Class II alleles have been less extensively studied, but Huang et al. reported an increased frequency of DR10 alleles in patients with EBV-positive cHL compared to controls, and we have detected protective effects of DRB1∗15:01 and DPB1∗01:01 [105, 107]. In addition, the SNP rs6457715, which is located close to the HLA-DPB1 gene, is strongly associated with EBV-positive but not EBV-negative cHL [108].

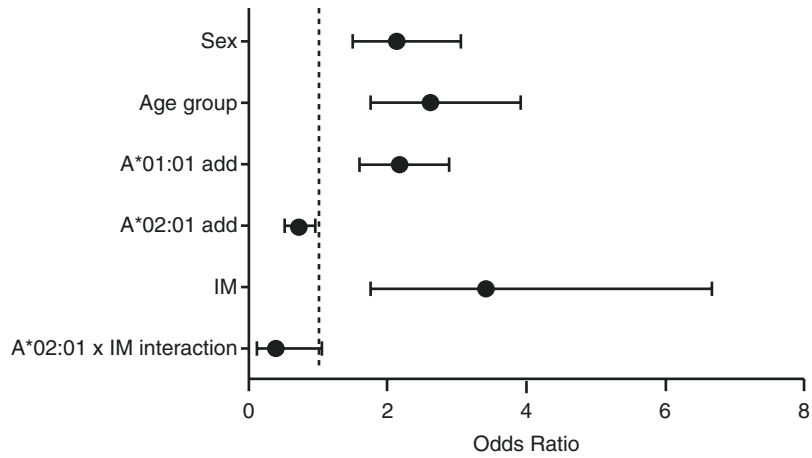

Fig. 2.4 Risk factors for EBV-associated classic Hodgkin lymphoma in adults. Forest plot showing odds ratios and 95% confidence intervals for development of EBV-associated Hodgkin lymphoma from a case series analysis of HLA and non-HLA risk factors [103]. Increased risk is associated with male sex, older age (age ≥50 years versus 15–34 years), possession of HLA-A∗01:01 alleles (add, additive effect), and prior history of infectious mononucleosis (IM). Possession of HLA-A∗02:01 alleles is associated with decreased risk, and abrogation of the increased risk associated with IM

Cytotoxic T-cell responses, restricted through HLA class I, are critical for the control of EBV infection, and A∗02 is known to present a wide range of peptides derived from EBV lytic and latent antigens, including those expressed by HRS cells [23, 24]. In contrast, there are no well-characterized A∗01-restricted EBV epitopes [24], and EBV-specific T-cell responses restricted through A∗01:01 have not been described [109]. The observed associations with HLA-A, therefore, seem biologically plausible. However, HLA-A∗01 is in strong linkage disequilibrium with HLA-B∗08, which is associated with immunodominant EBV-specific cytotoxic T-cell responses, and yet there is no protective effect associated with this allele [107]. The biological basis underlying associations between HLA alleles and EBV-associated cHL is therefore not clear. Further work is also necessary to determine whether the critical HLA-A-restricted cell-mediated immune responses are directed toward EBV-infected HRS cells or whether it is the control of persistent EBV infection, i.e., the host-virus equilibrium, which is all-important. The increased risk associated with individual class I alleles favors the idea that failure to respond to a particular protein, or very restricted group of proteins, determines risk; this focusses attention on EBV proteins expressed by HRS cells. Consistent with this, no EBNA1, LMP1, or LMP2 epitopes restricted by B∗37:01 have been identified although a B∗37:01-restricted EBNA3C epitope has been described [24].

As mentioned above, prior infectious mononucleosis has been associated with an increased risk of EBV-positive cHL [91–93, 110]. Infectious mononucleosis has also been associated with the same genotypic markers (microsatellites and SNPs) in the HLA class I region as EBV-positive cHL, albeit with lesser statistical significance [111]. These data raised the possibility that the association between infectious mononucleosis and EBV-associated cHL resulted from shared genetic susceptibility. However, HLA-A typing of over 700 cHL cases with available self-reported history of infectious mononucleosis revealed that prior infectious mononucleosis was independently associated with EBV-associated cHL after adjusting for the effects of HLA-A alleles [103]. In addition, a statistically significant interaction between prior infectious mononucleosis and HLA-A∗02 was detected; the effect of this was to abrogate the increased risk of EBV-associated cHL following infectious mononucleosis in HLA-A∗02-positive individuals [103]. These results suggest that the increased risk of EBV-associated cHL following infectious mononucleosis is modified by the EBV-specific cytotoxic T-cell response restricted through HLA-A∗02. Thus, it is possible that different HLA alleles exert their effects at different stages in the natural history of EBV-associated cHL.

Associations with childhood cHL and infectious mononucleosis suggest that there is a window of time following primary EBV infection when there is an increased risk of EBV-associated cHL and that genetic factors, specifically HLA-A genotype, modify this risk. EBV-associated cHL patients have higher numbers of EBV-infected cells than patients with EBV-negative disease [112], and infectious mononucleosis patients have very high numbers of circulating EBV-infected B-cells, which decrease over time [113]. The number of EBV-infected cells carried by an individual is therefore likely to influence the risk of EBV-associated cHL. It may, therefore, be possible to decrease the risk of EBV-positive cHL by EBV vaccination, even in the absence of sterilizing immunity [114], or by treatment of infectious mononucleosis with antiviral agents.

2.2.3 Epstein-Barr Virus and Hodgkin Lymphoma: A Causative Association?

In the absence of good animal models and the ability to prevent EBV infection, it is difficult to prove that the association between EBV and cHL is causal; however, consideration of the viral, molecular, and epidemiological data pro-

vides support for this idea. (1) The EBV infection in EBV-positive cHL tumors is clonal indicating that all the tumor cells are derived from a single EBV-infected cell. (2) In EBV-associated cases, all HRS cells are infected by the virus. Although EBNA1 facilitates both synchronous replication of the viral episome with cellular DNA and genome partitioning, this process is not 100% efficient [56]. If the virus were not required for maintenance of the transformed phenotype, a gradual loss of viral genomes from the tumor cells would be anticipated. (3) EBV is present in the tumor cells of a significant proportion of cHL cases. Although most adults are infected by EBV, only 1–50 per million B-cells are EBV-infected in healthy individuals [115]. If EBV were simply a passenger virus, i.e., present in a B-cell that was subsequently transformed by other mechanisms, EBV-associated cHL would be a rare occurrence. (4) LMP1 and LMP2A have plausible biological functions in the pathogenesis of cHL, as described above. (5) Crippling mutations of immunoglobulin genes have been described in a quarter of cHL cases, and almost all of these cases are EBV-associated [116]. This is consistent with the idea that EBV rescues HRS cells (or precursors) that have destructive mutations of their immunoglobulin genes from apoptosis. (6) Recent studies show that EBV-positive cHL has significantly fewer cellular mutations, including chromosomal breakpoints and aneuploid autosomes than EBV-negative cHL [117, 118]. Deleterious mutations of the *TNFAIP3* and *NFKBIA* genes, which are both negative regulators of NF-κB signaling, are also much more frequent in HRS cells from EBV-negative cases (see Chap. 3) [119–123]. (7) EBV-associated cHL cases share genetic risk factors for disease development, which are generally distinct from those associated with EBV-negative cHL [101–105, 107, 108, 124, 125]. (8) In some cases, the development of EBV-associated cHL is temporally related to primary EBV infection [92, 93, 95]. (9) Individuals who subsequently develop EBV-associated cHL have abnormal EBV antibody profiles before diagnosis [97].

2.2.4 Epstein-Barr Virus and the Clinicopathological Features of Hodgkin Lymphoma

Although the above data indicate that EBV-positive and EBV-negative cHL have distinct natural histories, the phenotypic expression of both processes appears remarkably similar. Gene expression profiling of HRS cells suggests that EBV has only a small influence on the transcription profile of established HRS cells [126]. However, EBV status does show clear associations with histological subtype. In a meta-analysis of published studies of EBV and cHL, Lee et al. reported that 66% of MCHL cases are EBV-associated, compared to 29% of NSHL cases [86]. Despite this difference, it is clear that "barn door" NSHL cases can be EBV-positive, and so the lack of a complete correlation between histological subtype and EBV status is not simply due to the criteria used in, and subjective nature of, histological subtyping. In industrialized countries, NSHL is much more common than MCHL, and in our experience, the majority (just) of EBV-positive cases in the UK are, in fact, NSHL and not MCHL.

Early studies investigating clinical outcome in relation to EBV status in cHL appeared conflicting, and the meta-analysis performed by Lee et al., which was not able to stratify patients by age, did not find any associations with survival. However, a consistent picture has emerged from population-based studies with age stratification of patients [127–130]. In young adult patients, there appears to be no significant difference in overall survival by EBV status. In contrast, EBV positivity is associated with inferior outcome among patients aged 50 years and over. It is not clear whether this difference is related to the disease process itself or whether it reflects an underlying comorbidity or immune dysregulation that potentially predisposes to EBV-associated cHL. EBV status is not routinely used in therapeutic decisions, but it is possible that this group of patients would benefit from alternative treatments, such as third-party cytotoxic lymphocyte infusions or novel therapies tar-

geting EBV. Biomarker levels may also vary by EBV status; for instance, CCL17 (TARC) levels are lower in patients with EBV-associated cHL, but monitoring of plasma EBV levels (a form of circulating tumor DNA) can be used to assess treatment response and detect relapse in these patients [131, 132]. Further studies investigating these issues are required.

2.3 Epstein-Barr Virus-Negative Hodgkin Lymphoma Cases

Adolescent and young adult cHL cases are the group least likely to be associated with EBV, and yet it is for these cases that there is most epidemiological evidence suggesting viral involvement. Early studies reported consistent associations between young adult HL and correlates of a high standard of living in early childhood [133]. Many of these associations with social class variables have not been detected in recent studies, most probably reflecting societal changes; however, an increased risk of young adult HL in individuals with less than 1 year of preschool attendance has been observed [6, 93]. Collectively, the data suggest that diminished social contact in early childhood is associated with an increased risk of this disease. Interview and questionnaire data generally support the idea that young adult HL patients have experienced fewer common infections in childhood [91, 134]. This has led to speculation that young adult HL is associated with delayed exposure to one or more common childhood infections.

A frequent suggestion is that EBV is involved in all cases of cHL but uses a hit-and-run mechanism in "EBV-negative" cases. This possibility is very difficult to exclude, but the available data indicate that it cannot account for all "EBV-negative" cases. Importantly, not all cases are EBV-infected [98, 135]; in fact, we found that EBV-negative cHL cases in the 15- to 24-year age group were more likely to be EBV-seronegative than age-matched controls [135]. Also, there is no evidence for integration of incomplete EBV genomes in "EBV-negative" cHL biopsies [135, 136].

Alternative hypotheses are that lack of exposure to pathogens in early life shapes the microbiome and immune defenses, leading to an increased risk of developing cHL in young adulthood [137], or that EBV-negative cHL is associated with delayed exposure to another common virus that is directly involved in disease pathogenesis. Candidate viruses that are common and have transforming potential include herpesviruses and polyomaviruses. Any virus with a direct transforming role would be expected to be present in all HRS cells within tumors.

2.3.1 Hodgkin Lymphoma and Herpesviruses Other Than Epstein-Barr Virus

At present, there are nine known human herpesviruses (HHVs), including EBV (officially HHV-4). All are widespread in distribution, except herpes simplex virus 2 (HHV-2) and HHV-8. EBV and Kaposi sarcoma herpesvirus (KSHV, officially HHV-8) belong to the gammaherpesvirus subfamily of herpesviruses; both infect lymphoid cells and are tumor viruses. KSHV causes Kaposi sarcoma and rare forms of lymphoma but is not associated with cHL [138–141]. There is also no evidence of involvement of the alphaherpesviruses, herpes simplex virus 1, and varicella zoster virus [140]. In contrast, genomes of the betaherpesviruses, human cytomegalovirus, HHV-6A, HHV-6B, and HHV-7, have been detected in cHL tumors using sensitive molecular assays. Schmidt et al. detected human cytomegalovirus genomes by PCR in 8/86 HL biopsies [139], although smaller case series failed to identify this virus in tumor samples [140, 142–144]. HHV-7 has been detected in 20–68% of HL biopsies by PCR [139, 140, 144, 145]. However, negative results were obtained using Southern blot analysis, which is much less sensitive than PCR but would be expected to detect a virus present in all HRS cells [146], and there is no evidence that the virus is present in HRS cells [145]. There is,

therefore, no evidence for direct involvement of HHV-7 in cHL pathogenesis.

HHV-6 deserves special mention because this lymphotropic virus has been consistently linked with cHL. HHV-6 is now classified as two distinct viruses, HHV-6A and HHV-6B [147], rather than two variants, but until recently many studies have not distinguished between the two viruses. Serological studies have shown that HHV-6 antibody titers and, in some studies, seroprevalence are higher in HL cases than controls [148–150]. We also found that young adults with non-EBV-associated HL had higher titers of HHV-6 antibodies than age-matched cases with EBV-associated disease (unpublished results). HHV-7 antibody titers were similar in the two groups of cases suggesting a specific association between HHV-6 and cHL.

HHV-6 genomes have been consistently detected in HL biopsies using PCR although detection rates range from 8% to 79% [139, 140, 144, 150–155], and some studies have reported similar detection rates in reactive lymph nodes [144, 152]. Differences in PCR assay sensitivity and the amount of DNA assayed most probably account for the differences in detection rate since viral genome copy numbers within biopsies are often low. Up to 87% of NSHL cases have been reported to be HHV-6-positive [155, 156], but it is clear that these PCR-positive cases include both EBV-associated and EBV-non-associated cases [140, 152, 155, 156]. Both HHV-6A and B have been detected within biopsies with four studies showing a clear bias toward HHV-6B [140, 151, 152, 155], one detecting a higher proportion of HHV-6A-positive tumors [139], and one detecting HHV-6A and B as well as dual infections [156]. The low viral genome copy in many tumors suggests that the virus cannot be present in every HRS cell and raises the suspicion that the virus is in cells in the reactive component of tumors. Very high viral copy numbers must also be interpreted with caution since inherited chromosomally integrated HHV-6 (iciHHV-6) is transmitted in the germline in around 1% of individuals and gives rise to high viral loads since viral genomes are present in every nucleated cell in the body [157–159]. Following exclusion of cases with iciHHV-6, studies using the less sensitive technique of Southern blot analysis have largely been negative suggesting a low viral copy number within tumors [138, 150, 152, 153, 160]. In contrast, in EBV-associated cHL, EBV genomes are almost always detectable using this technique [7, 20, 128]. The critical question is whether HHV-6 infects HRS cells and, if so, is the virus present in every HRS cell.

Early studies using in situ hybridization and IHC reported that the virus was present in cells in the tumor microenvironment, either exclusively [152, 161] or with occasional positive HRS cells [162, 163]. However, two recent studies described HHV-6-positive HRS cells [156, 164], and we detected HHV-6 transcripts in an RNAseq analysis of HRS cells enriched from an EBV-negative cHL biopsy (unpublished data), thus renewing interest in cHL and HHV-6. Lacroix et al. made a polyclonal antiserum to the DR7 open reading frame (ORF) of HHV-6B (designated DR7B) to examine the cellular localization of the virus in PCR-positive cases [164]. They selected this particular ORF because the equivalent HHV-6A ORF has transforming properties and the translated protein binds p53 and inhibits p53-activated transcription [153, 165]. It is likely that the DR7 ORF is expressed as the second exon of DR6, a larger nuclear protein [166, 167]. Using this antiserum, cytoplasmic staining of HRS cells was identified in 28/38 PCR-positive biopsies [164]. In 17 cases, positive staining was exclusive to HRS cells, and in further 17 cases, positive staining of cells in the microenvironment was noted. In 15 of the 38 biopsies, HRS cells were also positively stained using an antibody to the HHV-6 gp116/64/54 glycoprotein. Further analyses suggested that DR7B bound p53, upregulated NF-κB p105 and p65 promoters, significantly increased NF-κB activation, and induced upregulation of Id2. In the second study, Siddon et al. investigated biopsies from 21 NSHL cases, including 18 that were HHV-6-positive by PCR, using multiple approaches [156]. In ten cases, staining of HRS cells was demonstrated using a commercially available monoclonal antibody raised

against virus lysate (Santa Cruz Biotechnology); scattered positive HRS cells were also demonstrated using antibodies to the late viral proteins p41 and p98. Laser capture microdissection coupled with PCR confirmed the presence of HHV-6 DNA in pooled HRS cells from eight of the ten IHC-positive biopsies. This study provides the most convincing evidence to date that HHV-6 can infect HRS cells but does not show that the virus is present in every HRS cell. Furthermore, the IHC staining pattern suggests lytic replication (or abortive replication) rather than latent infection, and so the outcome of viral infection in these cells is not clear.

As mentioned above, some individuals inherit HHV-6 in the germline [157, 159]. The first study to demonstrate chromosomally integrated HHV-6 investigated three patients with high viral loads in peripheral blood, including one with cHL [168, 169]. To determine whether iciHHV-6 is associated with cHL, we examined 936 cHL cases and 563 controls but found no evidence that iciHHV-6 was overrepresented among cases [170].

Overall, the data do not support the idea that HHV-6 has a direct role in disease pathogenesis. However, it is possible that HHV-6 is frequently reactivated in cHL tumors. CD134 is the cellular receptor for HHV-6B [171], and it is possible that CD134-positive T-cells in the cHL microenvironment [74] facilitate replication of HHV-6B. Robust in situ hybridization assays for HHV-6 are required to confidently rule out a direct role in cHL.

To search for novel members of the herpesvirus family, we and others have designed degenerate PCR assays which amplify herpesvirus polymerase and glycoprotein B gene sequences [140, 172]. The primer sequences in degenerate assays are derived from well-conserved peptide motifs in amino acid sequences of proteins; therefore, these assays should have the ability to detect genomes from known and currently unknown viruses [173]. Using herpesvirus polymerase assays, we have not detected novel herpesviruses in cHL biopsies although the assays had sufficient sensitivity to detect EBV in EBV-associated cases, as well as low-level HHV-6 and HHV-7 infection [140] (and unpublished results).

2.3.2 Polyomaviruses and Hodgkin Lymphoma

There are now (at least) 14 human polyomaviruses (HPyVs) [174–178]. JCV and BKV were discovered over 40 years ago, but the others have all been discovered since 2007 with the advent of modern molecular techniques for virus discovery. Seroprevalence studies suggest that the majority of adults are infected by BKPyV, KIPyV, WUPyV, MCPyV, HPyV6 and 7, and TSPyV and a significant minority by JCPyV, HPyV9, and HPyV12 [176, 179–181]. Among this expanding list of HPyVs, only JCPyV, BKPyV, TSPyV (associated with trichodysplasia spinulosa in immunosuppressed persons), and MCPyV show clear disease associations. MCPyV is associated with Merkel cell carcinoma and has been categorized by IARC as a group2A carcinogen (probably carcinogenic to humans) [175, 182, 183]. It is the only HPyV to be unambiguously linked with a specific malignancy; however, other polyomaviruses have oncogenic potential.

Several laboratories have looked for evidence of HPyV genomes in cHL biopsies. Using sensitive quantitative PCR assays, we found no evidence of JCV or BKV genomes in 35 cHL biopsies [184]. Hernandez-Losa et al. detected JCV in 1/20 and BKV in 2/20 cHL samples using a multiplex, nested PCR [144]. Robles et al. reported that MCPyV seroprevalence was slightly higher in HL cases than controls, 84.4% compared to 81.2%, but differences were not statistically significant [185]. Two quantitative PCR studies detected MCPyV genomes in a small proportion (1/30 and 3/41) of cHL tumors [186, 187]; viral copy numbers were low making it extremely unlikely that this virus is playing any role in disease pathogenesis. To date, there have been no reports on the prevalence of the more recently identified viruses in cHL.

Degenerate PCR assays have also been applied to the study of PyVs and HL [184, 187]. Volter et al. examined five cases of HL using a degenerate PCR assay based on the viral VP1 protein but did not detect any evidence of polyomavirus infection [187]. We examined 35 cases of cHL, including 23 EBV-negative cases, using 3 degenerate PyV assays based on the large T antigen, and also obtained negative results [184]. The latter assays were designed before 2006 and therefore before most HPyVs were discovered. Alignment of large T antigen amino acid sequences from the recently identified viruses suggests that our assays would be able to detect KIPyV, WUPyV, TSPyV, and HPyV9 and 10 but not MCPyV, HPyV6, and HPyV7; however, given the tropism of the latter viruses for skin, it is unlikely that they are involved in cHL [176]. Overall, these results provide no evidence for HPyV involvement in the pathogenesis of cHL, but it remains possible that an unknown HPyV has escaped detection.

2.3.3 Measles Virus and Hodgkin Lymphoma

In 2003, Benharroch and colleagues reported an association between measles virus (MV) and cHL [188]. They subsequently reported that MV proteins were detectable by IHC in HRS cells from most HL cases [189]. MV RNA was also detected by RT-PCR and in situ hybridization in a significant minority of the cases examined [189]. Subsequent studies have failed to confirm these associations [190, 191]. Our group found no evidence of MV in 97 cHL cases examined by IHC and 20 cHL cases investigated using RT-PCR [191]. Similarly, Maggio et al. found no evidence of MV genomes or transcripts in HRS cells microdissected from biopsies from 18 German and 17 Israeli HL cases [190]; the latter cases had previously scored positive for MV antigens [190]. Epidemiological studies have also failed to show that MV infection is a risk factor for the development of cHL; on the contrary, the data suggest a mild protective effect of prior MV infection [91, 134, 192].

2.3.4 The Virome, Anelloviruses, and Hodgkin Lymphoma

It is now recognized that the microbiome, which is thought to play an important role in shaping the immune system, includes a large number of viral species (the virome). Anelloviruses account for around 70% of these viruses [193]. The anellovirus family includes a large number of genetically diverse viruses with small, circular, single-stranded DNA genomes, which are classified in the Torque teno virus (TTV), Torque teno midi virus (TTMDV), and Torque teno mini virus (TTMV) genera in humans. They are widely distributed, acquired early in life, and establish persistent infections, but have not yet been associated with any disease; however, it has been suggested that they can modulate both innate and adaptive immune responses [194]. In 2004, Jelcic et al. reported the isolation of 24 novel TTVs from a spleen of an HL patient [195]. This led zur Hausen and de Villiers to suggest that TTVs could play a role in the development of leukemias and lymphomas that are associated with a "protected childhood environment" [196]. In their model, they postulated that TTVs and related anelloviruses increase the risk of chromosomal abnormalities and that anellovirus load is increased in individuals who have experienced fewer infections [196]. Increased TTV loads could also contribute to cHL through modulation of immune defenses. TTVs have also been identified in cHL tumor biopsies by other groups [197, 198], but these studies detected TTVs at a similar frequency in other lymphomas [197] and reactive nodes [198]. In a recent metagenomic analysis, Pan et al. analyzed the virome in blood samples from 19 HL patients, 252 non-Hodgkin lymphoma patients, and 40 healthy controls from China [199]. Eleven novel, but closely related, TTMVs were identified in three of the HL patients but not in the other patients or controls. The significance of these findings is currently unclear. Further investigation of the virome in both cHL patients and individuals with lack of social contact in early childhood is required to understand the potential contribution of anelloviruses, the virome, and the microbiome to the risk of cHL.

2.4 Conclusions

While the evidence suggesting a causal relationship between EBV and a proportion of cHL cases appears strong, current data do not show a consistent and specific association between any virus and EBV-negative cHL. This does not exclude viral involvement since the difficulty of obtaining large numbers of highly enriched HRS cells has precluded the use of certain techniques, such as representational difference analysis, in the analysis of cHL [137]. Next-generation sequencing methods have opened new avenues for virus discovery and have led to the identification of numerous novel viruses in the last few years [139, 140, 156]. These techniques provide our best hope of discovering a new virus in EBV-negative HRS cells. It is possible that cellular mutations substitute for the functions of EBV genes in EBV-negative HRS cells [126]. Deleterious mutations of inhibitors of the NF-κB pathway, including genes encoding A20 and IκBα, appear to be present in the HRS cells of many cases of EBV-negative cHL (see Chap. 3) [90–94], and it is possible that these mutations substitute for LMP1. However, there is no obvious link between these mutations and the epidemiological features of cHL, and involvement of another virus(es) with either a direct or indirect role still appears attractive. Understanding the role of viruses in EBV-negative cHL could potentially open up possibilities for disease prevention as well as novel therapeutic targets and is a goal worth pursuing.

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3 Pathology and Molecular Pathology of Hodgkin Lymphoma

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Contents

3.1 Subclassification and Pathology

The history of Hodgkin lymphoma (HL) dates back to the first half of the nineteenth century (see Chap. 1), and it has also been an established view for quite some time that HL comprises two different disease entities, namely, classical Hodgkin lymphoma (cHL) and nodular lymphocyte-predominant Hodgkin lymphoma (LPHL) [1]. Both entities have in common that the neoplastic

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_3

cell population, which can be mononucleated or multinucleated, makes up only a small percentage of all cells present in an affected lymph node. However, morphological, clinical, epidemiologic, and molecular evidence strongly support the belief that the pathogenesis of these lymphomas is distinct enough to be considered separate entities. From a diagnostic point of view, morphological details and immunohistochemistry for a selected set of markers almost always allow for a proper classification of a given lymphoma into the group of LPHL or cHL, the latter of which can be further subdivided into nodular sclerosis cHL (NSCHL), mixed cellularity cHL (MCCHL), lymphocyte-depleted cHL (LDCHL), and lymphocyte-rich cHL (LRCHL) [1].

The following sections summarize the key morphological aspects and important immunohistochemical features of HL, as well as key biological and genetic features of the HL tumor cells. For microenvironmental, clinical, and epidemiologic parameters, please refer to the respective other chapters of this book.

3.1.1 Nodular Lymphocyte-Predominant Hodgkin Lymphoma

Although the morphology of the tumor cell population of LPHL can occasionally mimic Hodgkin and Reed-Sternberg (HRS) cells of cHL, in most instances the tumor cells in LPHL, which are termed lymphocyte-predominant (LP) cells according to the current WHO classification (previously called L&H cells, for lymphocytic and/or histiocytic Reed-Sternberg (RS) cell variants), carry one large nucleus that is often multilobated ("popcorn cell") (Fig. 3.1a). In contrast to classic HRS cells, the number of nucleoli is increased, but they are usually less prominent and less eosinophilic. LP cells are found in a nodular or follicular background that is dominated by small B lymphocytes that usually express IgD, but a more diffuse growth pattern can also be encountered, especially during progression. The follicular infiltration pattern is highlighted by the presence of CD21-positive follicular dendritic cells that tend to form a well-developed meshwork in the nodules. Immunohistochemically, LP cells demonstrate a complete B cell phenotype with expression of CD20, CD75, and, frequently, CD79a (Fig. 3.1b; Table 3.1). Moreover, the essential B cell transcription factors BOB.1 and OCT-2 are usually positive, and the expression of BCL6 and activation-induced cytidine deaminase (AID) is well in line with a germinal center (GC) derivation of the tumor cells, although CD10 is generally negative [1–3]. The negativity of the tumor cells for CD30, CD15, and Epstein-Barr virus (EBV) helps to distinguish LP cells from HRS cells in

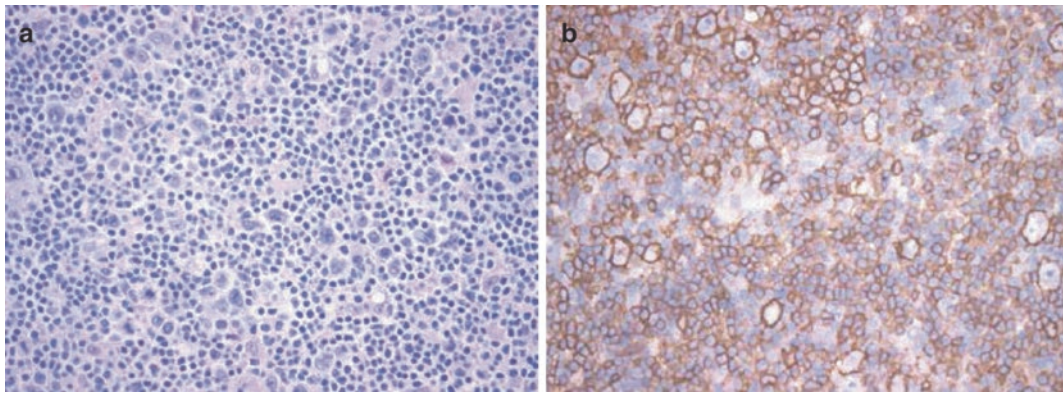

Fig. 3.1 Nodular lymphocyte-predominant Hodgkin lymphoma (LPHL). **(a)** HE-stained lymph node infiltrate showing multiple characteristic, multilobated tumor cells—termed lymphocyte-predominant (LP) cells—in a background of small lymphocytes and histiocytes (×400). **(b)** Strong CD20 expression in LP cells, but also in reactive, small B cells in the background (×400). Note that some of the tumor cells show rosetting by a CD20-negative lymphocyte population. These cells are T cells that often express the follicular T helper cell marker PD-1

Table 3.1 Genetic and phenotypic features of HRS and LP cells

Feature	HRS cells	LP cells
Phenotype		
CD30 expression	Yes	Rare
CD15 expression	Yes (~70%)[a]	No
B cell receptor expression	No	Yes
Loss of most B cell markers	Yes	Modest
Expression of germinal center (GC) B cell markers (e.g., BCL6, activation-induced cytidine deaminase (AID))	Rarely	Yes
Expression of markers for non-B cells (e.g., CD3, granzyme B, CCL17)	Frequently	No
Putative cell of origin	Defective, pre-apoptotic germinal center B cell	Germinal center B cell
EBV positivity	Yes (~40%)	No
Signaling pathways		
NF-κB activation	Yes	Yes
JAK/STAT activation	Yes	Yes
Aberrant expression of multiple RTKs	Yes (~60–100%)	Yes (~40%)
PI3K/AKT activation	Yes	n.a.
AP-1 activation	Yes	Partly
Genetic lesions		
NFKBIA mutations	Yes (~10–20%)	No
NFKBIE mutations	Yes (~10%)	n.a.
TNFAIP3 mutations	Yes (~40%)	No
REL gains/amplifications	Yes (~50%)	No
MAP3K14 (NIK) gains/amplifications	Yes (~25%)	n.a.
BCL6 translocations	Rare	Yes (~50%)
JAK2, PD-L1, PD-L2, JMJD2C gains/amplification	Yes (~30%)	No
STAT6 mutations, gains	Yes (~30%)	n.a.
SOCS1 mutations	Yes (~40%)	Yes (~50%)
PTPN1 mutations	Yes (~20%)	n.a.
GNA13 mutations	Yes (~20%)	n.a.
ITPKB mutations	Yes (~15%)	n.a.
XPO1 mutations	Yes (~20%)	n.a.
B2M mutations	Yes (~30%)	n.a.
MHC2TA translocations	Yes (~15%)	n.a.
SGK1	n.a.[b]	Yes (~50%)
DUSP2	n.a.[b]	Yes (~50%)
JUNB	n.a.[b]	Yes (~50%)

n.a. not analyzed, *RTK* receptor tyrosine kinase

[a]Numbers in brackets refer to the percentage of positive cases

[b]No mutations reported in 2 whole exome sequencing studies of together 44 cases of cHL and an exome sequencing analysis of 6 cHL cell lines [8–10]

cHL, although occasionally a weak positivity for CD30 can be present in LP cells (Table 3.1). Whereas in initial lesions small B cells dominate the background, histiocytes and T cells may become more prominent during the evolution of LPHL, to an extent that LPHL may be hardly distinguishable from T cell/histiocyte-rich large B cell lymphoma (THRLBCL). "Variant histology" (e.g., depletion of small B cells in the background or unusual localization of the LP cells) appears to be associated with an inferior prognosis [4]. A prominent feature of LPHL is the often impressive rosetting of LP cells by T cells that belong to the subset of follicular T helper cells and therefore express CD57 and PD-1 [5–7].

3.1.2 Classical Hodgkin Lymphoma: The HRS Cells

The characteristic tumor cell of cHL, the RS cell, is large and contains at least two nuclear lobes or nuclei, usually with a prominent nuclear membrane (Fig. 3.2a). In contrast to LP cells in LPHL, the nucleoli of RS cells are often eosinophilic. The mononuclear variant of RS cells is termed the Hodgkin cell. However, the morphological spectrum of the tumor cell population in cHL can be broad and includes variants such as lacunar cells and mummified cells. In general, the tumor cells in cHL are called Hodgkin and Reed-Sternberg cells. Immunohistochemically, the HRS cells stain positive for CD30 (Fig. 3.2c), and CD15 is coexpressed in the majority of cases, occasionally with prominent staining of the Golgi area of the tumor cell. However, CD15 is negative in a significant proportion of cHL (20–25%) and therefore not required to establish the diagnosis of cHL [1]. CD45 is usually negative, as are the B cell transcription factors BOB.1 and OCT-2. In the vast majority of cases, the derivation of the tumor cells from the B cell lineage is indicated by a nuclear positivity for the B cell-specific activator protein PAX5/BSAP, but the staining is usually weaker compared to the staining intensity in the small reactive B cell population in the background of the infiltrate [11]. CD20 expression can be observed in HRS cells in 30–40% of cases, but the expression is frequently restricted to a subset of the tumor cell population, and even within one HRS cell, it is of varying intensity in

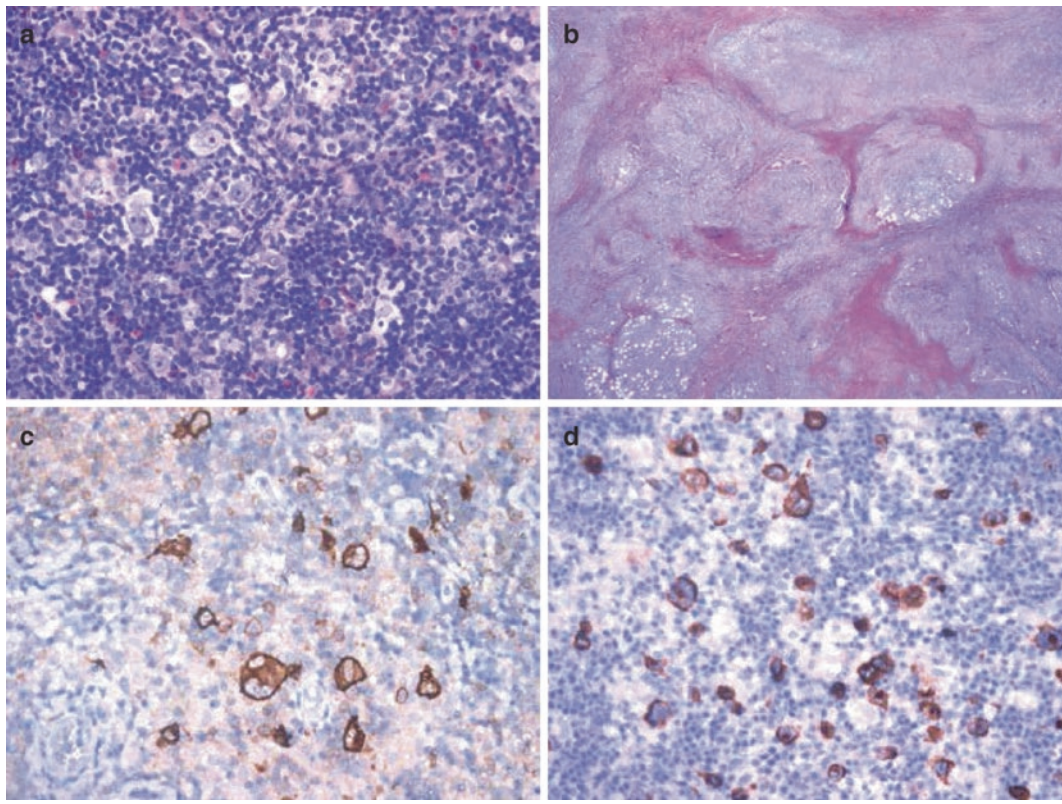

Fig. 3.2 Classical Hodgkin lymphoma (cHL). (**a**) Characteristic Hodgkin and Reed-Sternberg (HRS) cells in a mixed background of small lymphocytes, histiocytes, and eosinophils in a mixed cellularity cHL (MCCHL) (HE, ×400). (**b**) Nodular sclerosis subtype of cHL that demonstrates thick collagen bands surrounding the nodular infiltrates (PAS, ×20). (**c**) CD30 expression in HRS cells (×400). (**d**) Immunohistochemical staining for latent membrane protein 1 (LMP1) shows Epstein-Barr virus (EBV) association of HRS cells (×400)

different parts of the cell membrane. In comparison to CD20 expression, CD79a expression is observed less frequently [12, 13]. An EBV association, either demonstrated by immunohistochemical staining for LMP1 (latent membrane protein 1; Fig. 3.2d) or by EBER in situ hybridization, is found in a significant proportion of cHL, but the frequency varies considerably between different histological subtypes and across geographical areas [1]. Whether cHL cases exist with a *bona fide* derivation from the T cell lineage is currently a matter of debate. Single cases have been reported, in which a T cell receptor rearrangement could be proven in the HRS cells [14, 15], but others argue that such cases might represent only mimics of cHL which are not to be included in a disease entity that—based on fundamental principles of current lymphoma classification schemes—is of B cell derivation [16]. HRS cells reside in a cellular background that varies among the different histological subtypes of cHL which will be discussed in the following sections.

3.1.2.1 Nodular Sclerosis Classical Hodgkin Lymphoma

In NSCHL, affected lymph nodes frequently show a markedly thickened capsule and a nodular infiltrate whereby individual nodules are surrounded by broad collagen bands (Fig. 3.2b). HRS cells are present in a background of small lymphocytes and other nonneoplastic cells such as histiocytes and eosinophils. The number of HRS cells can vary significantly between NSCHL cases and also within a single infiltrated lymph node. Occasionally, HRS cells can form sheets that can be associated with necrosis and an intense fibrohistiocytic reaction. Morphologically, HRS cells in NSCHL often show a retraction artifact of the cytoplasmic membrane that appears to be a consequence of formalin fixation, which has led to the term "lacunar cell variant" of HRS cells. The immunohistochemical phenotype of HRS cells in NSCHL as described above is the classic phenotype; however, association with EBV is less common as compared to other cHL subtypes, especially MCCHL.

3.1.2.2 Mixed Cellularity Classical Hodgkin Lymphoma

HRS cells in MCCHL usually have a classic morphological appearance and are scattered in a background that can contain small lymphocytes, eosinophils, neutrophils, plasma cells, and histiocytes. The infiltration pattern can be diffuse or vaguely nodular; sometimes, the lymph node architecture and especially some B cell areas are partially preserved leading to an interfollicular infiltration pattern. The characteristic features of other histologic cHL subtypes (e.g., the formation of nodular collagen bands) are absent, and, thus, MCCHL is sometimes considered as the "wastebasket" of cHL. The EBV association of HRS cells is the highest among all cHL subtypes and can reach 75% [1].

3.1.2.3 Lymphocyte-Depleted Classical Hodgkin Lymphoma

LDCHL is the rarest histological subtype of cHL (<1% of cases) and probably the most problematic one to define. It is characterized by an increased number of HRS cells present in the infiltrate and/or depletion of small lymphocytes in the nonneoplastic background population. In some cases, HRS cells are of anaplastic appearance, and in other cases, the background is composed of extensive diffuse fibrosis. However, if the pattern of fibrosis is nodular and therefore characteristic of NSCHL, a given case should be classified as NSCHL, regardless of whether there is a high number of HRS cells. Since the definition of LDCHL has changed over the past decades, some of the established clinical and biological features appear outdated in the context of the current definition. Moreover, with the increase in knowledge and the development of additional immunohistochemical markers, some of the cHL cases that were previously assigned to the LDCHL category would nowadays be included into borderline categories or even different entities [1].

3.1.2.4 Lymphocyte-Rich Classical Hodgkin Lymphoma

In LRCHL, the HRS cells are present in a lymphocyte-rich background that can be nodular or, rarely, diffuse. Often, B cell follicles are

partially preserved with recognizable GC, and HRS cells can be found in expanded mantle and marginal zones, thus providing a B cell-rich background. HRS cells in LRCHL may resemble LP cells in LPHL morphologically to such an extent that they are indistinguishable from each other without additional immunohistochemical characterization. It is of significance that eosinophils and neutrophils should be absent from the nodular infiltrates and may only be found in low numbers in interfollicular zones and close to vascular structures. The immunophenotype of the HRS cells is classic, and an EBV association is occasionally observed, though at a lower frequency compared to MCCHL [1].

3.2 Differential Diagnosis

In most instances, the diagnosis of LPHL and cHL is unambiguous on the basis of morphological, clinical, and, especially, immunohistochemical features (Table 3.1). However, a gray area between cHL and diffuse large B cell lymphoma (DLBCL), specifically with primary mediastinal large B cell lymphoma (PMBL), has long been known, and the most recent WHO classification introduced the category of "B cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma" [1]. It is important to note that lymphomas falling into this category are not considered a separate disease entity; rather, it was felt that lymphomas in which there is a discordance between morphological aspects of the infiltrate and the expected immunophenotype should be labeled as "intermediate" to allow a more precise definition of biological and clinical features of these lymphomas in the future. Frequently, these borderline lymphomas present with large mediastinal masses. Morphologically, they consist of large, pleomorphic B cells that grow in a sheet-like pattern in a background of a fibrotic stroma. A subset of the tumor cells may resemble HRS cells, specifically the lacunar variant, and parts of the infiltrate may correspond to the growth pattern of cHL, particularly the nodular sclerosis subtype. Immunophenotypically, there is often a preserved expression program of cHL including expression of CD30 and CD15, while markers of the B cell lineage that are often downregulated in cHL, such as CD20 and CD79a, are equally expressed in the tumor cells [1]. It is important to note that these gray zone lymphomas appear to be more common in male patients, in contrast to NSCHL and PMBL that are more frequent in females [17]. Clinically, these tumors may behave more aggressively than NSCHL and PMBL; it has to be determined in the future whether treatment regimens for aggressive B cell lymphomas or for cHL are more beneficial.

The differential diagnosis between cHL and ALK-negative anaplastic large cell lymphoma (ALCL) of T cell lineage can usually be resolved using an appropriate panel of immunohistochemical markers including T cell, cytotoxic, and other markers. Problems arise when morphological features favor cHL, but tumor cells lack PAX5/BSAP expression while cytotoxic markers are expressed. As discussed above, it is a matter of current debate whether such cases should be grouped into the cHL category or diagnosed as ALCL. Remarkably, a global gene expression study revealed surprisingly few consistent differences in the gene expression of HRS cells and ALK-negative ALCL cells [18].

Finally, EBV-associated lymphoproliferations, e.g., in the context of a coexisting T cell non-HL as well as EBV-associated DLBCL of the elderly, a subgroup of DLBCL introduced in the new WHO classification [1], can harbor HRS or HRS-like cells and therefore mimic cHL [19]. Besides other morphological and immunohistochemical features and information on the clinical setting, the pattern of EBV infection, determined by LMP1 staining or EBER in situ hybridization, might help to distinguish between these tumors.

3.3 Histogenesis of HRS and LP Cells

3.3.1 Cellular Origin of HRS and LP Cells

The unusual immunophenotype of HRS cells, which does not resemble any normal hematopoietic cell, has hampered the identification of the

cellular origin of these cells considerably. Moreover, only few cell lines were available for detailed genetic studies, and the rarity of the HRS cells in the tissue posed a problem for their molecular analysis. Finally, by microdissection of HRS cells from tissue sections and single-cell polymerase chain reaction analysis of these cells, it was clarified that HRS cells derive from B cells in nearly all cases [20, 21]. This is because rearranged immunoglobulin (Ig) heavy (IgH) and light (IgL) chain gene rearrangements were detected in these cells. The detection of identical IgV gene rearrangements in the HRS cells of a given HL case also established the monoclonal nature of these cells, a hallmark of malignant cancer cells. With a few exceptions, somatic mutations were detected in the rearranged V genes of HRS cells [20–23]. As the process of somatic hypermutation, which generates such mutations, is specifically active in antigen-activated mature B cells proliferating in the GC microenvironment in the course of T-dependent immune responses [24], the presence of mutated IgV genes in the HRS cells established their derivation from GC-experienced B cells. A surprising finding was that about 25% of cases of cHL showed destructive IgV gene mutations, such as nonsense mutations or deletions causing frameshifts that rendered originally functional V region genes nonfunctional [20]. When such mutations happen in normal GC B cells, these cells quickly undergo apoptosis. On this basis, it was proposed that HRS cells in these cases derive from pre-apoptotic GC B cells that were rescued from apoptosis because they harbored or acquired some transforming events [20, 25]. It is important to note that crippling mutations, such as those generating premature stop codons, represent only a small fraction of disadvantageous IgV gene mutations that cause apoptotic death of GC B cells, and it is therefore likely that also most or even all other cases of cHL are derived from pre-apoptotic GC B cells. Even a few HL with unmutated IgV genes may derive from these precursors, because GC founder cells proliferating in GC become prone to apoptosis before the onset of somatic hypermutation activity [26]. The GC B cell origin of HRS cells was further supported by the molecular analysis of composite lymphomas, composed of a cHL and a B cell non-HL. Such cases are often clonally related and show an intriguing pattern of shared as well as distinct somatic V gene mutations [27–30]. This pattern supports the assumption that both lymphomas were derived from distinct members of a proliferating GC B cell clone.

A comparison of the transcriptomes of HRS cells and normal GC and extrafollicular $CD30^+$ B cells revealed that HRS cells are in their global gene expression pattern more similar to the normal $CD30^+$ B cells than to bulk GC B cells [31]. However, a direct derivation of HRS cells from $CD30^+$ GC B cells seems unlikely, as $CD30^+$ GC B cells are positively selected GC B cells with functional BCR that are preparing to return to the dark zone of the GC for a further round of proliferation and IgV gene mutation. Perhaps, in the course of their malignant transformation, the HRS cell precursors that managed to escape from apoptosis acquired the gene expression program of the positively selected and proliferation prepared $CD30^+$ GC B cells.

A few cases of cHL appear to originate from T cells, because T cell receptor gene rearrangements were detected in some cases diagnosed as HL and expressing some typical T cell molecules [14, 15]. However, it is debated whether these are true HL (see above). Remarkably, among HL cases with expression of one or more T cell markers, the majority nevertheless derives from B cells [14, 15].

The expression of multiple B cell markers by LP cells of LPHL already indicated a B cell derivation of these cells. Moreover, LP cells express several markers typically expressed by GC B cells, such as BCL6, AID, centerin, and hGAL, and the cells grow in a follicular pattern in close association with typical constituents of normal GC, i.e., follicular dendritic cells and GC-type T helper cells [2, 3, 5, 6, 32, 33]. This pointed to a close relationship between LP cells and GC B cells. This is indeed supported by the detection of clonally related and somatically mutated IgV genes in these cells [21, 34–36]. As opposed to cHL, the V genes are selected for functionality, and a fraction of cases shows ongoing somatic hypermutation during clonal expansion, a hallmark of GC B cells [21, 34, 35]. Thus, these

findings altogether indicate a GC B cell origin of LP cells. A large-scale gene expression profiling of isolated LP cells in comparison to the main subsets of mature B cells has led to a further specification of the derivation of LP cells by showing that the gene expression pattern of LP cells resembles that of GC B cells that have already acquired some features of post-GC memory B cells [37].

3.3.2 Relationship of Hodgkin Cells and Reed-Sternberg Cells and Putative HRS Cell Precursors

The relationship of the mononucleated Hodgkin cells to the multinuclear RS cells and the potential existence of HRS precursor cells has been a matter of debate. Based on the "mixed" phenotype of HRS cells and many numerical chromosomal aberrations in these cells, it has been speculated that HRS cells as such or, specifically, the RS cells may derive from cell fusions of different cells (e.g., a B cell and a non-B cell). However, a detailed study of antigen receptor loci revealed that HRS cells do not carry more than two different alleles of these loci, which strongly supports the assumption that these cells do not derive from cell fusions [38]. Several studies of HL cell lines showed that the mononuclear Hodgkin cells give rise to the RS cells and that the latter have little proliferative activity [39–41]. Long-term time lapse-microscopy analyses revealed that mononucleated Hodgkin cells undergo incomplete cytokinesis and refusion to give rise to the multinucleated RS cells [42, 43].

Two studies reported the existence of a small subpopulation of side population cells among the mononuclear Hodgkin cells. Side population cells extrude the Hoechst dye, because they express multidrug transporters, such as MDR1 and/or ABCG2. In several types of cancers, there is an overlap between side population cells and cancer stem cells. Side population cells of cHL cell lines were $CD30^{+}CD20^{-}$ and showed increased resistance against chemotherapeutic drugs [44, 45]. However, it has not yet been determined whether they have a higher capacity to sustain the HRS cell clone in long term than other mononuclear Hodgkin cells, and the fact that side population cells were not identified in all cHL cell lines analyzed argues against an essential role of these cells for the survival of the HRS cell clone.

Another debated issue relates to the question whether the $CD30^{+}$ typical HRS cells represent the entire tumor clone in HL or whether members of the HRS cell clones exist among small $CD30^{-}$ cells. An initial study for numerical chromosomal abnormalities indeed suggested that such $CD30^{-}$ clone members might exist [46]. However, trisomies of chromosomes as studied in that work are not a stringent clonal marker. Moreover, a molecular analysis of EBV-positive HL cases for members of the malignant clones among small, $CD30^{-}$ EBV^{+} B cells in the HL lymph nodes suggested that the small EBV^{+} B cells rarely, if at all, belong to the HRS cell clones [47]. Two HL cell lines were reported to contain small subpopulations of $CD20^{+}CD30^{-}Ig^{+}$ B cells coexpressing the stem cell marker aldehyde dehydrogenase (ALDH) [48]. These cells had clonogenic potential and gave rise to the typical HRS cells of these lines. It is important to note that $ALDH^{high}$ cells were also detectable in the peripheral blood of most HL patients, and it was reported that these cells were often clonally related to the HRS cells [48]. However, the clonal relationship between the HRS cells and $ALDH^{high}$ peripheral blood B cells was not clearly shown [49], so it remains to be clarified whether $ALDH^{high}$ B cells indeed represent precursors of the HRS cell clones. A previous study using a highly sensitive PCR for HRS cell-specific Ig gene rearrangements failed to detect members of the HRS cell clone in the peripheral blood or bone marrow of two HL patients [50].

3.4 Genetic Lesions

HRS cells have a much higher number of chromosomal aberrations, including multiple numerical as well as structural abnormalities, than most other lymphomas [51]. However, it is still unclear

whether this is mostly a side effect of some type of genetic instability and whether the expression of specific oncogenes or tumor suppressor genes is recurrently affected by these lesions. When the B cell origin of HRS cells became clear, HRS cells were studied for the presence of chromosomal translocations involving the Ig loci, as such translocations are a hallmark of many B cell lymphomas. Fluorescence in situ hybridization (FISH) studies indeed provided evidence for such translocations in about 20% of cases, but most of the translocation partners involved remain to be identified [52, 53]. In a few cases, the translocation partners were *BCL2*, *BCL3*, *REL*, *BCL6*, or *MYC* [52–55]. Recurrent translocations affecting the major histocompatibility complex (MHC) class II transactivator (*MHC2TA*) were detected in about 15% of cHL cases [56]. These translocations appear to cause downregulation of MHC class II expression by HRS cells. In LPHL, translocations of the *BCL6* gene have been found in about 30% of cases [57, 58]. These translocations can involve the Ig loci, but also multiple other partners [59].

Due to the difficulty to analyze the few HRS and LP cells for mutations in oncogenes and tumor suppressor genes, only relatively few of such genes have been analyzed so far in these cells. There was a major interest to understand the apoptosis resistance of HRS cells, but it turned out that mutations in the *CD95* gene, an important death receptor, as well as in members of the CD95 signaling pathway (FADD, caspase 8, caspase 10) were rare or not found at all [60–62]. Likewise, no mutations were found in the BCL2 family member *BAD*, and also *ATM* lesions are very rare [63–65]. The *TP53* tumor suppressor gene was mutated in less than 10% of cases where the exons of *TP53* usually carrying mutations were studied in isolated HRS cells [66, 67]. However, studies of HL cell lines indicate that HRS cells may additionally carry untypical *TP53* mutations and that the frequency of *TP53* mutations may therefore be higher than previously thought [68]. MDM2, a negative regulator of TP53, frequently shows gains in HRS cells, which might contribute to impaired functions of TP53 in these cells [69].

Further candidate gene mutation studies revealed frequent mutations in the exportin 1 gene (*XPO1*) [70], which encodes a nuclear expert receptor for numerous RNAs and proteins, and inactivating mutations in and deletions of *CD58* [71, 72]. CD58 is important for targeting of cells by cytotoxic T cells and NK cells, so that CD58 inactivation may contribute to immune escape of HRS cells from an attack by these cells.

HRS cells show constitutive activity of the NF-κB transcription factor (see below), which is essential for the survival of these cells. The mechanisms of this activation were originally not understood. Consequently, members and regulators of this signaling pathway were studied for genetic lesions (Table 3.1). Inactivating mutations in the main NF-κB inhibitor NFKBIA (IκBα) were found in about 10–20% of HL cases and also in several HL cell lines (Fig. 3.3) [73–76]. Recurrent mutations were also detected in another NF-κB inhibitor, NFKBIE (IκBε) [77, 78]. Inactivating mutations or deletions in two further negative regulators of NF-κB signaling, CYLD and TRAF3, have also been detected in HL cell lines and a few primary cases, but overall these events are rare [79, 80]. Moreover, HRS cells frequently harbor genomic gains or amplifications of the *REL* gene [81–83], encoding an NF-κB family member, and a correlation between such gains and strong REL protein expression was found [84]. The *MAP3K14* gene, which encodes the NIK kinase, a major activating component of the alternative NF-κB pathway, shows gains or amplifications in about 15% of cHL [79, 85]. Also the IκB family member BCL3, which acts as a positive regulator of NF-κB activity, is affected by chromosomal gains or translocations in a small fraction of cHL [86, 87]. Somatic and clonal inactivating mutations were found in the *TNFAIP3* gene in about 40% of cHL [88, 89]. *TNFAIP3* encodes for the A20 protein, which is a dual ubiquitinase and deubiquitinase that functions as a negative regulator of NF-κB. It inhibits signaling from the receptor-interacting protein (RIP) and TNF receptor-associated factors (TRAFs) to the IKK kinases, which are essential mediators of NF-κB signaling. *TNFAIP3* mutations were mainly found in EBV-negative cases.

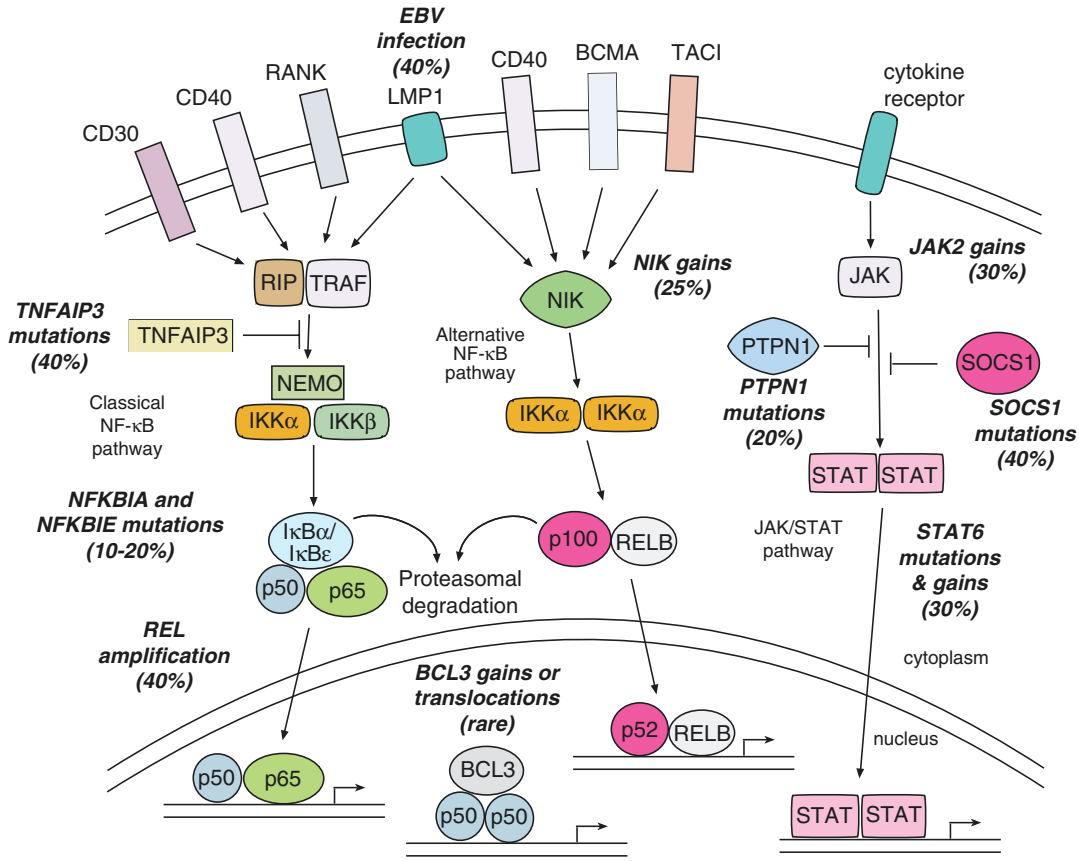

Fig. 3.3 NF-κB and JAK/STAT activity in HRS cells. In the classical NF-κB signaling pathway, stimulation of numerous receptors leads via TNF receptor-associated factors (TRAFs), which are often associated with the receptor-interacting protein (RIP), to activation of the IKK complex, which is composed of IKKα, IKKβ, and NEMO. The IKK complex subsequently phosphorylates the NF-κB inhibitors IκBα and IκBε. This marks them for ubiquitination and subsequent proteasomal degradation. Thereby the NF-κB transcription factors (p50/p65 or p50/REL heterodimers) are no longer retained in the cytoplasm and translocate into the nucleus, where they activate multiple genes. The signal transduction from TRAFs/RIP to the IKK complex can be inhibited by TNFAIP3, which removes activating ubiquitins from RIP and TRAFs and additionally links ubiquitins to these molecules to mark them for proteasomal degradation. In the alternative NF-κB pathway, activation of receptors such as CD40, BCMA, and TACI causes stimulation of the kinase NIK, which then activates an IKKα complex. Activated IKKα processes p100 precursors to p52 molecules, which translocate as active p52/RELB NF-κB heterodimers into the nucleus. HRS cells show constitutive activity of the classical and alternative NF-κB signaling pathway. This activity is probably mediated by diverse mechanisms, including receptor signaling through CD40, RANK, BCMA, and TACI; genomic *REL* and *MAP3K14* (NIK) amplification; destructive mutations in the *TNFAIP3*, *NFKBIA*, and *NFKBIE* genes; and signaling through the EBV-encoded LMP1. The role of CD30 signaling in HRS cells is controversially discussed. HRS cells may also harbor nuclear BCL3/$(p50)_2$ complexes, and in a few cases, the strong BCL3 expression appears to be mediated by genomic gains or chromosomal translocations. The JAK/STAT pathway is the main signaling pathway for cytokines. Upon binding of cytokines to their receptors, members of the JAK kinase family become activated by phosphorylation. The activated JAKs then phosphorylate and thereby activate STAT transcription factors. These phosphorylated factors homo- or heterodimerize and translocate into the nucleus where they activate target genes. Main inhibitors of the JAK/STAT pathway are the phosphatase PTPN1 and SOCS (suppressor of cytokine signaling) factors, which function by binding to JAK molecules and inhibiting their enzymatic activity and additionally by inducing proteasomal JAK degradation. In HRS cells, STAT3, 5, and 6 are constitutively active. Besides activation of cytokine receptors (e.g., IL13 receptor and IL21 receptor) through cytokines, activation of this pathway is mediated by genomic gains or rare translocations of the *JAK2* gene, activating mutations in the *STAT6* gene, and frequent inactivating mutations in the *SOCS1* and *PTPN1* gene. The frequency of genetic lesions and viral infections affecting NF-κB or STAT activity in cHL cases is indicated

Nearly 70% of EBV⁻ cases carried *TNFAIP3* mutations, indicating that EBV infection and A20 inactivation are alternative pathogenetic mechanisms in HL [88, 89]. As LMP1 of EBV, which is expressed in EBV-positive HRS cells, mimics an active CD40 receptor and signals through NF-κB [90, 91], LMP1 may replace the role of A20 inactivation in EBV⁺ HL.

As it was recently revealed that also the LP cells of LPHL show strong constitutive NF-κB activity [37], also these cells were studied for mutations in *NFKBIA* and *TNFAIP3*, but clonal destructive mutations were not found (Table 3.1) [92].

Genetic lesions were also found in members of the JAK/STAT pathway, which is constitutively activated in HRS and LP cells. In about 40% of cases analyzed, both HRS and LP cells showed somatic mutations in the *SOCS1* gene, which encodes a main inhibitor of STAT signaling (Fig. 3.3) [93, 94]. In HRS cells, recurrent mutations were additionally found in the gene of another negative regulator of JAK/STAT signaling, namely, the *PTPN1* gene, which encodes a phosphatase [95]. Furthermore, a fraction of cHL cases show genomic gains or amplifications of the *JAK2* locus, which encodes one of the kinases activating the STAT factors (Table 3.1) [82, 96]. Importantly, the genomic gains at 9p24 do not only affect the *JAK2* locus, but additionally the *PD-L1*, *PD-L2*, and *JMJD2C* genes [97, 98]. PD-L1 and PD-L2 are inhibitory receptors for PD1-positive T cells and may hence inhibit a cytotoxic T cell attack on HRS cells. *JMJD2C* encodes a histone demethylase and plays a role in the epigenetic remodeling of HRS cells. Finally, the *JAK2* gene is in rare instances also deregulated by chromosomal translocations [99]. Activating point mutations in the *STAT6* gene and genomic gains involving this gene were also detected in HRS cells [10, 100]. Thus, multiple types of genetic lesions cause a constitutive JAK/STAT signaling, suggesting an essential role of its deregulated activity for cHL pathogenesis.

With the availability of high-throughput sequencing methods, tumor cells can now be studied for genetic lesions at a genome-wide level. An exome sequencing analysis of six cHL lines and the only LPHL cell line (DEV) revealed over 400 genes mutated in at least two of the lines [8]. This is a valuable database that should be considered when performing functional studies with these cell lines. A first whole exome sequencing study of primary HRS cells used flow-cytometry isolated lymphoma cell from ten cases of cHL [9]. Between 100 and 500 somatic mutations were found per case. A main finding of this analysis was recurrent inactivating mutations in the *B2M* gene. B2M is essential for MHC class I expression, so that the loss of its expression presumably leads to immune evasion from CD8⁺ cytotoxic T cells. Other novel recurrent mutations identified in that work affect several histone genes, the inositol-trisphosphate 3-kinase B (ITPKB), the B cell transcription factor EBF1, and the G protein subunit GNA13 [9]. Tiacci and colleagues performed a whole exome sequencing analysis of pools of HRS cells microdissected from 34 cases of cHL [10]. A median of 47 non-silent somatic mutations in the exomes was found. This study confirmed recurrent mutations in *ITPKB* and *GNA13*, and newly revealed recurrent point mutations in *STAT6*, further adding to the complexity of JAK/STAT deregulation in cHL. Although only four EBV⁺ cases were included in the study by Tiacci et al., it seems that such cases carry considerably fewer somatic mutations than the EBV-negative cases. A mutation study of LP cells of LPHL was based on a whole genome analysis of DLBCL clonally related to LPHL in the same patient, followed by targeted sequencing analysis of microdissected LP cells. In this work, three genes were found to be each mutated in about half of the cases of LPHL (also in cases without co-occurring DLBCL), namely, the genes encoding the kinase SGK1, the AP-1 family member JUNB, and the phosphatase DUSP2 [101].

3.5 Deregulated Transcription Factor Networks and Signaling Pathways

3.5.1 The Lost B Cell Phenotype

Early immunohistochemical studies already revealed that HRS cells usually do not express typical B cell markers, such as CD20, CD79b, or

the BCR [13, 102–104]. This lack of expression of B cell markers was indeed one of the reasons why the B cell origin of HRS cells was not revealed until genetic studies for Ig gene rearrangements unequivocally demonstrated a B cell identity of these cells (see above). Gene expression profiling studies of HRS cells in comparison to normal B cells then showed that there is a global loss of the B cell typical gene expression in HRS cells [105]. This downregulation involved all types of genes with important functions in these cells, for example, cell surface receptors (CD37, CD53), components of signaling pathways (SYK, BLK, SLP-65), and transcription factors (PU.B, A-MYB, SPI-B). As plasma cells also show a downregulation of many B cell-typical genes, it had been speculated that HRS cells lost their B cell gene expression and acquired a partial plasma cell differentiation program [2, 106]. However, a gene expression profiling study of microdissected HRS cells revealed that HRS cells have not acquired a plasma cell phenotype [107].

Remarkably, HRS cells have retained expression of molecules that are involved in antigen-presenting functions and the interaction with $CD4^+$ T helper cells. HRS cells usually express CD40, CD80, and CD86 and often MHC class II [105, 108]. This indicates that an interaction with T helper cells is important for HRS cell survival. In line with this view, HRS cells are typically surrounded by CD40L expressing $CD4^+$ T cells [109].

We are now beginning to understand which factors contribute to the lost B cell phenotype of HRS cells. First, several transcription factors that positively regulate the expression of multiple genes in B cells are downregulated, including OCT-2, PU.1, EBF1, ETS1, and BOB.1 [102, 103, 110–112]. The downregulation of ETS1 may often be due to heterozygous deletions of the gene, which have been observed in over 60% of cHL analyzed [112]. Second, although E2A, a master regulator of the B cell transcription program, is still expressed, HRS cells also show deregulated expression of ID2 and ABF1 [113–115], which bind to E2A and inhibit its function [114]. The physiological role of ABF1 is poorly understood, but ID2 is normally expressed in dendritic cells and natural killer cells, and supports the generation of these cells concomitant with suppression of B cell development [116, 117]. Third, HRS cells express activated NOTCH1, which normally induces T cell differentiation in lymphocyte precursors and suppresses a B lineage differentiation of such cells [118, 119]. Activation of NOTCH1 is probably caused by interaction with its ligand Jagged-1, which is expressed by other cells in the HL microenvironment [119], and by high-level expression of the NOTCH coactivator mastermind-like 2 (MAML2) [120]. Moreover, HRS cells have downregulated the NOTCH1 inhibitor Deltex1 [118]. Fourth, STAT5A and STAT5B are activated in HRS cells and have been reported to induce an HRS cell-like phenotype in normal B cells [121]. Constitutive active STAT5 induced expression of CD30 and of the T cell transcription factor GATA3 in the B cells and led to downregulation of BCR expression. Aberrant GATA3 expression in HRS cells is furthermore mediated by NOTCH1 and NF-κB activity in HRS cells [122]. Fifth, the downregulation of multiple B cell genes in HRS cells is further caused by epigenetic mechanisms, as DNA methylation has been detected for numerous such genes [123–125]. Sixth, HRS cells express several transcription factors that have important roles in hematopoietic stem cells and early lymphoid precursors, including GATA2, BMI1, RING1, and RYBP [126–129]. The expression of these factors may contribute to a "dedifferentiated" phenotype of HRS cells.

Surprisingly, PAX5, the main B lineage commitment and maintenance factor, is still expressed in HRS cells, albeit at reduced levels [11]. As many of its direct target genes are not expressed, it is likely that PAX5 activity is inhibited. NOTCH1 is a candidate for this inhibition [118]. It may also be that PAX5 target genes are not expressed because other transcription factors needed for the efficient expression of these genes are missing.

Expression of the myeloid specific colony-stimulating factor 1 receptor (CSF1R) by HRS cells is a further important example of aberrant

expression of a non-B cell gene in HRS cells [130]. CSF1R expression promotes HRS cell survival. The mechanism of its deregulated expression is remarkable, because this is mediated by derepression of an endogenous long terminal repeat upstream of the *CSF1R* gene that replaces the function of the normal CSF1R promoter [130].

The downregulation of many B cell transcription factors that also suppress the expression of non-B lineage genes, combined with the upregulated expression of genes promoting expression of genes of other hematopoietic cell types (e.g., NOTCH1, ID2), not only explains the lost B cell phenotype of HRS cells but also the heterogeneous expression of genes specifically expressed by dendritic cells, T cells, or other cell types. It is an intriguing question whether the lost B cell phenotype of HRS cells is related to their origin from crippled GC B cells. Perhaps, due to the stringent selection of B cells for expression of a functional BCR (a high-affinity one in the GC), there is a selection in HRS cell pathogenesis downregulating the B cell gene expression program to escape the selection forces that induce apoptosis in GC B cells with unfavorable IgV gene mutations. The observation that enforced re-expression of the B cell transcription factors PU.1, FOXO1, or E2A or the pharmacological restoration of the B cell phenotype in HL cell lines induces apoptosis is in line with this view [131–134]. However, the lost B cell phenotype could also be a side effect of so far unknown transforming events.

3.5.2 Constitutive Activation of Multiple Signaling Pathways

It is obvious that tumor cells need to activate and deregulate signaling pathways and transcription factors that promote their survival and proliferation. Nevertheless, it is striking how many of such pathways are constitutively activated in HRS cells, and cHL appears to be rather unique among lymphoid malignancies in the extent to which multiple signaling pathways contribute to the survival and expansion of HRS cells. It has already been mentioned above that HRS cells show constitutive NF-κB activity. This activity is essential for HRS cell survival [135] and is most likely not only mediated by genetic lesions (see above) but also by signaling through receptors. NF-κB factors of both the canonical pathway (p50/p65) and the noncanonical NF-κB pathway (p52/RelB) are activated (Fig. 3.3). HRS cells express the TNF receptor family members CD30, CD40, RANK, TACI, and BCMA, which activate NF-κB, and cells expressing the respective ligands are found in the HL microenvironment [109, 136–140]. There are, however, conflicting data about the role of CD30 in NF-κB activation [141, 142]. In EBV-positive cases of cHL, the virally encoded LMP1 mimics an active CD40 receptor and hence also contributes to NF-κB activation [143].

Another central signaling pathway, which is like NF-κB activated both by genetic lesions and by ligand-mediated receptor triggering, is the JAK/STAT pathway (Fig. 3.3). This is the main signaling pathway for cytokines. Activation of cytokine receptors causes activation of JAK kinases which in turn phosphorylate and thereby activate STAT transcription factors. The phosphorylated STAT factors dimerize and then translocate into the nucleus where they activate transcription of target genes. HRS cells show activation of STAT3, STAT5, and STAT6 [121, 144–146]. The activation of STAT6 is at least partly mediated by signaling through IL13. As HRS cells express IL13 and its receptor, STAT6 activation can be mediated through an autocrine stimulation loop [147, 148]. Signaling through the IL21 receptor contributes to STAT3 and STAT5 activation in HRS cells, which is also enhanced by the NF-κB activity in the cells [121, 149, 150]. As mentioned above, STAT5 activity may contribute to the lost B cell phenotype of HRS cells. Inhibition of STAT activity in HL cell lines resulted in reduced proliferation of the cells, further supporting an important pathogenetic role of this signaling pathway [144, 145, 147].

Receptor tyrosine kinases (RTKs) are important regulators of cell growth, survival, and proliferation. In multiple cancers, specific RTKs are

activated, often by somatic mutations [151]. In contrast, HRS cells show multiple activated RTKs, and their activation does not appear to be due to activating mutations but at least partly to ligand-mediated stimulation [152]. RTKs that are often expressed in varying combinations in HRS cells include PDGFRA, DDR2, EPHB1, RON, TRKA, TRKB, CSF1R, and MET [130, 152, 153]. The expression of most of these is aberrant, as they are not expressed by normal GC B cells [130, 152]. They are also usually not expressed by other B cell non-HL, showing that this is a specific feature of HL among B cell lymphomas [152, 154]. Expression of multiple RTKs is most pronounced in EBV-negative cases of cHL, suggesting that EBV activates pathways in HRS cells replacing the function of RTKs [155]. For PDGFRA, TRKA, and CSF1R, a growth-inhibitory effect has been shown upon their inhibition in HL cell lines, giving a first indication that the activity of RTKs is important for HRS cell proliferation [130, 152, 156].

Signaling through various receptors is mediated by the mitogen-activated protein kinase (MAPK)/ERK pathway. In HRS cells, the serine/threonine kinases ERK1, ERK2, and ERK5 are activated [157, 158]. Inhibition of their activity has antiproliferative effects on HL cell lines [158]. Signaling through CD30, CD40, and RANK may contribute to the stimulation of this pathway [158].

The transcription factor AP-1 acts as homo- or heterodimers of JUN, FOS, and ATF components. In HRS cells, JUN and JUNB are overexpressed and constitutively active [159]. The overexpression of JUNB is mediated by NF-κB [159]. AP-1 induces many target genes and promotes proliferation of HRS cells. Target genes of AP-1 include CD30 and galectin-1, the latter of which has immunomodulatory functions [160, 161]. HRS cells also show strong expression of BATF3, another member of the AP-1 transcription factor family [162, 163]. BATF3 expression is induced by STAT3 and STAT6 in HRS cells. It forms heterodimers with JUN and JUNB, and the proto-oncogene MYC was identified as one of the direct BATF3 target genes [162]. Importantly, downregulation of BATF3 in HL cell lines is toxic for these cells, revealing an essential role of this factor in cHL pathophysiology [162].

Finally, also the phosphatidylinositol 3-kinase (PI3K)/AKT pathway, which is a main promoter of cell survival, shows activity in HRS cells [164, 165]. AKT is a serine/threonine kinase that is activated in HRS cells, as evident from its phosphorylated state and phosphorylation of known target proteins [164, 165]. Inhibition of AKT in HL cell lines causes cell death, suggesting an important role of active AKT in HRS cell survival [164, 165]. PI3K may be activated in HRS cells by signaling through CD30, CD40, RANK, and RTK. Moreover, downregulation of the AKT inhibitor INPP5D in HRS cells may further contribute to strong AKT activity in these cells [107].

While we have a relatively detailed insight into signaling pathways active in HRS cells, less is known about signaling pathways constitutively active in LP cells of LPHL. However, LP cells also show a high constitutive activity of NF-κB [37]. RTKs are partly also aberrantly expressed by these cells [152], and activation of the JAK/STAT pathway has been observed [93].

In conclusion, HRS cells are characterized by the deregulated and constitutive activation of multiple signaling pathways and transcription factors that contribute to the survival and proliferation of these cells. The multitude of different stimulated pathways appears to be rather unique among human B cell lymphomas. Often, these pathways are activated by common mechanisms, and they may interact in numerous ways.

3.6 Anti-apoptotic Mechanisms

With a presumed origin from pre-apoptotic GC B cells, it is critical to understand through which mechanisms HRS cells escape from apoptosis. A number of factors contributing to HRS cell survival have already been discussed in the previous section: constitutive activity of NF-κB, STAT, PI3K, NOTCH1, AP-1, RTK, and ERK. Several specific inhibitors of the two main apoptosis pathways deserve specific mentioning. Although HRS cells express the CD95 death receptor of the extrinsic apoptosis pathway as well as its

activating ligand, HL cell lines are resistant to CD95-mediated death induction, suggesting a specific inhibition of this pathway [166–168]. As mentioned above, this resistance is neither due to mutations in the CD95 receptor itself nor in its interaction partners FADD, caspase 8, or caspase 10. However, HRS cells show strong expression of the CD95 inhibitor CFLAR (previously known as cFLIP, cellular FADD-like interleukin 1b-converting enzyme-inhibitory protein), and this factor impairs CD95 signaling in HRS cells [166, 167]. Inhibition of the intrinsic (mitochondrial) apoptosis pathway is probably mediated through strong expression of the anti-apoptotic factors BCLXL and XIAP (X-linked inhibitor of apoptosis) and downregulation of the pro-apoptotic factor BIK [107, 169, 170]. BCLXL inhibits apoptosis at the level of the mitochondrial apoptosis induction, whereas XIAP inhibits activity of caspases 3 and 9, which are downstream executioners of the mitochondrial apoptosis program. Although HRS cells also express pro-apoptotic SMAC, which can inhibit XIAP, the cells show an impaired release of SMAC from the mitochondria into the cytoplasm [171]. As mentioned above, HRS cells express high levels of the pro-apoptotic TP53 factor, but resistance to TP53-mediated apoptosis appears to be rarely due to inactivating mutations in the TP53 gene. An important factor for the inhibition of TP53 activity is MDM2, which is expressed at high levels in HRS cells [172]. The functional role of MDM2 as a TP53 inhibitor in HRS cells is supported by the fact that HL cell lines expressing wild-type TP53 are rendered apoptosis-sensitive toward pharmacological apoptosis inducers upon inhibition of MDM2 by its antagonist nutlin 3 [173, 174].

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4 Microenvironment, Cross-Talk, and Immune Escape Mechanisms

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_4

4.1 Microenvironment

4.1.1 Hodgkin Lymphoma Subtypes

When discussing the microenvironment in Hodgkin lymphoma (HL), it is important to recognize the different HL subtypes described by the WHO classification [1, 2]. The classical HL (cHL) subtypes are defined in large part by the composition of the reactive infiltrate (Table 4.1). The most prevalent subtype is the nodular sclerosis type that consists of a nodular background with thick fibrotic bands, usually with a thickened lymph node capsule. In addition to the lacunar type of Hodgkin/Reed-Sternberg (HRS) cells, there is a microenvironment consisting of T cells, eosinophils, and histiocytes, with a variable admixture of neutrophils, plasma cells, fibroblasts, and mast cells. The second most common subtype is mixed cellularity, which is defined by the presence of typical HRS cells and a diffuse infiltrate of T cells, eosinophils, histiocytes, and plasma cells, sometimes with the formation of granuloma-like clusters or granulomas (Fig. 4.1). Lymphocyte-rich cHL also comprises typical HRS cells in a nodular or diffuse microenvironment and small B and/or T lymphocytes dominating the background, sometimes with admixture of histiocytes. Granulocytes are not present in this subtype. The rare lymphocyte-depleted subtype harbors a high percentage of HRS cells in a background consisting of fibroblasts and a low number of T cells. Nodular lymphocyte predominance (NLP) HL is an entity that is fundamentally different from cHL. The morphology may closely resemble that of the nodular variant of the classical lymphocyte-rich subtype, both involving follicular areas with many small B cells, but NLPHL can also show other growth patterns [3]. The characteristics of the tumor cells and the T cells in NLPHL are different from cHL. HRS cells show a loss of B cell phenotype, while in NLPHL the lymphocyte-predominant (LP) tumor cells share many markers with germinal center B cells. The T cells in cHL have features of paracortical T cells, while those in NLPHL are similar to germinal center T cells (T follicular helper cells) [4–6].

4.1.2 Epstein-Barr Virus

The presence of latent Epstein-Barr virus (EBV) genomes in HRS cells appears to influence the composition of the microenvironment. Positive EBV status is strongly associated with the mixed

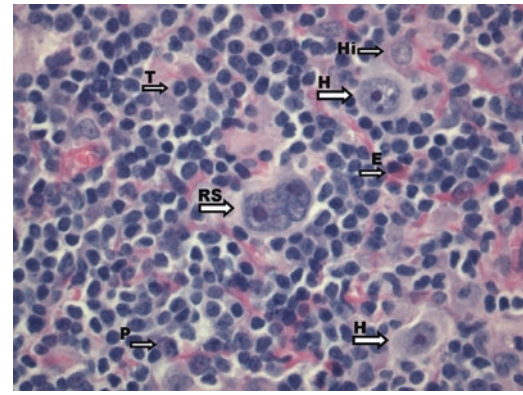

Fig. 4.1 The microenvironment in mixed cellularity classical Hodgkin lymphoma. *RS* classical Reed-Sternberg cell, *H* mononuclear Hodgkin tumor cell, *T* T lymphocyte, *Hi* histiocyte, *E* eosinophil, *P* plasma cell. Hematoxylin and eosin staining

Table 4.1 Composition of the microenvironment in different Hodgkin lymphoma (HL) subtypes

Subtype	EBV (%)	Background	T cells	Other cells
Nodular sclerosis	10–40	Nodular + fibrosis	CD4 > CD8, Th2, Treg > Th1	Eosinophils, histiocytes, fibroblasts, B cells, mast cells (neutrophils)
Mixed cellularity	75	Diffuse	CD4 > CD8, Th2, Treg > Th1	Eosinophils, histiocytes, plasma cells, B cells
Lymphocyte rich	40–80	Nodular or diffuse	CD4 > CD8	Histiocytes
Lymphocyte depleted (including HIV+)	80–100	Diffuse	–	Fibroblasts
Nodular lymphocyte predominant	~2	Nodular (+diffuse)	Th2, PD1+/CD57+ Tfh, CD4+/8+	Histiocytes, B cells

cellularity subtype (~75% EBV-positive) and is almost always absent in NLPHL [7]. Depending on the geographic locale, EBV is present in the HRS cells in 10–40% in nodular sclerosis cases. The percentage of EBV-positive lymphocyte-rich cHL cases is not very clear, but is probably between 40% and 80%. EBV infects more than 90% of the world population and establishes a lifelong latent infection in B cells in its host. Potent cytotoxic immune responses keep the number of EBV-infected B cells at approximately 1/100,000 and usually prevents EBV-driven malignant transformation in immunocompetent individuals. Accordingly, EBV-positive cHL cases contain slightly more CD8+ cytotoxic T cells in the reactive background compared to EBV-negative cHL cases [8].

4.1.3 Human Immunodeficiency Virus

In patients with an impaired immune response, cHL occurs more frequently. After solid organ transplantation, there is a small increase in the incidence of cHL that can largely be attributed to EBV-positive cHL. Human immunodeficiency virus (HIV)-infected individuals have an approximate 10 times increased risk of developing cHL [9]. In comparison to non-HIV-associated cHL, these tumors are more often EBV-associated, mixed cellularity and lymphocyte depletion subtypes, and usually contain more tumor cells. This may reflect a functional defect in the immune response, in particular to EBV, presumably caused by the impairment of CD4+ T cells by HIV. On the other hand, the importance of CD4+ T cells for supporting the growth of HRS cells is also illustrated in HIV-positive patients, in which an increase in the incidence of HIV-associated cHL has been observed after introduction of highly active antiretroviral therapy (HAART) [10].

4.1.4 T Cell Subsets in cHL

A unifying feature of the reactive infiltrate in virtually all cHL subtypes is the presence of large numbers of CD4+ T cells. Besides being widely distributed in the background, these CD4+ T cells form a tight rosette around the tumor cells. T cells within these rosettes often have a distinct phenotype, which is different from the phenotype of the T cells that are located further away from the cHL tumor cells (Fig. 4.2).

In general, CD4+ T cells are divided into naive (CD45RA+) and memory (CD45RO+) subsets based on whether they have previously been stimulated by an antigen or not. A large subset of CD4+ T cells consists of the so-called helper T (Th) cells; these cells play an important role in helping other cells to induce an effective immune response. Th cells can be further divided into Th0 (naive), Th1 (cellular response), Th2 (humoral response), Th17 (IL-17 producing), and Treg (regulating responses of other cells) cells. The Treg cells can be further divided into Th3 (transforming growth factor-β (TGF-β) producing), Tr1 (IL-10 producing), and CD4+CD25+ Treg (originating from the thymus) subpopulations. Some, but not all, Treg cells express the transcription factor FoxP3.

The T cells in cHL consist mainly of CD4+ T cells that have a memory phenotype (CD45RO+) and express several activation markers including CD28, CD38, CD69, CD71, CD25, and HLA-DR, as well as markers like CD28, CTLA-4, and CD40L. However, these T cells lack expression of CD26 [11]. This lack of CD26 expression is most striking in the areas surrounding the tumor cells. CD26, dipeptidyl peptidase IV, regulates proteolytic processing of several chemokines, e.g., CCL5 (Rantes), CCL11 (Eotaxin), and CCL22 (MDC) [12]. CD26 is also associated with adenosine deaminase (ADA) and CD45RO and when interacting with anti-CD26 antibodies leads to enhanced T cell activation through triggering of the T cell receptor [13]. CD26 is preferentially expressed on CD4+CD45RO+ cells and is normally upregulated after activation. However, CD26 cannot be upregulated by ex vivo activation of the CD26-negative cells from cHL lesions. In general, a high CD26 expression level correlates with a Th1 subtype.

The transcription factor expression pattern indicates that the CD4+ T cells in cHL are predominantly Th2 (c-Maf) and Treg (FoxP3) [4, 14].

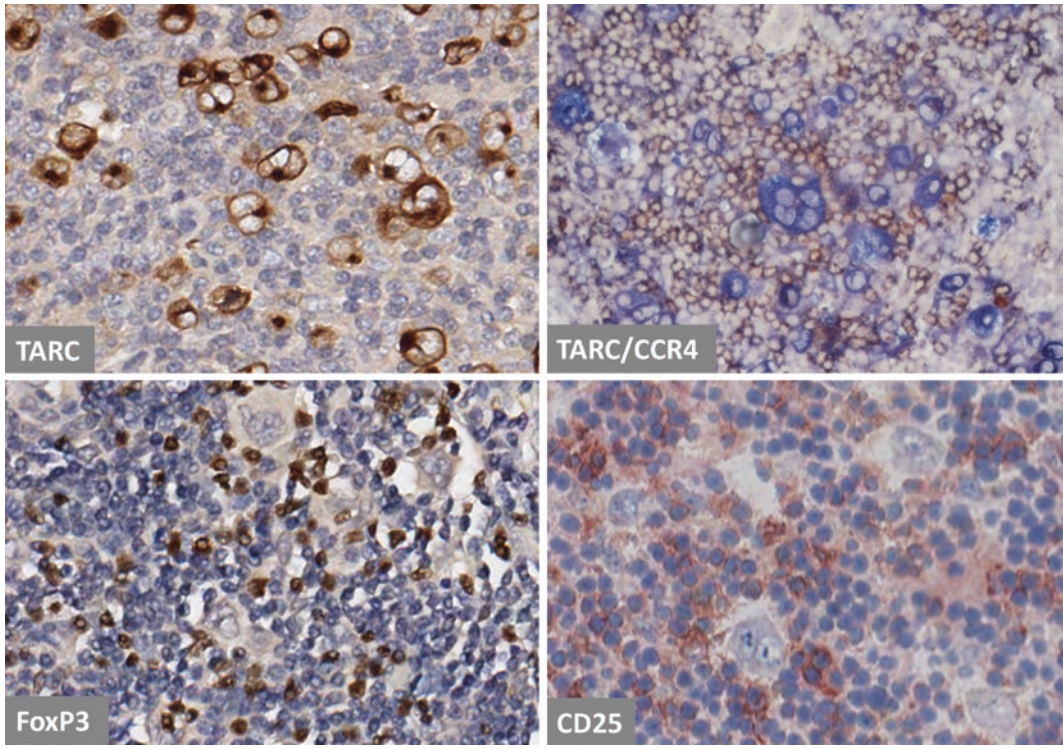

Fig. 4.2 Shaping the microenvironment in classical Hodgkin lymphoma (HL). Immunohistochemistry of classical HL cases. In the upper panel left, strong and specific staining of Hodgkin/Reed-Sternberg (HRS) cells for chemokine CCL17 (TARC). This chemokine attracts CCR4+ lymphocytes (upper panel right). A large proportion of reactive T cells are Treg cells, as shown by positive staining for transcription factor FoxP3 (lower panel left) and activation marker CD25 (lower panel right)

The CD4+CD26− T cell subset in cHL has reduced mRNA levels of Th1- and Th2-associated cytokines in comparison to the CD4+CD26+ T cells from cHL and CD4+ T cells (both CD26− and CD26+) in reactive lymph nodes [15]. Based on much higher mRNA expression levels of IL-2RA (CD25), CCR4, FoxP3, CTLA4, TNFRSF4 (OX-40), and TNFRSF18 (GITR) observed in the CD4+CD26− T cells from cHL, it has been postulated that these cells have a Treg phenotype (Fig. 4.2). In addition, mildly enhanced IL-17 levels can be observed both in CD4+CD26− and CD4+CD26+ T cells from cHL in comparison to the T cells from tonsil. Upon stimulation, the CD4+CD26− T cells fail to induce expression of cytokines, suggesting that the T cell population rosetting around the HRS cells or located in the direct vicinity of the HRS cells have an anergic phenotype (i.e., do not respond to stimulation) [15]. Immunohistochemistry for several Treg-associated molecules demonstrates that the rosetting T cells in cHL express GITR, CCR4, and CD25, but not FoxP3. Scattered FoxP3-positive cells are present in the infiltrate, but only rarely in the direct vicinity of the HRS cells, whereas CTLA-4 shows a more diffuse presence [15]. Likewise, a small number of scattered IL-17-positive cells can be found in the reactive infiltrate. Th17 cells are generally pro-inflammatory, but given the abundance of TGF-β and IL-6 in the Hodgkin microenvironment, the observed IL-17-positive cells might be yet another type of regulatory cells, termed Treg17 cells. Although the vast majority of studies indicate that the CD4+ T cells in cHL are (anergic) Th2 cells and Treg cells, some studies showed a predominant Th1-type pattern in whole lymph node cell suspensions, with a mild increase in EBV-positive cHL [16]. These findings

are not contradictory, as these Th1-like cells are located mainly outside the areas where R-S cells and T cell rosettes are found [17, 18].

4.1.5 T Cell Subsets in NLPHL

The CD4+ T cells in NLPHL resemble the CD4+ T cells in cHL, regarding the expression of CD45RO, CD69, CTLA4, and CD28 and lack of CD26. However, the T cells in NLPHL do not express CD40L, and a significant proportion of the T cells that immediately surround the LP cells express CD57 and PD-1 [19, 20]. Similar to the Th2 cells in cHL, the rosetting cells in NLPHL strongly express the Th2-associated transcription factor c-Maf (Fig. 4.3; [4]).

Characterization of the cytokine profile of the CD4+CD57+ T cell subset shows lack of IL-2 and IL-4 mRNA, but elevated interferon-γ (IFN-γ) mRNA levels in comparison to CD57+ T cells from tonsils. Stimulation of these cells fails to induce IL-2 and IL-4 mRNA levels [21], which is similar to the lack of cytokine induction upon stimulation of the CD26− T cells in cHL. In normal tissue, CD4+CD57+ T cells are found almost exclusively in the light zone of reactive germinal centers and also lack CD40L expression. CD57 is known as an activation marker, but it has also been demonstrated to be a marker for senescent cells. Senescence is the phenomenon by which normal diploid cells lose the ability to divide, normally after about 50 cell divisions. PD-1+ T follicular helper cells are present in NLPHL;

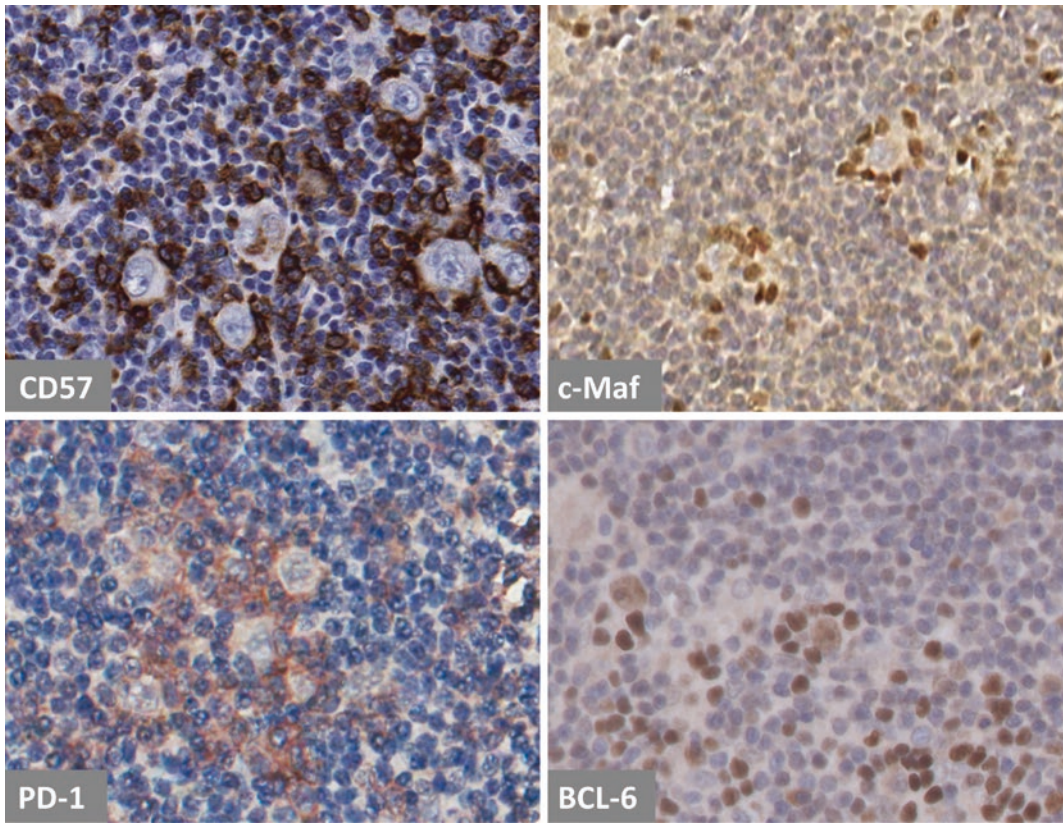

Fig. 4.3 T cells in nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). Immunohistochemistry of an NLPHL case showing a variable but usually high number of reactive T cells that express CD57. In this case these T cells form a rosette around the tumor cells (upper panel left). The CD57+ T cells also express the transcription factor c-Maf, indicating a Th2-type nature (upper panel right). In addition, these cells express the T follicular helper cell-associated markers PD-1 (lower panel left) and BCL-6 (lower panel right)

these cells normally provide help to B cells during the germinal center reaction. Another cell population, consisting of CD4+CD8+ dual positive T cells, has been reported to be present in more than 50% of NLPHL tumors. A similar population was found in reactive lymph nodes with progressively transformed germinal centers, which can also be seen in conjunction with NLPHL. In normal peripheral blood, they constitute 1–2% of T cells. The function of these cells is ill defined, and currently they are considered to be potent immunosuppressors and/or to have high cytotoxic potential [22].

4.1.6 Fibrosis and Sclerosis

The presence of bands of collagen surrounding nodules and blood vessels is typical of the nodular sclerosis subtype. Several factors can induce the activation of fibroblasts and the subsequent deposition of extracellular matrix proteins. The Th2 cells in cHL might provide a profibrogenic microenvironment by the production of the Th2 cytokine IL-13. IL-13 is expressed at a higher level in nodular sclerosis than in mixed cellularity cHL. Moreover, the percentage of IL-13 receptor-positive fibroblasts is increased in nodular sclerosis cHL cases [23]. IL-13 stimulates collagen synthesis in vitro and also stimulates the production of TGF-β, another potent stimulator of fibrosis. TGF-β can interact with basic fibroblast growth factor (bFGF) to induce formation of fibrosis in cHL. In a mouse model for fibrosis, the simultaneous application of TGF-β and bFGF causes persistent fibrosis [24]. Both TGF-β and bFGF are produced by HRS cells as well as the reactive background [25, 26]. They are produced more prominently in nodular sclerosis than in mixed cellularity cHL [27]. The third factor that stimulates fibroblasts in cHL is the engagement of CD40. CD40, a member of the tumor necrosis factor receptor (TNFR) superfamily, can be upregulated on fibroblasts by IFN-γ. The ligand of CD40 (CD40L) is present on activated T cells, mast cells, and eosinophils present in the cHL microenvironment.

4.1.7 Eosinophils, Plasma Cells, Mast Cells, and B Cells

Presence of eosinophils in the reactive infiltrate can be promoted by both IL-5, produced by Th2 cells, and by IL-9. In cHL patients with eosinophilia in the peripheral blood, HRS cells produce IL-5 and IL-9 [28]. In addition, eosinophils are attracted to cHL tissues by the production of the chemokine CCL11, especially in nodular sclerosis cHL. CCL11 levels can be enhanced by the production of tumor necrosis factor-α (TNF-α) by the HRS cells, which in turn can induce CCL11 production in fibroblasts. This process is specific for cHL since other lymphomas with tissue eosinophilia show no expression of CCL11 [29]. HRS cells also produce CCL28 (MEC), and expression of CCL28 correlates with the presence of eosinophils and plasma cells in cHL. CCL28 attracts eosinophils by signaling through the chemokine receptor CCR3 and attracts plasma cells through CCR10 [30]. CCL5 is produced at high levels by the reactive infiltrate in cHL and can attract eosinophils as well as mast cells. CCL5 and IL-9 may both contribute to the attraction of mast cells in cHL [31]. The stimulation and recruitment of eosinophils in cHL can be illustrated in bone marrow biopsies that often show enhanced granulopoiesis with many eosinophils in the absence of HRS cells. IL-6 produced by HRS cells in some cases of cHL may explain the presence of variable numbers of plasma cells [32]. B cells that express CD20, CD21, IgM, and bcl-6 can be found in the microenvironment of cHL [33]. It is possible that these cells are remnants of the original lymph node B cell areas. Plasma cells, mast cells, and eosinophils are generally absent in NLPHL.

4.2 Cross-Talk between HRS Cells and Microenvironment (Fig. 4.4)

4.2.1 Factors Supporting Tumor Growth

It is likely that HL tumor cells originate from a precursor B cell that has become addicted to

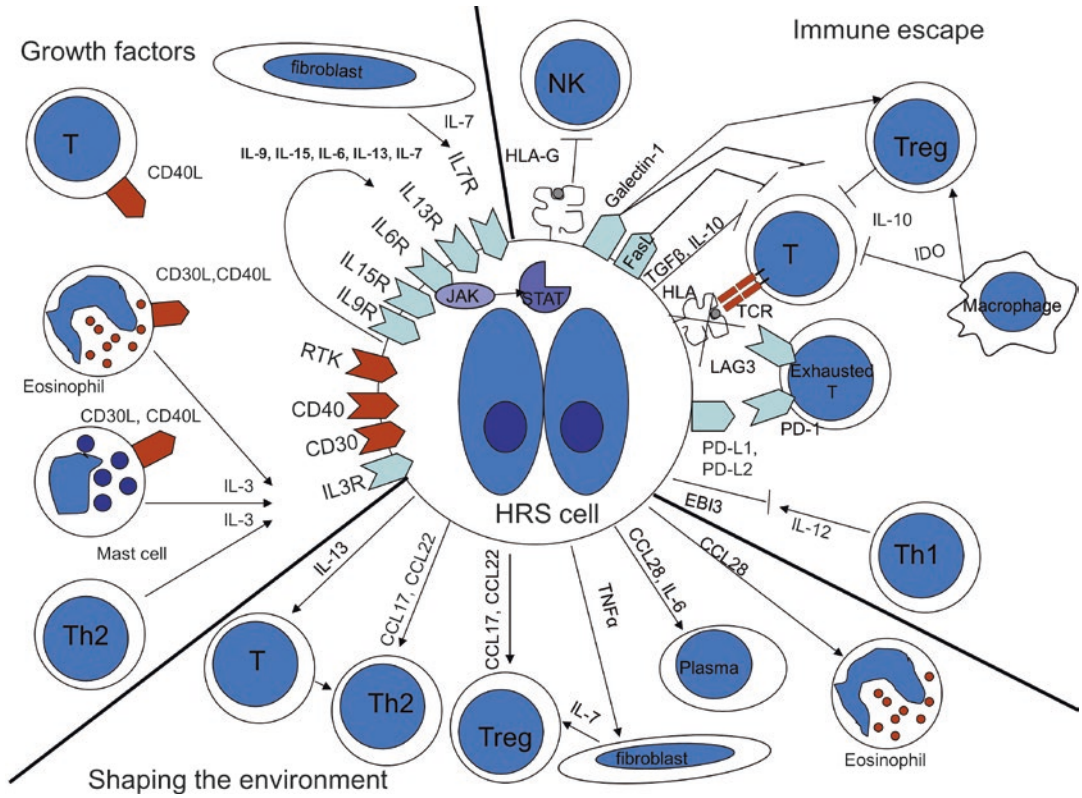

Fig. 4.4 Schematic overview of the cross-talk between Hodgkin/Reed-Sternberg (HRS) cells and the microenvironment. HRS cells attract specific subsets of cells by producing chemokines, are dependent on growth factors, and use mechanisms of immunosuppression and immune escape. Arrows indicate stimulating effects; the other lines indicate inhibitory effects

activating and growth-supporting stimuli during a deregulated immune response. Many additional events are needed to account for the highly deregulated malignant phenotype of HRS and LP cells. Although the tumor cells attain multiple alternative mechanisms to circumvent the dependence on growth-stimulating signals from the reactive infiltrate, they usually are not self-sufficient at the time of diagnosis. This is reflected by the inability to generate cell lines from primary HL cell suspensions.

IL-3 can function as a growth factor for B cells and is produced by activated Th2 cells, mast cells, and eosinophils. Its functions include protection against apoptosis and stimulation of proliferation. Most HRS cells express the IL-3 receptor, and exogenous IL-3 promotes growth of cHL cell lines. Costimulation of HL cell lines with IL-3 and IL-9 results in a further enhancement of cell growth [34]. There is no evidence that HRS cells produce IL-3, so this signaling pathway depends on IL-3 produced by the reactive infiltrate. In contrast, IL-7 is most likely an autocrine as well as a paracrine growth factor for HRS cells, since HRS cells express both the IL-7 receptor and produce IL-7 [35]. cHL cell lines also produce IL-7, albeit at very low levels, and anti-IL-7 treatment has some effect on cell growth. Addition of IL-7 to HL cell line cultures increased proliferation and protected against apoptosis. Moreover, fibroblasts isolated from cHL tissues are able to produce IL-7 [36]. Other growth factors important for HRS cells are IL-9, IL-13, IL-15, and, possibly, IL-6. IL-9 is expressed by the tumor cells and not by the infiltrating cells, and the IL-9 receptor is expressed on cHL tumor cells and mast cells. IL-9 supports tumor growth in cell lines and functions as an autocrine factor in cHL tissue [31]. IL-13 produced by HRS cells as well as the

surrounding T cells drives proliferation and is mostly autocrine [37]. Both IL-15 and the IL-15R are expressed by HRS cells. IL-15 induces proliferation of HL cell lines and protects them against apoptosis [38]. IL-6 is mainly produced by HRS cells and occasionally by the infiltrating cells [32]. In general, IL-6 is found at higher levels in EBV-positive cases [39]. IL-6 might have an autocrine effect although neutralizing antibodies have no effect on the growth of cHL cell lines.

The signaling of cytokines upon binding to their receptors leads to activation of the JAK-STAT pathway. This pathway is constitutively activated in HL cell lines [40, 41], and several of the STAT family members are expressed in HRS cells of primary cHL cases [42, 43]. In addition to the presence of cytokines, amplifications of 9p24.1, including the JAK2 gene locus found in part of the cHL cases [44], can further enhance constitutive activation of this pathway. Functional studies in cHL cell lines have shown that STAT3 is involved in proliferation [45], while STAT1 and STAT6 play a role in protection against apoptosis [46]. Binding of IL-21 to the IL-21R expressed on HL cell lines causes phosphorylation of STAT5 and induces proliferation [47].

HRS cells express several members of the TNFR superfamily including CD30, which has been used as a marker for cHL since the early 1980s. The CD30 ligand (CD30L) is expressed on eosinophils [48] and mast cells [49] that are present in the cHL infiltrate. Circulating eosinophils in cHL patients also have increased expression levels of CD30L [48]. Binding of CD30L to CD30 causes enhanced secretion of IL-6, TNFα, lymphotoxin-α, increased expression of ICAM-1 and B7, and, possibly, increased clonogenic growth and protection against apoptosis in cHL cell lines [50]. Another TNFR expressed on HRS cells is CD40. CD40 is generally found on B cells, and B cells can be activated through CD40. In vitro rosetting of activated CD4+ T cells around HRS cells is mediated through the CD40L adhesion pathway [51]. Engagement of CD40 is important for the prevention of apoptosis. Similar to stimulation of CD30, stimulation of HRS cell lines with CD40L causes enhanced secretion of several cytokines and upregulation of costimulatory molecules [50].

Several receptor tyrosine kinases (RTKs) are expressed by HRS cells and can have a role in cell growth. Their ligands are expressed on cells present in the microenvironment or by the HRS cells themselves. Inhibition of PDGFRA, expressed by the HL tumor cells, by imatinib blocks proliferation. Its ligand, PDGFA, is also produced by the HRS cells indicating autocrine signaling [52]. DDR1 [53] and DDR2 [52] can protect HRS cells from cell death by binding to collagen, which is present in the immediate surrounding of HRS cells. Knockdown of DDR1 decreases survival of the L428 cHL cell line [53]. TRKA, the receptor for NGF, is expressed by granulocytes [52], and TRK inhibition decreases growth of cHL cell lines [54]. EPHB1 and its ligand ephrin-B1 are both expressed by HRS cells [52]. The HGF receptor c-Met is expressed on HRS cells and inhibition causes G2/M cell cycle arrest in HL cell lines. HGF is produced by the tumor cells in a small group of patients and by dendritic reticulum cells [55]. Insulin-like growth factor receptor (IGF-1R) is expressed in 55% of cHL patients, and inhibition of IGF-1R decreases cell growth and induces G2/M cell cycle arrest in HL cell lines [56]. Its ligand IGF-1 is expressed by cells in the microenvironment [57]. PDGFRA, DDR2, EPHB1, RON, TRKA, and TRKB are found especially in EBV-negative HL [58], while DDR1 is upregulated by LMP1 [53].

The Notch1 receptor is an upstream regulator of NFκB [59]. It is highly expressed by HRS cells and stimulation via Jagged1 induces proliferation and survival of cHL cell lines [60].

4.2.2 Shaping the Environment

In addition to the production of several growth factors, HRS cells also produce large amounts of chemokines to attract specific beneficial or non-reacting cells. The lack of CD26 on the T cells surrounding the HRS cells may result in an incapability to cleave chemokines and thereby modulates the chemotactic effects exerted by the HRS cells. The attraction of specific populations of cells is an important immune escape mechanism exerted by the tumor cells.

The most abundant and cHL-specific chemokine is CCL17 (TARC); it binds to CCR4 on Th2 cells, Treg cells, basophils, and monocytes. CCL17 is highly expressed by HRS cells in ~95% of cHL patients but not in NLPHL and most non-Hodgkin lymphomas [61, 62]. CCL17 can be measured in serum and plasma and is a sensitive and specific marker reflecting cHL tumor burden [63–67]. High expression levels of CCL17 might explain the influx of lymphocytes with a Th2- and Treg-like phenotype, and CCL17-positive cases are indeed associated with a higher percentage of CCR4-positive cells (Fig. 4.2; [62, 68]). In turn, Th2-type cytokines (IL-4, IL-13) can induce the production of CCL17 by HRS cells. CCR4-positive T cells are found especially in the rosettes immediately surrounding the HRS cells [15, 69]. CCL22 is another chemokine that has a similar function as CCL17. High CCL22 protein expression levels were found in the cytoplasm of HRS cells in 90–100% of cHL patients and also in tumor cells in the majority of NLPHL and non-HL patients [70–73]. CCL22 production can also be stimulated by Th2 cytokines, IL-4 and IL-13, and may reinforce the attraction of Th2 and Treg cells, initiated by CCL17. Stimulation of the IL-21 receptor on HRS by IL-21 activates STAT3, which can induce CCL20 (MIP3α) production. CCL20 in turn attracts memory T cells and Treg cells [74]. HRS cells express both IL-21 and the IL-21 receptor, indicating presence of an autocrine signaling loop. The expression of some chemokines is more pronounced in EBV-positive cHL (i.e., CXCL9 and CXCL10), and as a result the composition of the reactive background is somewhat different from that in EBV-negative cHL, with a slightly higher proportion of CD8+ T cells in EBV-positive cases and more T cells with a Tr-1 phenotype (expressing LAG3, ITGA2, and ITGB2) [75]. T cell recruitment is also enhanced by the upregulation of adhesion molecules on endothelial cells, induced by LTα [76] produced by HRS cells [77].

In addition to attracting specific cell subsets by chemotaxis, HRS cells also shape their environment by inducing differentiation of specific T cell subsets that are favorable for HRS cell survival and growth. The expression of IL-13 by the HRS cells stimulates differentiation of naïve T cells to Th2 cells [37]. The production of IL-7 by HRS cells and fibroblasts can induce proliferation of Tregs [36]. Also, cHL cell lines with antigen-presenting functions like KMH2 and L428 have been shown to promote the differentiation of Treg like cells in vitro (expressing CD4, CD25, FoxP3, CTLA4, and GITR and producing large amounts of IL-10). Interestingly, these cell lines can also induce the formation of CD4+ cytotoxic T cells (expressing granzyme B and TIA-1) that can kill tumor cells directly, suggesting that CD4+ cytotoxic T cells have the potential to attack tumor cells in vivo [78].

4.3 Immune Escape Mechanisms (Fig. 4.4)

4.3.1 Antigen Presentation

The importance of antigen presentation in the pathogenesis of cHL has been suggested by the association of specific HLA subtypes with increased cHL incidence. cHL is more common in Caucasians as compared to Asians and about 4.5% of cHL cases occur in families [79, 80]. A three- to sevenfold increased risk has been observed in first-degree relatives and siblings. In monozygotic twins, the co-twin has an approximate 100-fold increased risk of developing cHL compared to dizygotic twins [81]. From the 1970s, a number of serological HLA types have been associated with the occurrence of cHL. More recently, a genetic screen of the entire HLA region showed a strong association between the *HLA-A* gene and EBV-positive cHL and the HLA class II region with EBV-negative cHL [82, 83]. Four independent genome-wide association studies have confirmed that the HLA region is the strongest genetic susceptibility locus in cHL [84–87]. In EBV-positive cHL, it can be hypothesized that this association is related to insufficient presentation of EBV antigenic peptides. These antigenic peptides most likely are derived from the latency type II genes that are expressed in cHL, i.e., LMP1, LMP2, and EBV-related nuclear antigen 1 (EBNA1). EBV partially escapes cytotoxic

immune responses by downregulating immunodominant latent genes (*EBNA2* and *EBNA3*). In addition, the glycine-alanine repeat in EBNA1 largely prevents its presentation by HLA class I by blocking its degradation into antigenic peptides through the proteasome [88]. However, subdominant immune responses to LMP2 and to a lesser extent LMP1 are present in healthy EBV-infected individuals [89]. In fact, adoptive immunotherapy in relapsed EBV-positive cHL has been used in some small studies with success. In these studies, peripheral blood from cHL patients was used to generate EBV-specific cytotoxic T cells in vitro, and these were reinfused. Some durable complete responses were observed, with better responses if the cytotoxic T cells were specifically targeted to LMP2 [90–92] (Fig. 4.4). Interestingly, the genetic association of the *HLA-A* gene with EBV-positive cHL is attributed to the presence of the HLA-A∗01 type and absence of the HLA-A∗02 type [93]. HLA-A∗01 is known to have a low affinity for LMP2- and LMP1-derived antigenic peptides, while HLA-A∗02 can present these peptides very well. This suggests that EBV-positive cHL is more likely to occur after primary EBV infection if an individual's set of HLA class I molecules cannot properly present LMP2 and LMP1 to the immune system [94].

4.3.2 HLA Class I Expression

Defects in the antigen-presenting pathways are very common in solid malignancies, as well as in many B cell lymphomas, and are an obvious mechanism to escape from antitumor immune responses. In EBV-negative cHL, less than 20% of cases retain expression of cell surface HLA class I on the HRS cells at the time of diagnosis. Paradoxically, HLA class I expression by HRS cells is retained in ~75% of EBV-positive cHL patients [95–97]. One common mechanism of HLA class I loss is presence of somatic mutations in the β2-microglobulin gene. This leads to loss of β2-microglobulin protein, which is necessary for HLA class I assembly and transport to the cell surface. Other mechanisms also appear to be involved as immunohistochemistry has shown cytoplasmic β2-microglobulin expression in part of the cases that lost HLA class I heavy chain expression [98]. These different mechanisms may indicate that downregulation of HLA class I is based on clonal selection by continuous cytotoxic immune responses. This may be related to the presence of antigenic peptides that are related to malignant transformation or disease progression. However, downregulation of HLA class I generally induces activation of natural killer (NK) cells. These cells contain HLA class I-specific inhibitory receptors and are sparse in the reactive infiltrate of cHL. The inhibitory receptors can also be engaged by the nonclassical HLA class I-like molecule known as HLA-G. In about two thirds of the HLA class I-negative cHL cases, the HRS cells indeed express HLA-G [98]. Besides NK cell inhibition, HLA-G might also induce Treg cells and inhibit cytotoxic T cell responses. Another immune escape mechanism consists of the proteolytic cleavage of MHC (HLA) class I-related chain-A (MIC-A) by ERp5 and ADAM10, which are both expressed by HRS cells. MIC-A is a membranous ligand for the activating NKG2D receptor present on cytotoxic T cells. In addition, the NKG2D receptor expression by these cytotoxic T cells is reduced in the presence of TGF-β [99].

4.3.3 HLA Class II Expression

HLA class II cell surface expression on HRS cells is lost in approximately 40% of all cHL patients [95]. In addition, translocations involving CIITA have been found in 15% of cHL patients and may result in partial downregulation of HLA class II expression [101]. The absence of HLA class II is weakly related to extranodal disease, EBV-negative status, and absence of HLA class I cell surface expression. Lack of HLA class II expression has been associated with adverse failure-free survival and relative survival and is independent of other prognostic factors [95]. It can be hypothesized that antigen presentation in the context of HLA class II is involved in recruitment and activation of CD4+ T cells early in cHL pathogenesis. Under the influence of immunomodulating mechanisms, these T cells are important in providing trophic factors for HRS cells

and also have a role in inhibiting Th1 responses. In the initial stages of cHL pathogenesis, HRS cells are probably highly dependent on the reactive infiltrate and expression of HLA class II, but as the lymphoma develops, this dependency may weaken because of alternative trophic and immunosuppressive strategies. Thus, downregulation of HLA class II without loss of viability of HRS cells might occur when the HRS cells have grown less dependent on the reactive infiltrate. This is supported by the finding that downregulation of HLA class II is associated with extranodal disease [95].

4.3.4 Immune Checkpoints

Immune checkpoint molecules have gained much attention due to their use as treatment targets. Both CTLA-4 and PD-1 blockade have shown remarkable results in cHL patients in clinical trials.

CTLA-4 is expressed exclusively on T cells upon activation. It gives an inhibitory signal early after T cell activation, by binding to CD80/CD86 with a higher avidity than the costimulatory molecule CD28. This limits T cell activation and proliferation [101, 102]. Interestingly, CTLA-4 is present on the characteristic CD26− T cells in HL [15]. Moreover, HL cell lines are able to induce differentiation of naïve T cells into CTLA4+ Tregs [78]. So far, two clinical trials have exploited the use of a monoclonal antibody targeting CTLA-4 in relapsed and refractory HL after allogeneic hematopoietic cell transplantation. Objective response rates were observed in 2 out of 14 and 1 out of 7 cases [103, 104].

The interaction partner of PD-L1, PD-1, is present on activated T cells, B cells, macrophages (which also express PD-L1), and NK cells within the microenvironment [105, 106]. PD-L1 is highly expressed on HRS cells [105, 107], due to a selective amplification of the PD-L1 region on 9p24.1 [44], activation of AP-1 and LMP-1 [107], or chromosomal alterations involving the CIITA locus [100]. Anti-PD-1 therapy in relapsed and refractory HL patients, using the monoclonal antibodies nivolumab or pembrolizumab, showed objective response rates in 65–87% of the cHL patients [108–111]. The mechanism of action of PD-1 blockade in HL remains unknown, but multiple mechanisms have been studied. In contrast to solid tumors where CD8+ cytotoxic T cells seem to be the main effector cells [112], CD4+ T cells might have an important role in mediating the antitumor immune response in HL. CD8+ T cells recognize the tumor cells through (neo)antigens presented in the context of HLA class I, which can ultimately lead to eradication of the tumor cells. However, HLA class I is often absent on HRS cells, making a central role for CD8+ T cells in immune checkpoint efficacy unlikely [96]. In HL, the inflammatory infiltrate is mainly dominated by CD4+ T cells, which are more often in direct contact with the HRS cells when compared to CD8+ T cells. In addition, CD4+PD-1+ T cells are more frequently bound to PD-L1+ HRS cells [113]. The majority of complete responders to nivolumab lack membranous HLA class I expression, while being positive for membranous HLA class II expression. Also, presence of HLA class II is predictive for a prolonged progression-free survival in patients treated with nivolumab >12 months after myeloablative autologous stem cell transplantation, in contrast to presence of HLA class I [114]. Although many studies on PD-1 blockade focused on T cells, expression of PD-1 on T cells in direct contact with HRS cells is rare, and their numbers are significantly lower in cases with PD-L1 gain [115]. Interestingly, exhausted PD-1+ CD3+CD56^{hi}CD16− NK cells are enriched in HL, and their activation can be inhibited by PD-L1+CD163+CD14+ tumor-associated macrophages, which are also increased in HL. This inhibition was effectively reversed by PD-1 blockade [106]. This indicates the importance of other cell types in responses to PD-1 blockade that are currently less well characterized.

An interesting molecule with regard to the role of CD4+ T cells in responses to anti-PD-1 therapy is LAG-3. LAG-3 is an immune checkpoint molecule expressed on activated T cells, NK cells, B cells, and plasmacytoid dendritic cells [116]. The main interaction partner for LAG-3 is HLA class II, to which LAG-3 binds with higher affinity than CD4 [117]. LAG-3 is upregulated on Tregs, and LAG-3-positive lymphocytes are enriched in the

proximity of HRS cells [118, 119]. Increased LAG-3 expression was observed especially in EBV-positive cHL cases [118, 120]. Interestingly, the percentage of LAG-3-positive cells was enriched in CD4+ T cells that express a high intracellular CTLA-4 and GITR, but not FOXP3+ [118]. The $GITR^{hi}$ CD4+ T cells are frequently in direct contact with HRS cells [15]. Moreover, CD4+LAG-3+ cells are significantly expanded in patients with active disease, which is in concordance with the ability of HL cell line supernatant to increase expansion of CD4+LAG-3+ regulatory T cells within PBMCs. In addition, higher FOXP3 and LAG-3 expression on tumor-infiltrating lymphocytes is associated with decreased LMP1- and LMP2-specific CD8+ T cell function [118]. Altogether this implicates an important role for LAG-3 in inhibiting (EBV) mediated cellular immunity in HL and points to LAG-3 as an interesting treatment target in combination with PD-1 blockade.

Currently, more and more immune checkpoint molecules are emerging as potential targets for therapy. Some of these are less well studied in the context of HL. For example, HRS cells express HVEM and CD200/CD200R [121] in addition to the earlier mentioned checkpoints, whereas TIM-3+ T cells are present within the inflammatory infiltrate [120], indicating the complexity of immunosuppressive mechanisms within the HL microenvironment.

4.3.5 Immunosuppression

As normal B cells are professional antigen-presenting cells, HRS cells are expected to present antigens to the immune system, at least early in disease pathogenesis. Indeed, most components of the HLA class I and HLA class II antigen-presenting pathways have been detected in the HRS cells at the time of diagnosis. However, Th1 cells are not actively attracted by the HRS cells and CD8+ T cells are relatively scarce. Moreover, HRS cells have gained the capacity to prevent CD8+ T cells from attacking by producing high amounts of the strongly immunosuppressive cytokines TGF-β and IL-10. TGF-β is produced by HRS cells in nodular sclerosis cHL [25, 26], whereas IL-10 is more frequently found in EBV-positive (mixed cellularity) cHL [122, 123]. In normal cells, TGF-β is produced in an inactive form, which can be activated by acidification. TGF-β produced by cHL cell lines is active at a physiological pH and has a high molecular weight [124]. The same high molecular weight form of TGF-β can also be found in the urine of cHL patients [125] indicating that in patients HRS cells are able to produce the active TGF-β form.

Tregs present in the microenvironment of cHL are highly immunosuppressive and contain Tr1 (IL-10-producing Tregs) as well as CD4+CD25+ Tregs. IL-10, cell-cell contact, and CTLA4 play a main role in executing their immunosuppressive function [126]. In addition, HRS cells express galectin-1, an animal lectin, which can cause apoptosis in activated T cells, induce differentiation into Treg cells, and contribute to the elimination of an effective antitumor response in cHL [127]. Galectin-1 expression blocks CD8+ T cell responses against LMP1 and LMP2 in EBV-positive cHL [128]. HRS cells express FAS and the FAS ligand. However, there are some mechanisms protecting the HRS cells from apoptosis induction, such as FAS mutations in a small proportion of cases and c-FLIP overexpression in all cases [129]. Presumably, activated Th1 and CD8+ T cells expressing FAS are driven into apoptosis by the FAS ligand expression on the HRS cells. Also, indoleamine 2,3-dioxygenase (IDO), a known immunosuppressor, is expressed by histiocytes, dendritic cells, and endothelial cells in the microenvironment of cHL. IDO is found more often in EBV-positive HL, upregulates the number of Tregs [130], and potentially blocks the CD8+ T cell response [131]. In EBV-positive cHL, the Th1-inducing cytokine IL-12 is expressed in T cells surrounding the HRS cells, and its presence suggests that these T cells have the potential to induce antitumor activity [132]. However, an EBV-induced IL-12-related cytokine called EBI3 can block this Th1 response and is produced by HRS cells [133].

4.4 Prognostic Impact of the Microenvironment

Several research groups studied the cHL reactive infiltrate in relation to prognosis. Gene expression profiling of whole tissue and subsequent validation by immunohistochemistry showed that high numbers of CD68-positive cells are related to adverse outcome [134]. In a meta-analysis of almost 3000 patients, a high density of CD68+ tumor-associated macrophages predicted overall survival, shorter progression-free survival, and poor disease survival in adult cHL [135]. Similar findings were obtained for CD163+ macrophages in this study. Analysis of 100 pediatric cHL revealed that especially M2 macrophages, characterized by co-expression of CD163 and c-Maf, are associated with poor survival, while M1 macrophages are associated with better survival [136]. In some studies tumor-associated macrophages were associated with EBV-positive tumors [135, 137] and presence of other cell types in the microenvironment, such as cytotoxic T cells [136] and mast cells [138]. Patients with a higher degree of mast cell infiltration or with tissue eosinophilia have an adverse failure-free survival, probably because the CD30L expression by these cell types is advantageous to the HRS cells [48, 49, 138].

Large numbers of Th2 cells in the microenvironment, as determined by c-Maf expression, correlate with improved disease-free survival [14]. Also, increased numbers of infiltrating Treg cells seem to correlate with improved survival as this effect was observed in two out of three studies [14, 139, 140]. Accordingly, a high percentage of activated CD8+ granzyme B+ T cells is a strong indicator of unfavorable clinical outcome [141]. More recently, a high proportion of Treg cells and the associated anergic phenotype of the microenvironment has been associated with a shorter time to progression [137]. A high CD4/CD8 T cell ratio was associated with treatment failure [142]. A high ratio of FoxP3 to cytotoxicity markers granzyme B [140] or Tia-1 [139] gives the best predictive value for a good prognosis and has also been correlated to the presence of macrophages [136, 138], which might—in part—explain these effects. In other malignancies the presence of Tregs and the absence of CD8+ T cells have been associated with adverse prognosis. One explanation of this opposite effect might be that HRS cells are expected to behave more aggressively as they develop a stronger independency from the reactive infiltrate. In this situation a hostile microenvironment is allowed, because the HRS cells have acquired alternative immune evasive strategies. This theory fits with the adverse prognostic impact of absence of HLA class II expression.

4.5 Conclusion

The microenvironment is a fundamental component of the tumor mass and an essential pathogenetic factor in cHL and NLPHL. It supplies the tumor cells with growth factors and inhibits antitumor immune responses. In fact, it could be stated that the infiltrate does not consist of 'innocent bystanders' but contains 'guilty opportunists' [31]. As the tumor cells and the reactive infiltrate grow up together, there is an extensive cross-talk between these two components. The tumor cells actively attract and shape their environment for their own benefit and make use of a number of mechanisms to fend off antitumor immune responses.

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5 What Have We Learnt from Genomics and Transcriptomics in Classic Hodgkin Lymphoma

Davide Rossi and Christian Steidl

Contents

5.1 Introduction

A prominent pathological feature of cHL is the abnormal immune response represented by the abundant TME. It is thought that the majority of the immune cells in the TME are recruited by a variety of cytokines expressed by the HRS cells [1]. Cytokines are low-molecular-weight proteins with a wide variety of functions that work either in a paracrine manner to modulate the activity of surrounding cells or in an autocrine fashion to affect the cells that produce them. Furthermore, it is a widely accepted concept that the overexpression of regulatory cytokines and TGFβ leads to a microenvironment that suppresses cell-mediated immunity and in return favors HRS cell survival highlighting the bidirectional crosstalk of cells involved in the pathogenesis of HL [2].

The recent advances in HRS cell genomics and profiling the tumor microenvironment have already led to better insight into the molecular underpinnings of the disease, and we are anticipating discovery of additional clues explaining

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_5

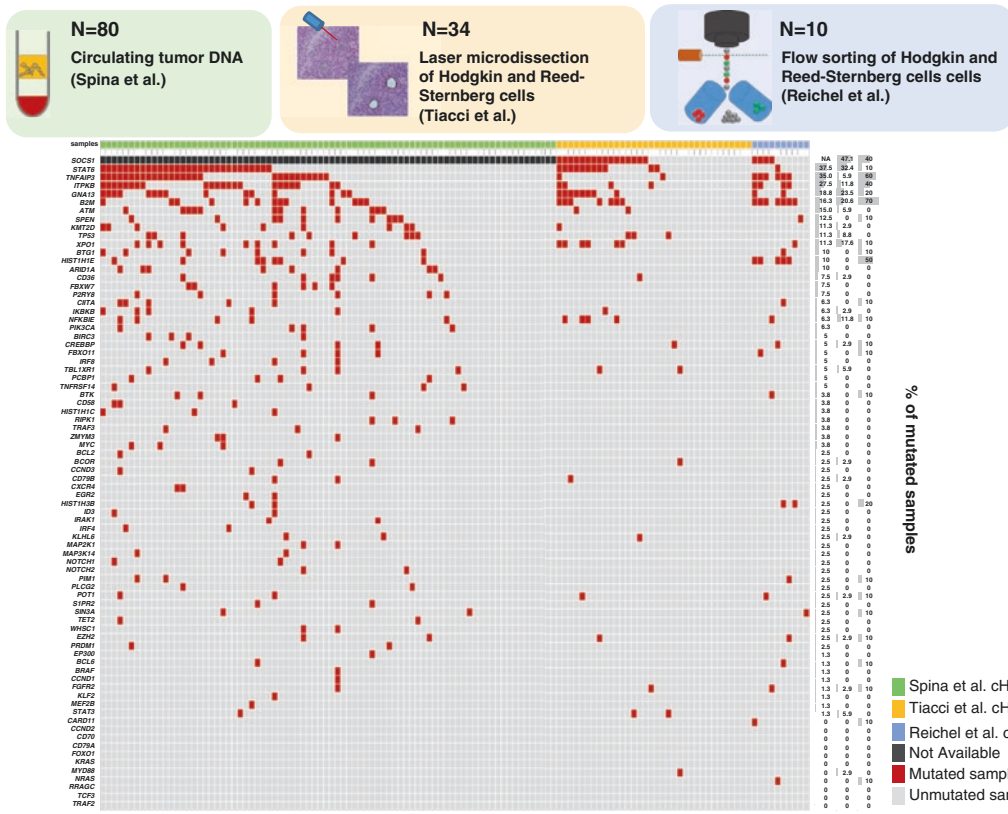

Fig. 5.1 The mutational profile of newly diagnosed cHL. The heatmap shows individual non-synonymous somatic mutations detected in three different cohorts (Spine et al., green; Tiacci et al., yellow; Reichel et al., blue). Each cohort has a different source of tumor DNA (i.e., circulating tumor DNA, DNA from laser microdissected Hodgkin and Reed-Sternberg cells, and DNA from flow-sorted Hodgkin and Reed-Sternberg cells). Each row represents a gene and each column represents a primary tumor. The heatmap was manually clustered to emphasize mutational co-occurrence. Mutations are color-coded in red. The horizontal bar graph shows the gene mutation frequency found in each different cohort

the unique crosstalk and symbiosis of the malignant cells with the non-malignant cells in the TME. In the following, we will highlight recent advances and future directions in (1) HRS cell genomics (Fig. 5.1) and (2) gene expression profiling.

5.2 Genomics of Hodgkin and Reed-Sternberg Cells

5.2.1 Cytokine Signaling

Constitutive activation of cytokine signaling pathways is a long recognized molecular hallmark of HRS cells. A number of studies provided evidence that various molecular mechanisms, including gene mutations and chromosomal alterations, can converge along with deregulated surface receptor signaling to lead to exuberant activation of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway [3–5].

Chromosomal aberrations of the *JAK2* locus on 9p24.1 in HRS cells were reported in one study in the large majority of cHL cases, including copy gain in 60% of cases, amplification in 30%, and polysomy in 10% [5]. Almost ubiquitous (~90% of cases) are genetic alterations of a variety of other JAK-STAT pathway members, which goes beyond previous estimates based on the presence of copy number gains of *JAK2*.

These include mutational disruption of the *SOCS1* (40%) and *PTPN1* (20%) negative pathway regulators, activating mutations of *JAK1* (10%), and multiple STAT transcription factors (*STAT6*, 30%; *STAT3*, 10% *STAT5B*, 10%) [4].

The association between convergent and recurrent point mutations in genes coding for interacting proteins of the JAK-STAT pathway is a common mechanism shared by CD30+ lymphomas, in particular cHL and anaplastic large cell lymphoma. Concurrence of these multiple somatic events indicates that these synergistic mutations are strongly selected for beyond single alterations to sustain pathway activation [6].

The pervasive targeting of JAK-STAT signaling genes in cHL, along with functional genomic studies, confirmed that JAK-STAT pathway activation represents a vulnerability of cHL and makes clinically available JAK or STAT inhibitors an attractive therapeutic approach in this disease [4].

5.2.2 NF-κB Signaling

Overall, genetic lesions in the NF-κB pathway occur in most of cHL cases, confirming their important role in the pathogenesis of this disease. Genomic gains/amplifications of the NF-κB transcription factor *REL* have been described in about 70% of cHL cases causing protein overexpression [7].

Mutations in negative regulators of NF-κB constitute a second important mechanism of pathway activation. *NFKBIA*, encoding IκBα, an inhibitor that binds NF-κB factors and prevents their nuclear translocation, is mutated in about 20% of cHL [8]. *NFKBIE*, encoding IκBε, an inhibitor that binds NF-κB factors and prevents their nuclear translocation, has been found in 30% of cases [9]. *TNFAIP3* the master negative regulator of NF-κB pathway is mutated in 30% of cases [3, 10].

Overall, NF-κB pathway mutations have been described in cHL with a higher frequency in EBV-negative cases, consistent with data establishing expression of the EBV-latent membrane protein 1 (LMP-1) as an independent contributor to constitutive activation of NF-κB in cHL [11, 12].

5.2.3 PI3K/AKT/mTOR Signaling

Mutations within the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway occur in 50% of cHL, consistent with the pre-clinical evidence that cHL is addicted to this actionable cellular program [13]. *ITPKB* is mutated in 25% of cases. ITPKB is a non-canonical antagonist of PI3K. Physiologically, ITPKB dampens PI3K/AKT signaling by producing IP4, a soluble antagonist of the AKT-activating PI3K-product PIP3.

ITPKB mutations are quite specific for cHL, being rare or absent in other lymphomas, and cause the subcellular delocalization of the mutated protein in primary HRS cells. Moreover, *ITPKB* mutations correlate with PI3K/AKT signaling activation at both the gene expression and protein levels and, consistent with linkages to the downstream PI3K pathway, associate with resistance to PI3K inhibitors [3, 4].

The Ga13 G-protein subunit encoded by *GNA13* is mutated in 10% of cHL [3, 4]. By transmitting signals from the G-protein-coupled receptors S1PR2 and P2RY8 that result in the inhibition of AKT phosphorylation, Ga13 ensures the proper confinement of proliferating germinal center (CG) B cells within secondary lymphoid follicles and at the same time constrains their expansion by facilitating apoptosis in this potentially dangerous niche. Inactivating *GNA13* mutations promote altered GC B-cell migration within and beyond the GC, as well as impaired cellular adhesion, resulting in cells that may have a reduced ability to establish interactions with GC helper cells. Under normal conditions, a GC cell that is unable to form these helper cell interactions, due to either GC exit or ineffective cellular adhesion, would undergo apoptosis. However, *GNA13*-mutated GC B cells are resistant to programmed cell death by leading to elevated levels of pAKT [14].

Importantly, the genomic studies of microdissected HRS cells and ctDNA strongly suggest that mutations of *STAT6*, *TNFAIP3*, *GNA13*, and *ITPKB* are preferentially occurring in the ancestral clones, indicating that they are an early event in cHL pathogenesis [3, 4].

5.2.4 Immune Escape

Classical HL leverages multiple genetic mechanisms to escape immunosurveillance. First, reduction or loss of antigen presentation through *B2M* inactivating mutations/deletion has been described in 30% of cases [4, 15]. *B2M* encodes β2 microglobulin, a key component of the major histocompatibility complex (MHC) class I which is required for its expression and antigen presentation on the cell surface. Consistently, genetic disruption of *B2M* results in the loss of MHC class I protein expression on lymphoma cells [16, 17].

Second, gene rearrangements involving the MHC class II transactivator *CIITA* were found in 15% of cases. *CIITA* rearrangements result in the disruption of its transcriptional proprieties and loss of MHC class II expression on cHL cells. Both MHC class I and MHC class II losses are predicted to abrogate the interaction of the T-cell receptor (TCR) with a MHC-bound antigen presented on the cell surface, which is the first signal required to activate T-cell antitumor response [18]. Loss of both MHC I and II expression and related lack of neoantigen expression have been consistently found to induce "cold" immune microenvironments in lymphoma and other cancers [19, 20].

Third, PD-L1 and PD-L2 overexpression driven by copy gain of 9p24.1 is a frequent event in cHL. Alterations of the *PD-L1* and *PD-L2* loci were reported to include polysomy in 5% of cHL, copy gain in 56%, and amplification in 36%. The 9p24.1 amplification in cHL acts through two distinct mechanisms resulting in copy number-dependent increases of PD-L1 and PD-L2 expression and increased JAK/STAT signaling promoted by JAK2 protein expression which is almost exclusively co-regulated with PD-L1 and PD-L2 in the 9p24.1 amplicon [21].

5.3 The Transcriptome of HRS Cells

Overall, gene expression profiling experiments have contributed substantially to an improved understanding of the disease with respect to the inherent phenotypic features of the malignant HRS cells and the specific composition of the tumor microenvironment. Furthermore, first steps could be made to establish outcome correlations with the potential to improve treatment outcome prediction. However, many questions remain including often contradictory results derived from different patient cohorts. Focusing on HRS cells, the first major contribution of gene expression profiling was made by investigating HL-derived cell lines. These pivotal studies first established a transcriptome-wide view of the malignant cell compartment describing a unifying gene signature for cHL [22]. Together with other important similar studies, this gene expression work helped to elucidate the loss of B-cell signature phenotypes and the deregulated expression of transcription factor networks in comparison to the normal germinal center B-cell counterparts [23–26]. Major advances have also been made examining microdissected HRS cells from clinical biopsy material that further characterized transcriptional changes in primary cells [27–29]. Steidl and colleagues identified significant phenotypic heterogeneity within cHL and described for the first time genome-wide association with treatment outcome [28] (Fig. 5.2). The second study by Tiacci and colleagues added significant texture to the primary HRS cell expression phenotype emphasizing the differences in comparison to HL-derived cell lines [29]. Furthermore, two molecularly distinct cHL subtypes were discovered related to the transcription factor activity of NOTCH1, MYC, and IRF4. Another study for the first time also focused on gene expression profiling of microdissected cells from nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) describing a close relationship to classical Hodgkin lymphoma and T-cell-rich B-cell lymphoma [27].

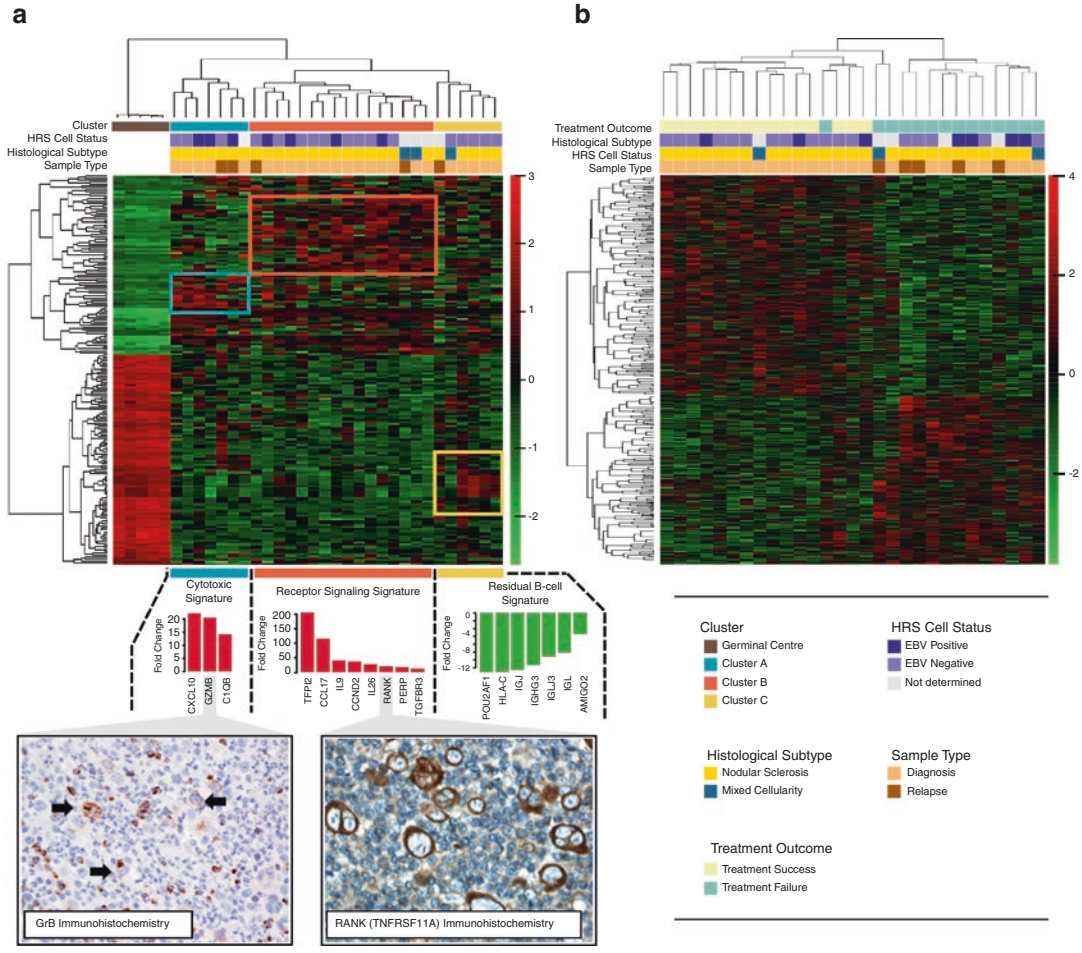

Fig. 5.2 Expression profiling of 29 samples of microdissected Hodgkin and Reed-Sternberg cells. (**a**) Unsupervised hierarchical clustering of gene expression profiles is shown using high variance genes. Red indicates relative overexpression and green relative under-expression. Patient clusters, histological subtype, EBV positivity of HRS cells by EBER in situ hybridization, and sample type are shown. The average fold changes of genes representative of the three main signatures are shown in the bar plots. Representative immunohistochemistry images are depicted demonstrating cytoplasmic positivity of Granzyme B (GrB, black arrows) and RANK in HRS cells. (**b**) Unsupervised hierarchical clustering of the cohort using the most differentially expressed genes between primary treatment failure and success. Treatment outcome, histological subtype, EBV positivity of HRS cells by EBER in situ hybridization, and sample type are shown. Cases cluster according to the outcome groups (two main clusters)

5.4 Microenvironment Profiling

Focusing on the HL microenvironment, a number of genome-wide gene expression studies have been published to date analyzing whole tissue lymph node biopsy material. Since the HRS cells are largely outnumbered by reactive cells in most biopsies, these studies on whole frozen biopsies are regarded as a reflection of the microenvironment [30–33]. However, some of these data provide evidence that at least parts of the apparent signatures are derived from HRS cells [31, 33]. In one study a specific gene expression signature could be linked to EBV positivity with genes overexpressed indicative of an increased Th1/antiviral response in comparison to the EBV-negative cases [32]. In addition to a better characterization of certain Hodgkin lymphoma subtypes

defined by specific gene signatures, these experiments also allowed for the study of outcome correlations using supervised analyses.

5.5 Biomarker-Driven Prognostication and Risk Stratification in cHL

The lack of extensive genotyping of microdissected HRS cells from large cHL patient cohorts has so far limited the identification of mutations affecting cHL outcome. ctDNA has been established as a source of tumor DNA for cHL mutational profiling. By overcoming the major technical hurdles that have so far limited cHL genotyping, ctDNA technology will allow large-scale assessment of mutations in different clinical phases ranging from newly diagnosed to refractory disease, and longitudinally during disease treatment, which in turn can reveal yet unknown prognostic and predictive biomarkers for cHL [3] (Fig. 5.3).

Beside disclosing tumor mutation profiles, ctDNA can also provide an estimate of the levels of residual disease during treatment in cHL. Consistently, ctDNA quantification after two chemotherapy courses has prognostic implications. A drop of 100-fold or 2-log drop in ctDNA after two chemotherapy courses, a threshold proposed and validated also in DLBCL, associates with complete response and cure in advanced-stage cHL treated with ABVD [3]. Conversely, a drop of less than 2-log in ctDNA after two ABVD courses associates with progression and inferior survival. Quantification of ctDNA complements interim PET/CT in determining residual disease. Indeed, cured patients who are inconsistently judged as interim PET/CT positive have a >2-log drop in ctDNA, while relapsing patients who are inconsistently judged as interim PET/CT negative have a <2-log drop in ctDNA. On this basis, incorporation of both PET/CT and ctDNA monitoring into clinical trials should allow to precisely define their cumulative sensitivity and specificity in anticipating the clinical course of cHL patients. Indeed, though interim PET/CT response assessment is a novel approach to refine management strategies before completing treatment in cHL, meta-analyses demonstrated a certain degree of inaccuracy of this application. In order to fill this gap, an area of growing interest is pairing interim PET/CT with biomarkers,

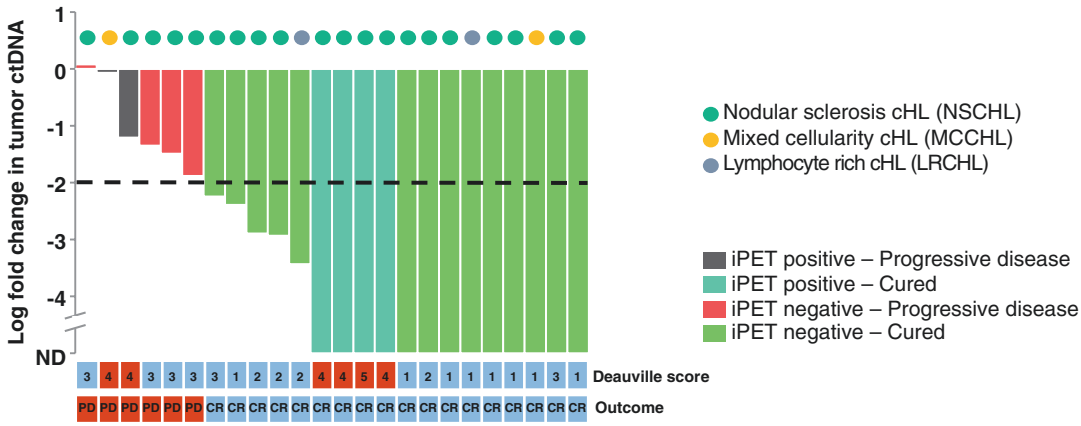

Fig. 5.3 Change in tumor ctDNA is a prognostic biomarker in cHL treated with chemotherapy. Waterfall plot of the log-fold change in ctDNA load after two courses of ABVD in 24 advanced-stage cHL cases. At the bottom of the graph, the interim PET/CT response scored according to the Deauville criteria, and the final outcome of the patient is indicated. Histological subtype of cHL is shown above the plot. Each column is color-coded according to the interim PET/CT results and the final patient outcome. Levels of ctDNA are normalized to baseline levels. The dashed line tracks the −2-log threshold (*iPET* interim PET/CT, *ND* not detectable, *PD* progressive disease, *CR* complete remission and cure)

such as ctDNA or serum TARC, to enhance their cumulative predictive value.

The type of 9p24.1 chromosomal aberration affects cHL outcome in both chemotherapy and immunotherapy treatment settings. Among chemotherapy-treated cHL, 9p24.1 amplification, but not polysomy or copy gain, associates with inferior progression-free survival [21]. Among patients treated with checkpoint blockade antibodies, those with higher-level 9p24.1 alterations and PD-L1 expression on HRS cells had superior PFS [34]. These analyses highlight the importance of quantifying and specifically delineating PD-L1 expression in malignant HRS cells for prognostic purposes.

Beside genetics, the tumor/TME phenotype has been prominently involved in past and ongoing biomarker considerations in cHL. Studies have used dichotomized clinical data sets based on slightly different definitions of clinical extremes according to the outcome after systemic treatment (i.e., treatment success versus treatment failure). However, these types of analyses have in part yielded conflicting results regarding the specific signatures that best define these clinical extremes. While one study found overexpression of genes involved in fibroblast activation, angiogenesis, extracellular matrix remodeling, and downregulation of tumor suppressor genes to be linked with an unfavorable prognosis, another study found a correlation of fibroblast activation, fibroblast chemotaxis, and matrix remodeling with improved outcome [30, 31]. While small sample sizes in both studies might have hampered interpretation, a more recent study investigated gene expression profiles of 130 patients including 38 patients whose primary treatments failed [33]. This study validated previously reported outcome correlations and furthermore showed that a gene signature of macrophages was linked to primary treatment failure. In a number of immunohistochemistry-based follow-up studies, multiple groups demonstrated that the enumeration of CD68+ macrophages in lymph node biopsies was a strong and independent predictor of disease-specific survival [35]. Specifically, an elegant retrospective study using Intergroup E2496 trial material (comparing ABVD to the Stanford V regimen) showed that high abundance of both CD68+ and CD163+ cells was correlated with shorter progression-free and overall survival independent of the IPS [36]. Importantly, the latter study used a computer-based scoring algorithm (Aperio) and systematically derived scoring thresholds that were tested in an independent validation cohort. Maximizing the concept of combining markers for building outcome predictors, a recent study used the same E2496 trial material to train a predictive model using intermediate density digital gene expression profiling developed in and applicable to routinely collected formalin-fixed paraffin-embedded tissue [37]. In this study the authors developed a 23-gene predictive model and associated thresholds to distinguish high-risk from low-risk advanced-stage Hodgkin lymphoma using overall survival as the end point. Encouragingly, when applied to an independent cohort treated with ABVD chemotherapy, the model validated the results in the E2496 training cohort identifying the patient at high risk of death. Follow-up studies are needed to further validate and implement biomarker assays for potential routine clinical use, risk stratification, and assessment as a predictive biomarker possibly guiding initial treatment decisions.

To date, cHL research has been for the most part focused on primary specimens, and only a few studies have explored the biology of relapse. However recently, the feasibility of biomarker studies and assay development at the time point of relapse was demonstrated in the context of outcome prediction of salvage therapy and ASCT [38]. The authors demonstrated that gene expression patterns, reflecting TME composition, differ significantly between matched primary and relapse specimens in a subset of cHL patients. Based on the superior predictive properties of gene expression measurements in relapse specimens, a novel clinically applicable prognostic model/assay (RHL30) was developed that identifies a subset of patients at high risk of treatment failure following salvage therapy and ASCT. Specifically, RHL30 identifies a high-risk group of patients with significantly inferior post-ASCT-FFS compared to the low-

risk group (5-year: 23.8% high-risk vs. 77.5% low-risk) and also inferior post-ASCT-OS (5-year: 28.7% high-risk vs. 85.4% low-risk). Importantly, the prognostic power of RHL30 was reproduced in two separate validation cohorts of relapse specimens, and the RHL30 was statistically independent of all previously described prognostic markers in the validation cohorts, including post-salvage therapy response assessment by PET/CT [38].

5.6 Conclusions and Future Perspective

The advent of next-generation sequencing has significantly added to the armamentarium of genomics techniques interrogating tumor genetics of cHL and elucidating the molecular underpinnings of the unique crosstalk of the malignant HRS cells with their immune microenvironment. The sequencing studies of ctDNA and enrichment of HRS cells confirmed the importance of, and added texture to, the known molecular hallmarks of NFκB, JAK-STAT, and PI3K signaling as well as immune privilege phenotypes. Moreover, gene expression profiling studies of the microenvironment have reached more maturity in comprehensively describing cellular compartments in the TME and validated key correlations to pathologic and clinical outcome data. In particular, effective biomarker assay translation appears more and more realistic with the emergence of methods that are compatible with FFPE tissues that can be applied to relapse biopsies and are minimally invasive (e.g., serial peripheral blood draws) for dynamic biomarker testing. Despite these most recent advances, a number of challenges and open questions remain that need to be addressed in future studies. First, with respect to cHL biology, no unique and specific somatic gene mutations have been identified that would explain the unique histopathology of cHL in contrast to other lymphomas, leaving room for future discoveries. Second, systematic integration of HRS cell genomics with features and cellular components of the TME are lacking. Third, sample numbers for genomic landscape studies are still limited to be fully powered for mutational pattern analysis and robust outcome correlates in patients treated with standard of care. Finally, with the emergence of targeted therapies (e.g., brentuximab vedotin [39]) and modern immunotherapies (e.g., checkpoint inhibitors [40] or bispecific antibodies [41]), predictive biomarker development using genomics has to be prioritized alongside the next generation of clinical trials and population-based outcome studies of patients receiving these novel therapies in the standard of care setting. Excitingly, novel cutting-edge genomics techniques might also overcome some of the described obstacles, including HRS cell sequencing, to interrogate the non-coding space (e.g., whole genome sequencing), epigenetic profiling (e.g., ATAC-seq, bisulfite sequencing), and RNAseq at the single cell level to characterize the TME. Integrating these novel genomics approaches for dynamic, multi-time point biomarker testing alongside existing and novel therapeutic approaches holds the great promise to fully realize the benefits of precision medicine by genomics-driven clinical decision-making.

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Part II

Diagnosis and First-Line Treatment

Clinical Evaluation

6

James O. Armitage and Jonathan W. Friedberg

Contents

6.1 Presenting Manifestations

Hodgkin lymphoma can come to clinical attention in a variety of ways. These include symptoms caused by a growing mass and systemic symptoms that are presumably cytokine induced, and a diagnosis can be made incidentally as part of an evaluation for an unrelated problem. By far the most common presentation of Hodgkin lymphoma is the enlargement of lymph nodes that is typically painless and progressive. Although the most common place for lymph nodes to be found is in the neck and supraclavicular region, any lymph node-bearing area can be involved. Patients typically find enlarged nodes above the clavicle and seek medical attention when they do not regress, while physicians are relatively more likely to discover lymph nodes in other areas as part of a physical examination. Mediastinal lymphadenopathy is a particularly common finding in young women with Hodgkin lymphoma. This might be found incidentally on a chest X-ray or can be symptomatic.

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_6

Although unusual, patients with Hodgkin lymphoma can present with superior vena cava syndrome, but chest pain, cough, and shortness of breath are more common symptoms caused by a large mediastinal mass. Lymphadenopathy found only below the diaphragm is more common in males and in elderly patients. Mesenteric lymphadenopathy is unusual in Hodgkin lymphoma. Retroperitoneal lymphadenopathy can be painful, but is more commonly asymptomatic and found on a staging evaluation or as part of the investigation to explain system symptoms such as fever, night sweats, or weight loss. Epitrochlear lymph node involvement is unusual in Hodgkin lymphoma.

Hodgkin lymphoma can involve essentially any organ in the body as either a site of presentation or by spread from lymphatic involvement. However, extranodal presentation of Hodgkin lymphoma is unusual. The most common sites to be involved are the spleen, liver, lungs, pleura, and bone marrow, although Hodgkin lymphoma confined to these sites is rare. Hodgkin lymphoma can rarely present in unusual extranodal sites. Primary CNS [1] and cutaneous [2] Hodgkin lymphoma are rare but well described. Perianal presentations are seen more commonly in patients with HIV infection. Gastrointestinal system, bone, genitourinary system, and other unusual sites are extremely rare but have been described. Bone involvement can be seen as an "ivory vertebrae," i.e., a densely sclerotic vertebrae [3].

By far the most common systemic symptoms that occur as the presenting manifestations of Hodgkin lymphoma are fevers, night sweats, weight loss, pruritus, and fatigue. These occur in a minority of patients but can present diagnostic challenges. Hodgkin lymphoma is one of the illnesses that can cause fever of unknown origin. Occasionally the fevers of Hodgkin lymphoma occur intermittently with several days of fevers alternating with afebrile periods. This is the Pel-Ebstein fever [4, 5] that is rare, but typically occurs in the evening. Fevers from Hodgkin lymphoma can be prevented with nonsteroidal anti-inflammatory drugs such as naproxen [6].

The presence of drenching night sweats (i.e., as opposed to dampness of the head and neck) and unexplained weight loss are both characteristics of Hodgkin lymphoma and, along with fever, are associated with a poor prognosis. Pruritus can be the presenting manifestation of Hodgkin lymphoma. Such patients sometimes have severely excoriated skin and sometimes have been diagnosed as having neurodermatitis. Patients who present with refractory pruritus are often grateful to find the explanation of their symptoms which usually disappear with the initiation of therapy. As with other lymphomas, fatigue can be an important, although nonspecific, symptom and also usually improves with therapy. There are many unusual, but well-described, presentations for Hodgkin lymphoma. One rare but very characteristic presentation is alcohol-induced pain [7, 8]. The pain typically begins soon after drinking alcohol and occurs primarily in areas of involvement by lymphoma. The pain can be quite severe and last for variable periods of time. Patients with the symptom have often discontinued alcohol before the diagnosis of Hodgkin lymphoma, and to elicit the symptom often requires specific questioning by the physician.

Patients can present with Hodgkin lymphoma involving the skin, but cutaneous abnormalities are more often paraneoplastic phenomenon. These can include erythema nodosum [9]; ichthyosiform atrophy [10]; acrokeratosis paraneoplastica [11]; granulomatous slack skin [12]; nonspecific urticarial, vesicular, and bullous lesions [13]; and others.

A variety of other unusual presentations of Hodgkin lymphoma have been reported. Patients can present with nephrotic syndrome [14], symptoms of hypercalcemia [15–17], jaundice due to cholestasis without involvement of the liver by the lymphoma, and the "vanishing bile duct syndrome" [18, 19].

Hodgkin lymphoma very rarely presents with a primary tumor in the CNS causing the symptoms of a brain tumor characteristic of the site of involvement. Other neurological manifestations that can be present at the diagnosis of Hodgkin lymphoma involve a variety of paraneoplastic syndromes. These include paraneoplastic

cerebellar degeneration [20], which typically presents with ataxia, dysarthria, nystagmus, and diplopia. The symptoms may precede the diagnosis of Hodgkin lymphoma by many months. Hodgkin lymphoma can, of course, present with spinal cord compression from retroperitoneal and osseous tumors. Other rare manifestations include limbic encephalitis (i.e., which presents with memory loss and amnesia), peripheral neuropathy, and others.

6.2 Physical Findings and Laboratory Abnormalities

By far the most common physical findings in Hodgkin lymphoma are enlarged lymph nodes that might be in any lymph node-bearing area. The lymph nodes are typically firm (i.e., "rubbery") and vary from barely palpable to large masses. However, almost any aspect of the physical examination can be made abnormal by the presence of Hodgkin lymphoma. This might include icterus, involvement of Waldeyer's ring, findings of superior vena cava syndrome, a sternal or suprasternal mass from tumor growing out of the mediastinum, findings of a pleural effusion or pericardial fusion, an intra-abdominal mass, hepatomegaly or splenomegaly, skin involvement, and, rarely, cutaneous or neurological abnormalities.

Almost any laboratory test can be abnormal at the time of diagnosis of Hodgkin lymphoma, but certain tests are characteristic and should be specifically evaluated. Patients can have leukocytosis or leukopenia. Neutrophilia and lymphopenia are sometimes seen and can confer a poor prognosis. Eosinophilia can be found incidentally before the diagnosis of Hodgkin lymphoma, and Hodgkin lymphoma should always be included in the differential diagnosis of unexplained eosinophilia [21]. In some cases, the explanation of the eosinophilia is related to production of interleukin-5 by the tumor cells [22, 23].

The most common hematological manifestation of Hodgkin lymphoma is anemia. The most usual explanation seems to be a normocytic anemia associated with the presence of the tumor that resolves after therapy. However, patients can also have autoimmune hemolytic anemia [24] and a microangiopathic hemolytic anemia as part of the syndrome of thrombotic thrombocytopenic purpura has been reported.

Patients can present with thrombocytopenia for a variety of reasons including hypersplenism and bone marrow involvement. However, idiopathic thrombocytopenic purpura can be a presenting manifestation of the disease [25].

Other rare hematological manifestations of Hodgkin lymphoma have included autoimmune neutropenia [26], hemophagocytic syndrome [27], coagulation factor deficiencies [28], and unexplained microcytosis [29].

Routine chemistry screening should be done in patients with Hodgkin lymphoma and might reveal renal or hepatic dysfunction, protein abnormalities, hypercalcemia, and hyperuricemia.

Elevated erythrocyte sedimentation rate and C-reactive protein are frequently seen and have been associated with a poor prognosis.

6.3 Pathologic Diagnosis: The Biopsy

The oncologist must be certain that the Hodgkin lymphoma diagnosis was based on an adequate biopsy specimen that was examined using appropriate morphologic and immunohistochemical criteria. Whole lymph node excision is preferable for pathologic examination. The pathologic diagnosis of Hodgkin lymphoma is fully discussed in Chap. 3.

The site of biopsy must be determined with the radiologist and surgeon. In general, the largest abnormal peripheral lymph node should be excised. If a fluorine-18-deoxyglucose positron emission tomography (FDG-PET) has been performed, the patient should be biopsied in the most avid site to avoid a partially necrotic zone.

If there are only deep nodes, the following types of biopsy can be proposed. A thoracoscopic or laparoscopic approach under general

anesthesia with, if necessary, preoperative localization to facilitate resection can be performed [30]. Image-guided core needle biopsy is increasingly used and has a rising success rate of more than 90% [31–33]. However, the method has the disadvantage of only permitting relatively small biopsies. In addition, this type of biopsy is capable of sampling several core specimens with a single biopsy tract. Large-volume cutting needles, ranging from 18 to 14 G, yield enough tissue for most immunochemistry stainings and even for RNA extraction from frozen tissue (Fig. 6.1). Fine-needle aspiration cytology should *not* be used for diagnosis of Hodgkin lymphoma, but may help in a screening procedure, before biopsy [34].

Several pathologic pitfalls or differential diagnoses should be kept in mind. Drugs such as phenytoin or antibiotics may cause histologic changes within lymph nodes that may mimic Hodgkin lymphoma, particularly the mixed cellularity subtype. Other benign conditions like infectious mononucleosis, lymphoid hyperplasia, or Castleman disease may produce lymphadenopathy with histologic features similar to those of Hodgkin lymphoma. In fact, the distinction between different diseases, including certain forms of non-Hodgkin lymphoma (NHL), has been made clearer, thanks to a better definition of the entities by the WHO classification. T-cell-rich large B-cell lymphoma is usually included in the differential diagnoses of both nodular lymphocyte-predominant Hodgkin lymphoma and classical Hodgkin lymphoma, while anaplastic CD30-positive NHL may display similar histology to that of classical Hodgkin lymphoma. Nevertheless, molecular studies require adequate material, sometimes including frozen tissue in difficult cases, and the role of the clinician is to make sure that the node to be analyzed is given to an experienced laboratory. If the clinical presentation of disease is not typical for the given pathologic diagnosis, then a review of the pathology by an expert hematopathologist should be considered or even a second biopsy.

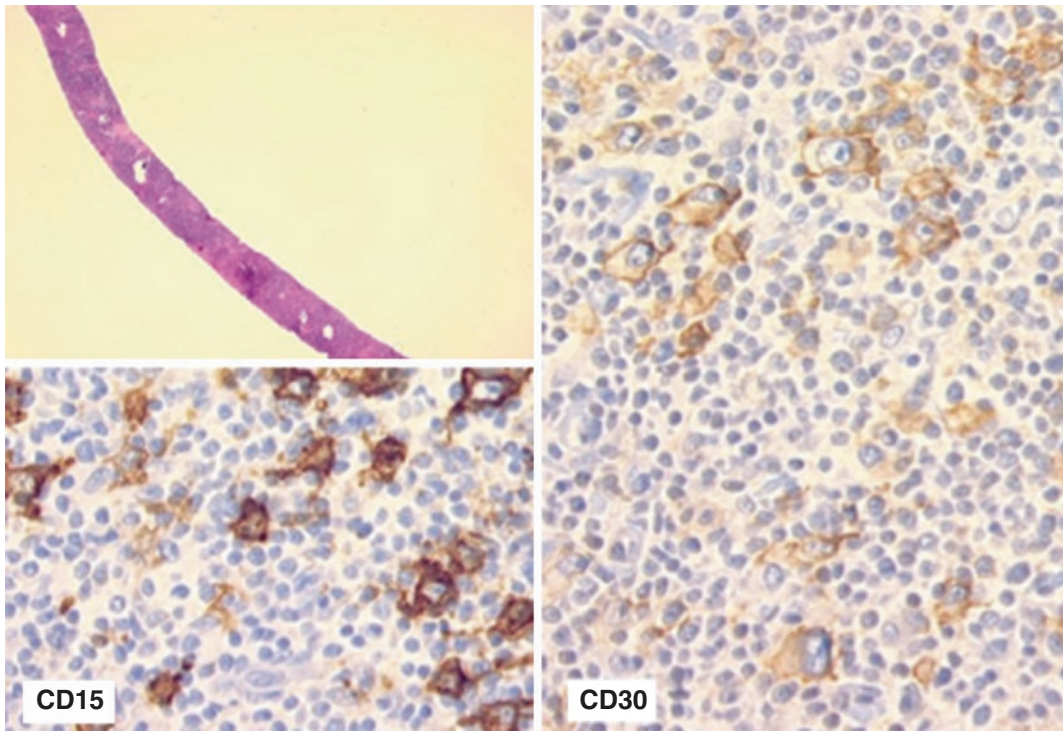

Fig. 6.1 Core needle biopsy for Hodgkin lymphoma with immunostainings for CD15 and CD30

6.4 Staging Systems for Hodgkin Lymphoma

The initial clinical evaluation and staging of patients with Hodgkin lymphoma serve to confirm the Hodgkin lymphoma diagnosis, determine the extent and distribution of disease, evaluate the patient's fitness for standard treatments, and provide prognostic information (Table 6.1).

Several staging systems were developed very early and modified according to the progress made in imaging and treatment of the disease. The Ann Arbor staging was developed in the

Table 6.1 Lugano classification

Revised staging system for primary nodal lymphomas				
Stage	*Involvement*			*Extranodal (E) status*
I	One node or a group of adjacent nodes			Single extranodal lesions
II	Two or more nodal groups on the same side of the diaphragm			Stage I or II
II bulky[a]	II as above with "bulky" disease			Not acceptable
Advanced III	Nodes on both sides of the diaphragm, nodes above the diaphragm with spleen involvement			Not acceptable
IV	Additional noncontiguous extralymphatic involvement			Not acceptable
NOTE: Extent of disease is determined by positron emission tomography for avid lymphomas and computed tomography for non-avid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue [a]Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors				
Criteria for involvement of site				
Tissue site	*Clinical*	*FDG avidity*	*Test*	*Positive finding*
Lymph nodes	Palpable	FDG-avid histologies	PET-CT CT	Increased FDG
Spleen	Palpable	FDG-avid histologies Non-avid disease	PET-CT CT	Diffuse uptake with SUV > liver, solitary mass, miliary lesions, nodules >13 cm
Liver	Palpable	FDG-avid histologies Non-avid disease	PET-CT CT	Diffuse uptake, mass nodules
CNS	Signs, symptoms		CT MRI CSF assessment	Mass lesion(s), leptomeningeal infiltration, mass lesions, cytology, flow cytometry
Other (leg, skin, lung, GI tract, bone, bone marrow)	Site dependent		PET-CT[b], biopsy	Lymphoma involvement
CSF cerebrospinal fluid, *CT* computed tomography, *FDG* fluorodeoxyglucose, *MRI* magnetic resonance imaging, *PET* positron emission tomography [b]PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary				

(continued)

Table 6.1 (continued)

Revised criteria for response assessment	
Response and site	*PET-CT-based response*
Complete Lymph nodes and extralymphatic sites	Complete metabolic response Score 1, 2, or 3[c] with or without a residual mass on 5PS+ It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within the spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal in the mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than the surrounding normal tissue even if the tissue has high physiologic uptake
Non-measured Organ enlargement New lesions Bone marrow	Not applicable Not applicable None No evidence of FDG-avid disease in marrow
Partial Lymph nodes and extralymphatic sites	Partial metabolic response Score of 4 or 5+ with reduced uptake compared with baseline and residual mass(es) of any size At interim, these finding suggest responding disease At the end of treatment, these finding indicate residual disease
Non-measured lesions Organ enlargement	Not applicable Not applicable
New lesions Bone marrow	None Residual uptake is higher than the uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan
No response or stable disease Target nodes/nodal masses, extranodal lesions	No metabolic response Score 405 with no significant change in FDG uptake from baseline at interim or end of treatment
Non-measured lesions Organ enlargement New lesions Bone marrow	Not applicable Not applicable None No change from baseline
Progressive disease Individual target nodes/nodal masses Extranodal lesions	Progressive metabolic disease Score 4 or 5 with an increase in intensity or uptake from baseline New FDG-avid foci consistent with lymphoma at interim or end of treatment assessment

Table 6.1 (continued)

Non-measured lesions	None
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., leg infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or internal scan may be considered
Bone marrow	New or recurrent FDG-avid foci

5PS 5-point scale, *CT* computed tomography, *FDG* fluorodeoxyglucose, *IHC* immunohistochemistry, *LDi* longest transverse diameter of a lesion, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *PPD* cross product of the LDi and perpendicular diameter, *SDi* shortest axis perpendicular to the LDi, *SPD* sum of the product of the perpendicular diameters for multiple lesions

_A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than the surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors)

[c]PET 5PS: 1, no uptake above background; 2, uptake _ mediastinum; 3, uptake _ mediastinum but _ liver; 4, uptake moderately _ liver; 5, uptake markedly higher than the liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma

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1970s, when radiotherapy was the main curative treatment option, and was based on the tendency of Hodgkin lymphoma to spread to contiguous lymph nodes [35].

Since the Ann Arbor staging, several significant changes in the management of Hodgkin lymphoma have taken place. The Cotswolds modification of the Ann Arbor staging system was introduced in 1989 to approve the use of CT scanning for the detection of intra-abdominal disease, to formalize a definition of disease bulk, and to provide guidelines for evaluating the response to treatment [36]. The current standard is the Lugano classification which addresses both staging and re-staging (Table 6.1) [37].

A prognostic factor score for advanced Hodgkin lymphoma treated by chemotherapy has been worked out, based mostly on biological parameters, including serum albumin <4 g/dL, hemoglobin <10.5 g/dL, male sex, stage IV disease, age >45 year, white cell count >15,000 mm^{-3}, and lymphocyte count <600 mm^{-3} [38].

These prognostic factors are used to define risk-adapted therapy. However, as combined modality treatment with modern chemotherapy has become the standard procedure for patients with early-stage disease, the risk of relapse is reduced, and some of these factors are no longer associated with a high risk of relapse. In addition, computed tomography (CT) and fluorine-18-deoxyglucose positron emission tomography (FDG-PET) are now routinely used for the staging and evaluation of the response to treatment. PET-CT provides reliable information on treatment efficacy.

6.5 Imaging Evaluation of the Extent of Disease

Thanks to the progress and availability of imaging techniques, it has been possible to improve the accuracy of clinical staging, so that invasive pathologic procedures are rarely necessary. At present, the established radiological technique for the diagnosis of Hodgkin lymphoma is FDG-PET [39].

FDG-PET is based on the increased glycolysis of cancer cells. This is visualized using the radioactive glucose analog FDG, which after phosphorylation is metabolically trapped within the cell. Thus, FDG-PET has become an established imaging modality to stage, restage, and monitor therapy and detect recurrent lymphoma. PET and CT, which, respectively, supply metabolic and anatomic information, are complementary, and interpretation of the PET portion of the study is more accurate when the results of PET correlate with those of CT [40, 41]. Therefore, integrated PET-CT systems were developed which are now the standard care [42]. If PET-CT is not available, an alternative imaging technique is computed tomography (CT) scan of the neck, chest, abdomen, and pelvis. In rare cases where it is desirable to avoid radiation exposure (such as pregnancy), MRI may be utilized as a substitute for CT imaging.

It is important that imaging results be interpreted within the framework of the known patterns of spread and other prognostic factors. A certain degree of variation in the size of mediastinal and hilar nodes is normal, but those measuring more than 10 mm on the shortest cross section can be considered abnormal. However, although clearly abnormal findings on CT scanning may be indicative of Hodgkin lymphoma, there is a risk of false positives, particularly in the abdomen, when interpreting these findings. Therefore, when lymph nodes in the 15–20 mm range are seen, uptake on FDG-PET-CT is indicative of involvement by lymphoma.

Substantial variations in stage assignment have nevertheless been demonstrated among patients with extranodal involvement, specifically regarding the distinction between stage IV and early-stage extranodal disease. Thus, even experienced oncologists vary in their stage assignment of patients with nearby but discontinuous extranodal involvement [43]. However, the involvement of two or more noncontiguous extranodal sites should typically be considered indicative of stage IV disease. The use of risk-adapted treatment with chemotherapy has reduced the importance of such factors.

The definition of bulk has varied considerably in the literature. For the mediastinum, one definition involved measuring the greatest transverse diameter of the mediastinal mass on a standard posteroanterior chest radiograph and dividing it by the maximal diameter of the chest wall at its pleural surfaces, usually at the level of the diaphragm or alternatively at the T5–T6 interspace (Cotswolds approach) [36]. A ratio exceeding one third (1:3) was considered bulky and a negative feature among patients treated with RT alone or chemotherapy alone. There are no widely accepted criteria for the definition of bulk using measurements obtained from CT scans: the Cotswolds Committee recommended that to constitute bulk, a nodal mass must be greater than 10 cm in diameter [36], whereas in some ongoing trials, bulk was defined as confluent nodal masses greater than 7 cm [44]. The Lugano criteria states that a single nodal mass, in contrast to multiple smaller nodes, of 10 cm or greater than a third of the transthoracic diameter at any level of thoracic vertebrae as determined by CT is the definition of bulky disease for HL. A chest X-ray is not required to determine bulk because of its high concordance with CT [37].

It appears that FDG-PET can largely eliminate the necessity for doing bone marrow biopsies in patients with Hodgkin lymphoma. One report of 454 patients found that no patients with a FDG-PET scan assigned stage of 1 or 2 had a positive bone marrow biopsy. The presence of focal skeletal FDG-PET scan lesions identified positive and negative bone marrow biopsies with a sensitivity and specificity of 85% and 86%. A negative FDG-PET scan for skeletal lesions had a 99% negative predictive value for the results of a bone marrow biopsy [37, 45].

6.6 Clinical Evaluation During Therapy

Clinical evaluation during treatment can be an important component of the individualization of treatment intensity. A rapid early response to initial therapy is increasingly recognized as a favorable prognostic factor among Hodgkin lymphoma patients. Response can be evaluated by FDG-PET-CT after two or three cycles of chemotherapy. Performing PET early during treatment has also proved to be prognostically important and has been incorporated into the response criteria. Thus, a meta-analysis demonstrated that for low- to intermediate-risk Hodgkin lymphoma patients, PET may be a good prognostic indicator after a few cycles of standard chemotherapy [46].

FDG-PET scans performed after two cycles of therapy are increasingly being utilized to guide subsequent treatment [47–50]. The results of interim FDG-PET scans have been used to shorten the duration of therapy, to complete a "standard" course of chemotherapy, to escalate treatment to more intensive chemotherapy in patients with a slow response, and to deescalate therapy in patients with an excellent response.

6.7 Definition of the Response to Treatment

FDG-PET scans have revolutionized determination of response to therapy in patients with Hodgkin lymphoma. The often called "Lugano criteria" have become the standard approach in determining treatment response [51]. A key to improving our ability to determine response to therapy was standardization of interpretation of PET scans. The so-called 5-point or Deauville scoring system is recommended in the Lugano criteria (Table 6.2) [37].

This system appears to have a high interobserver agreement. There has been debate about what should be the definition of a complete remission using the 5-point score. The consensus appears to be a 5-point score of 3 or less is the definition of a complete remission at the end of therapy. Some studies of interim PET scans, where the interim PET scan will be used to guide possible treatment changes, have chosen to use a more conservative 5-point score of 2 or less to identify an early complete remission [47]. Ongoing studies are evaluating other criteria, such as total metabolic tumor volume change, and SUV change over time which may have less variability between observers.

Table 6.2 5-point score (Deauville score)

Score	Definition
1	No uptake in sites of suspected lymphoma
2	Uptake but less than that seen in the mediastinum
3	Uptake greater than seen in the mediastinum, but less than seen in the liver
4	Uptake moderately higher than seen in the liver
5	Uptake markedly higher than the liver and/or new lesions

6.8 Complete Remission

The patient has no clinical, radiologic, or other evidence of Hodgkin lymphoma. Changes due to the effects of previous therapy (i.e., radiation fibrosis) may, however, be present.

The category (CRu) has been eliminated from the updated response criteria and now denotes patients whose remission status is unclear, because they display no clinical evidence of Hodgkin lymphoma, but some radiologic abnormality that persists at a site of previous disease. In this respect, it is generally recognized that imaging abnormalities may persist following treatment and do not necessarily signify active disease [52].

It must be borne in mind that after mediastinal RT, thymic rebound, reactive lymph node hyperplasia, or subclinical radiation pneumonitis may lead to abnormalities on FDG-PET [53]. To avoid false-positive interpretations, some authors recommend that FDG-PET re-evaluation should be delayed until 3 months after the completion of mediastinal RT, although the characteristic appearance of post-RT lung changes occurring before 3 months can usually be distinguished from lymphoma by experienced nuclear radiographers [42].

The inclusion of PET in the new response criteria and the removal of CRu have simplified the management of lymphoma patients by removing some of the limiting factors of CT, which include the size of lymph nodes that indicates involvement, the differentiation of unopacified bowel from lesions in the abdomen and pelvis, the inability to distinguish viable tumor from necrotic/fibrotic lesions after therapy, and the characterization of small lesions. A combined PET-CT scan with a Deauville score of 1, 2, or 3 is consistent with complete remission.

6.9 Follow-Up Management

The manner in which patients are evaluated after completing treatment may vary according to whether treatment was administered in a clinical trial or clinical practice and whether it was delivered with curative of palliative intent. In a clinical trial, the requirement of uniform reassessment may lead to follow-up studies that would not be routinely done in practice.

Follow-up should involve identifying relapse but also focus on identifying and dealing with long-term adverse effects of treatment. These can include secondary cancers, cardiac toxicity, thyroid disease, depression, and fertility issues [54].

Good clinical judgment, careful recording of history, and a thorough physical examination are the most important components of monitoring patients after treatment. A complete blood count, selected serum chemistry studies, and a sedimentation rate are frequently done with each visit. However, there is no evidence to support the need for regular surveillance CT scans. The patient or physician identifies the relapse in more than 80% of cases without imaging studies [55]. The most important potential reason to do surveillance imaging would be the detection of early relapse that allowed early institution of salvage therapy and increased survival. However, there is no evidence to support this hypothesis. One study of 241 patients that compared patients treated at different centers who did or did not do routine surveillance imaging found a 97% overall survival rate in patients who received routine surveillance imaging and a 96% 5-year survival rate in patients who were only followed clinically [56]. In both groups, salvage therapy was effective with only one patient in the routine surveillance imaging group dying of Hodgkin lymphoma. It was calculated that each relapse detected by surveillance imaging costs $629,615, with no benefit in eventual outcome. Similar results have been found in the use of surveillance imaging in pediatric Hodgkin lymphoma [57].

In addition to financial costs, surveillance imaging has other "side effects." One study found that patients undergoing surveillance imaging had increased anxiety and fear associated with the images [58]. In addition, it is known that CT scans deliver a high level of radiation and are a significant cause of cancer [59, 60].

An alternative to using CT scans would be the use of FDG-PET scans as a potential tool for the detection of relapse. However, in a prospective study of 36 Hodgkin lymphoma patients, routine FDG-PET correctly identified all 5 relapses that followed treatment, but had a false-positive rate of 55% [61]. A more recent study using PET-CT scans showed a positive predictive value of only 28% for routine PET-CT scans for surveillance for relapse [62]. Given the observation that patients with cHL who are event-free at 2 years have an excellent outcome regardless of baseline prognostic factors, surveillance imaging beyond 2 years has not been demonstrated to have value [63].

6.10 Conclusion

The careful and accurate clinical evaluation of patients with Hodgkin lymphoma from presentation to follow-up in remission has a significant impact on treatment outcome. The ability to perform an excellent history and physical and knowledge regarding when, where, and how to perform laboratory evaluations, images, and biopsies are necessary for excellent care.

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7 Functional Imaging in Hodgkin Lymphoma

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_7

7.1 Introduction

Hodgkin lymphoma (HL) has become a highly curable malignancy with more than 90% of patients alive and 80% considered cured after long-term follow-up [1, 2]. Risk-adapted strategies have further led to improved outcomes for high-risk patients, with less toxicity for low-risk patients [3–7].

The staging of HL has undergone a major evolution. Imaging technology in this disease has evolved over the past decades from the lymphangiogram to the intravenous pyelogram, ultrasound, liver-spleen radionuclide scan, computed tomography (CT), and magnetic resonance imaging. Gallium scanning required a 2-day interval between injection and scanning, which was not clinically practical [8]. Today, positron emission tomography combined with computed tomography (PET-CT) is the basis for staging and response assessment [9–12]. Response assessment with CT uses changes in tumor size as the main criterion. However, tumor shrinkage occurs over time, and fibrosis in HL may take years following treatment to disappear. With these limitations, CT does not provide a sufficiently accurate early assessment of response [13]. In contrast, PET depends on tumor metabolism rather than anatomy. Positron emission tomography using [18F]-fluoro-2-deoxy-D-glucose (FDG-PET) provides an assessment of chemosensitivity when performed early during standard treatment [14–17].

In HL tissue, scattered neoplastic Hodgkin Reed-Sternberg cells usually account for less than 1% of the total cell count. Recently it has been recognized that the malignant cells are able to evade the immune system because of overproduction of the programmed death ligands (PDL) PDL-1 and PDL-2 [18], despite the extensive infiltration of lymph nodes by inflammatory cells. The consequence is suppression of T-cell activation and failure of immune recognition. The relevance of this interaction is exemplified by the efficacy of checkpoint inhibitors in HL patients [19–21].

Functional imaging is critical for accurate staging, restaging, and follow-up assessment of patients with HL [9, 10]. Metabolic imaging is currently performed using FDG-PET. This technology has become the most sensitive and specific technology, allowing us to better manage HL patients [10]. A variety of clinical studies have established the role of PET-CT scanning in the risk-adapted management of HL patients, leading to improved outcomes and reduced toxicity [3, 4, 22].

Despite major advances in patient outcome, further refinements are warranted not only in the interpretation of PET-CT but also in determining how best to incorporate PET into patient management. In this chapter, we will review the history of metabolic imaging in HL and its usefulness in the staging and response assessment, including its role in risk-adapted strategies allowing for improved outcome for high-risk patients and decreased toxicity for low-risk patients. We will also discuss the current gaps in the application of PET-CT, potential means to improve the current response criteria, and speculate on the future of metabolic imaging in the management of HL patients. Newer and potentially more specific PET tracers are also under investigation and will be discussed in this chapter.

7.2 History of Imaging in Hodgkin Lymphoma

HL has been for long considered the paradigm for tumor staging in oncology [23]. In the early 1970s, the Ann Arbor conference [23] and later the Cotswold revised classification [24] introduced the concept that the disease spread per se is able to identify distinct categories of patients with different prognosis and treatment outcome. Staging laparotomy using splenectomy and multiple nodal and organ biopsies including bone marrow trephine biopsy (BMB) was originally proposed as an accurate diagnostic means for tumor staging [25]. This procedure had the merit of shedding more light on the physiopathology of tumor spread, becoming the "gold standard" to assess sensitivity, specificity, and overall accuracy of newly emerging radiological imaging [26].

In April 1970, during the Ann Arbor conference in Michigan, the concept of four-stage clinical staging (CS) was initially introduced to distinguish patients staged with clinical and radiological means from those more accurately staged with pathological staging (PS) [23]. Nonetheless, the high accuracy of surgical staging was deemed no longer necessary with the advent of active multi-agent chemotherapy such as MOPP (mechlorethamine, vincristine, procarbazine, and prednisone). However, MOPP also led to sterilization in more than 80% of patients treated [27]. Bipedal lymphography and contrast-enhanced computed tomography (ceCT) very soon superseded the invasive procedures of PS including staging laparotomy, with the notable exception of BMB. The latter became the only invasive technique used for staging, as CT proved insufficient for evaluation of HL infiltration in the bone marrow. Meanwhile, the disease burden and the host reaction against the tumor proved as the main prognostic parameters correlating with survival. This subsequently provided the basis for a new classification of prognostic factors in HL as (a) tumor related, (b) host related, and (c) environment related [28], providing the frame for three different risk groups of HL patients with different long-term prognosis: the early favorable, early unfavorable, and advanced HL [29].

The clinical and radiological procedures of HL staging, the definition of bulky nodal lesion, and the nomenclature to define response to treatment have been described and standardized during the Cotswold meeting in 1989 [24]. In the early nineties, another step forward in the tumor staging accuracy was the use of functional imaging with ^{67}Ga scintigraphy initially, and later with positron emission tomography (PET), using the glucose analogue ^{18}F-fluorodeoxyglucose (FDG). The latter was able to trace viable tumor tissue selectively, thus resulting in the more accurate diagnostic tool so far evaluable for lymphoma staging and restaging. With the introduction of integrated FDG-PET/CT scanners, unsuspected nodal and extranodal lesions were detected, which otherwise would have been missed by the current diagnostic tools, including ceCT and BMB [30]. FDG-PET/CT showed a better sensitivity and a similar specificity compared to FDG-PET stand alone and CeCT in detecting nodal and extranodal disease [9, 10]. In HL and diffuse large B-cell lymphoma (DLBCL), the bone and bone marrow was by far the most frequently detected extranodal site followed by the liver, lung, and spleen. Due to the lower overall accuracy of BMB compared to FDG-PET/CT in detecting bone or bone marrow, BMB was abandoned as the standard diagnostic tool to detect BMI by HL and DLBCL [31, 32].

7.3 Background of PET and the FDG Tracer

7.3.1 Basic Principles of PET

PET is a functional imaging modality based on measurements of radiation from the decay of positron-emitting radioactive nuclides. These nuclides have excess protons which transform to neutrons under the emission of positrons (β+-decay). The positron randomly travels 2–3 mm in the tissue before it annihilates via collision with an electron, and thereby emitting two photons (each 511 keV) at an angle very close to 180°. The two photons are registered by the ring of scintillation detectors in the PET scanner. Two

511 keV photons registered simultaneously (or within a very narrow time frame) by two opposing detectors are considered a coincidence event originating from positron annihilation. A PET scanner holds several thousands of scintillation detectors, organized in detector rings. The detector rings may be separated by leaded ring collimators (2D mode) in order to limit sources of noise in the PET images. Data acquisition can be either static or dynamic, and the data generated provide both quantitative information and images. The spatial resolution of PET is typically around 3–5 mm, limited by the number of detectors and by the random travel of the positron [33]. The unstable positron-emitting isotopes used in PET are produced by fusion of stable nuclei with other particles. This is possible in a cyclotron, in which the electrical repulsion between particles is overcome by accelerating particles up to 30% of the speed of light with a beam toward the target [34]. A radiochemistry laboratory is needed to attach the isotopes to relevant tracer molecules. The most common PET isotope molecules are ^{15}O, ^{13}N, ^{11}C, and ^{18}F [35]. PET tracers of relevance to oncology target glucose metabolism, hypoxia, blood flow, proliferation, amino acid transport, protein synthesis, DNA synthesis, apoptosis, and specific receptors.

Fusion PET/CT scanners incorporate the hardware of high-resolution CT and PET into one scanner, so that PET and CT as well as fusion images are obtained in one scanning session. PET/CT scanners have been available commercially since the late 1990s and have now replaced the single-modality PET scanners. PET/CT provide anatomical localization of the FDG uptake, as well as better distinction between pathological findings and normal physiological uptake [36].

7.3.2 The FDG Tracer

The glucose analogue 2-[18F]fluoro-2-deoxyglucose (FDG) is the most versatile and the most widely used PET tracer. FDG is administered by intravenous injection. The use of FDG in tumor imaging is based on Warburg's finding that cancer cells show accelerated glucose metabolism [37]. FDG is transported into the cell via glucose transporter molecules (GLUT 1–5), which are overexpressed in cancer cells [38–40]. In the cell, FDG is phosphorylated by hexokinase to FDG-6-phosphate, which does not cross the cell membrane. Due to the low levels of glucose-6-phosphatase in cancer cells and the inability of FDG-6-phosphate to enter glycolysis, the tracer is retained in the cancer cells [41]. Generally, the uptake of FDG is related to the number of viable tumor cells [42, 43], but is dependent also on a number of physiological factors including regional blood flow, blood glucose level, and tissue oxygenation [44, 45]. FDG uptake is very high in HL, but since the HRS cells only make up a small fraction of the tumor volume, the surrounding cells are accountable for most of the increased FDG metabolism. FDG uptake is not tumor specific and accumulates in a range of non-malignant tissues, such as the brain, heart, and kidneys. Furthermore, activated inflammatory cells take up FDG, which can cause false-positive results in cancer imaging studies [46, 47]. This is obviously important not only since HL patients frequently experience infections but also because chemotherapy and radiotherapy induce inflammatory responses in the tumor cells and the surrounding tissue. Increased tracer uptake is seen in response to the early-phase tissue inflammation induced by chemotherapy, while a "stunned" uptake is observed immediately after therapy [48, 49].

7.4 PET in Clinical Management of Hodgkin Lymphoma

7.4.1 Staging

Currently, the original Ann Arbor nomenclature for HL staging is the standard tool to define disease prognosis and to guide treatment [23]. In the recent consensus statement of Lugano in 2014 for the use of FDG-PET for HL staging, the presence or absence of Systemic symproms (A or B substage definition) was still considered useful in HL to guide treatment as "B symptoms" were still considered adverse prognostic indicators [9].

As previously mentioned, a committee of experts convened in 2014 so that FDG-PET/CT

became the standard method to stage and restage the vast majority of lymphomas, including HL [9, 10]. FDG-PET became a paradigmatic example of the superiority of functional over classic radiological imaging for the following reasons: (1) FDG-PET showed a higher sensitivity for nodal staging; (2) FDG-PET was clearly superior in detecting extranodal disease, both in the bone marrow and in other organs; and (3) FDG-PET had a consistent, large influence on HL staging, with a potential impact on treatment strategy in a substantial number of patients, and this became even more evident upon introduction of integrated FDG-PET/CT scanners [50]. In an early pioneer study using FDG-PET alone, CT and fused FDG-PET/CT were prospectively compared in 99 newly diagnosed HL patients. In nodal regions, the sensitivity of PET and PET/CT was higher than that of CT (92% and 92% vs. 83%). FDG-PET had more false-positive nodal sites than CT and FDG-PET/CT (1.6% vs. 0.7% and 0.5%). For evaluation of organs, FDG-PET and FDG-PET/CT had higher sensitivity (86% and 73%), while CT detected only 37% of involved organs. In conclusion, FDG-PET/CT upstaged 19% and downstaged 5% of patients, leading to a treatment modification in 9% of patients [30]. A recent study prospectively compared a cohort of 96 HL patients [51]. Similar to the previous study, radiologists and nuclear medicine physicians were blinded to the outcome of the other modality and to the clinical course of the patients. The breakdown of patients according to stage I to IV based on CT vs. FDG-PET/CT was: 5 vs. 7, 49 vs. 37, 28 vs. 22, and 14 vs. 30, respectively. FDG-PET/CT changed the stage in 33 (34%) patients, 28% were upstaged and 6% downstaged. Upstaging was mainly caused by detection of new extranodal involvement (47 sites in 26 patients) including the bone marrow, spleen, and lung. Downstaging resulted from the absence of FDG uptake in enlarged nodes (<15 mm) in the abdomen and pelvis. FDG-PET/CT led to a treatment modification in 20 (21%) of the patients, with 16 patients being allocated to more intensive treatment [51]. The role of bone marrow infiltration (BMI) in stage upgrading was even more evident in recent reports on the role of FDG-PET/CT in staging of patients enrolled in the prospective UK National Cancer Research Institute RATHL clinical trial [52]. Out of 938 enrolled patients, FDG/PET-CT led to upstaging in 159 patients (14%) and downstaging in 74 (6%). The most frequent staging migration was from stage III to IV due to detection of disease spread to extranodal sites (ENS), most frequently in the bone marrow, lung, and others. In the cases of discrepant results, follow-up images confirmed the HL nature of the lesion detected by FDG-PET/CT only.

CT is insufficient for BMI evaluation in HL, while PET/CT detects skeletal FDG uptake in 10–20% of patients [53, 54]. This observation changed the perception that BMI is a rare occurrence in HL. Most studies using BMB for HL detection in the bone report a BMI frequency of only 5–8% [55]. The use of iliac crest bone marrow biopsy as a surrogate for the whole bone marrow compartment has been challenged by frequent finding of focal FDG lesions in the bone marrow in patients undergoing PET/CT staging. In addition, one-sided BMI has been reported in nearly half of the HL patients undergoing bilateral bone marrow biopsies [56]. In a recent large retrospective study performed by the German Hodgkin Study Group, Voltin et al. showed a PET/CT- detected BMI in 129/832 (15%) patients, while BMB was positive in only 20 (2%) [57]. With the gold-standard reference of either a positive PET scan (which becomes negative in subsequent follow-up scans) or a positive BMB or both, the sensitivity, specificity, positive, and negative predictive values of PET to detect BMI were 99.25%, 100%, 100%, and 99.9%, respectively. In conclusion, PET/CT has higher sensitivity for BMI than conventional BMB [31, 57, 58]. Rare patients with an undetected BMI by PET/CT at baseline almost exclusively present with advanced-stage disease based on PET/CT. Thus, the added diagnostic information from BMB very rarely leads to changes in clinical management [31]. As far as the pattern of FDG uptake is concerned, only focal uptake, defined as a single spot of FDG uptake at the bone level visible in at least two PET/CT slices with an intensity of FDG uptake $\geq$ liver, is considered as a harbinger of BMI. On the other hand, patients with a diffuse

FDG uptake (with an intensity ≥ liver) had disease outcomes identical to patients without any FDG uptake [53, 54].

Finally, one of the most interesting technological progress in PET/CT is the measurement of metabolic tumor volume (MTV) with more sophisticated software counting all voxel contained in a single contoured tumor lesion. To overcome the so-called partial volume effect, only voxel with an activity higher than a given threshold are counted. By multiplying the number of counted voxels using a fixed coefficient, it is possible to calculate the MTV expressed in cubic centimeters. (Fig. 7.1) Upon identification of the best cutoff value with ROC curve analysis, Cottereau et al demonstrated that, in early stage HL, a MTV value higher than 147 cm^3 could single out a smaller (46 vs. 157) patient subset with poor prognosis compared to unfavorable patients [59]: the 3-Y PFS was 71% vs. 84% [60]. Since the actual standard of care for early-stage HL is tailored to EORTC prognostic criteria or similar score systems, MTV could guide the treatment intensity of early-stage HL. However, standardization problems due to intrinsic variability of PET-extracted semiquantitative variables such as SUV (standardized uptake value), different protocols for patient scanning and image acquisition/reconstruction, as well as different thresholds of SUVmax still hamper the use of this biomarker for risk stratification and treatment guidance in HL [61].

7.4.2 Early Assessment of Chemosensitivity

Dimensional parameters providing readout of tumor growth have extensively been used in standard radiological imaging to assess therapeutic effects early during treatment using the so-called RECIST criteria [62]. However, the kinetics of tumor shrinkage and regrowth are not linear and might overtake the prognostic impact of tumor size variation. Patients with residual mass persisting at the end of treatment need longer follow-up for judging response to treatment [63–65]. FDG-PET/CT is the ideal tool to assess viable neoplastic cells in the context of residual masses detectable with CeCT. Since metabolic silencing is immediately visible after chemotherapy [13], response assessment with FDG-PET could be performed during treatment, as early after one [66, 67] or two [13, 15, 16, 68–70] cycles of chemotherapy, both in early- and advanced-stage HL.

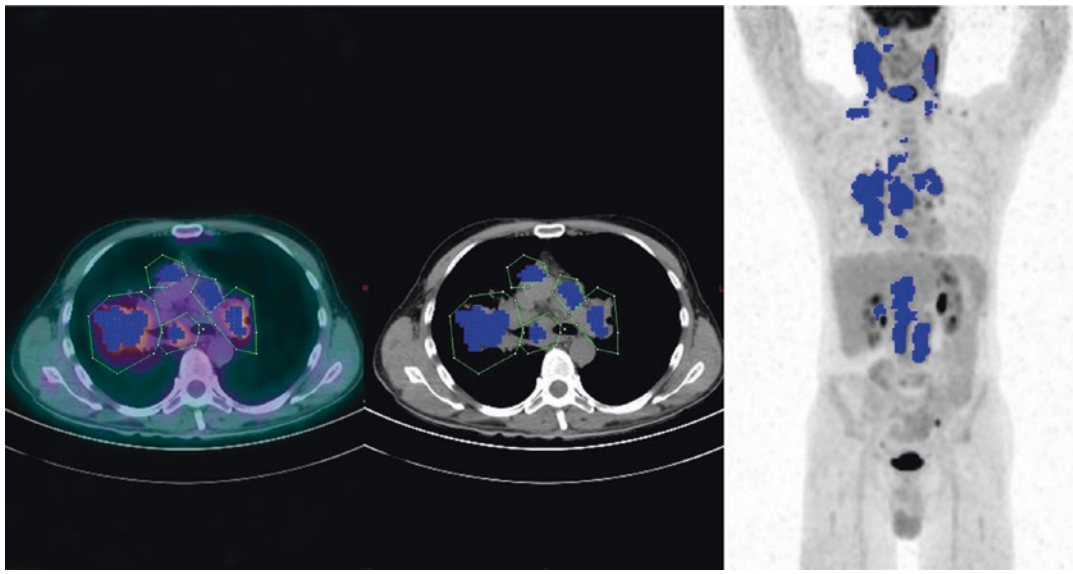


Fig. 7.1 Metabolic tumor volume: calculation example and VOI drawing depending on software (By Kanoun et al.: Plos One 2015;10(10):e0140830 (by permission))

Despite the high FDG affinity of neoplastic Reed-Sternberg cells attributed to the "Warburg effect" of neoplastic tissue [37] or an m-TOR-mediated increase of transmembrane GLUT-1 protein [71], the high performance of interim FDG-PET in predicting HL outcome probably relies on the high affinity for the tracer of nonneoplastic microenvironment cells, which account for more than 95% of the total cells present in HL tissue [18]. Several publications stressed the role of interim PET (iPET) in predicting ABVD treatment outcome in advanced-stage HL [13, 15, 66–70]. In a meta-analysis by Terasawa et al., interim PET in advanced-stage HL showed a sensitivity of 43–100% and specificity of 67–100%, respectively [70]. iPET proved to predict treatment outcome also in early stage, albeit with conflicting results [16, 72–74] and a lower specificity and positive predictive value [74].

Two questions concerning the ideal time for early interim FDG-PET scanning are still unsettled: (1) what is the best time point for FDG-PET after chemotherapy administration, and (2) what is the ideal number of chemotherapy cycles before the early interim FDG-PET scan? As far as the point (1) is concerned, in mice undergoing FDG scan, the FDG uptake by neoplastic cells and reactive inflammatory macrophages was minimal 14 days after chemotherapy administration [49]. An earlier evaluation, immediately after chemotherapy, could coincide with the stunning of the cellular glucose metabolism by immediate effects of chemotherapy compromising the sensitivity of the test [75]. In a review on interim FDG-PET during early treatment, Kasamon concluded that the optimal time for performing interim PET during chemotherapy ranges between 7 and 14 days after chemotherapy [76]. The answer to point (2) could depend on the aggressiveness of the tumor and the efficacy of the chemotherapy. In HL, there is most evidence for the use of FDG-PET after two courses of chemotherapy. More recently, two observational prospective studies have been published, stressing the good overall accuracy of interim PET performed as early as after one single cycle of chemotherapy, with very high sensitivity and negative predictive value [66, 67] especially in early-stage disease [67].

7.4.3 Final Response Assessment

Between 1999 and 2001, several papers reported high sensitivity and specificity of FDG-PET in tumor response assessment. In a meta-analysis of 13 studies on 408 HL patients, Zijlstra and colleagues demonstrated a pooled sensitivity and specificity of PET in defining treatment outcomes of 84% and 90%, respectively [77] (Fig. 7.2).

As a consequence, FDG-PET was proposed as the essential tool for the definition of treatment response in the majority of different FDG-avid lymphoma, including HL. The most recent definitions of CR, PR, SD, or progressive disease were integrated into the International Harmonization Project for treatment response in lymphomas [78] and the revised Lugano criteria [9]. The Deauville 5-point scale [79] has been used to quantify and standardize the residual FDG uptake [10]. The traditional concept of CR and CRu were abandoned, and the term complete metabolic response (CMR) was proposed instead; similarly, the old concept of partial remission (PR) based on dimensional criteria was replaced by partial metabolic response (PMR) in FDG-avid lymphoma. No metabolic response (NMR) was suggested for nonresponse or stable disease patients, while progressive metabolic disease (PMD) was proposed for clearly progressive patients. Traditionally, dimensional criteria were maintained for the rare non-FDG-avid lymphomas [9]. Preliminary reports showed a better accuracy in defining treatment response and long-term outcome of the 5-point Deauville scale (5-PS) over the International Harmonization Project (IHP) criteria, both in early and advanced HL [78, 80, 81]. Fallanca et al. in a small cohort of 101 patients including 35 advanced HL cases were able to show a better specificity, positive predictive value, and overall accuracy of 5-PS over IHP criteria (87% vs. 67%, 74% vs. 57%, and 86% vs. 76%, respectively). Therefore, the reduced number of false-positive outcomes in the end-of-treatment PET proved to spare a significant number of patients from unnecessary treatment.

Despite the good response to therapy, treatment of HL can result in residual masses in up to 80% of patients by conventional staging modalities, which

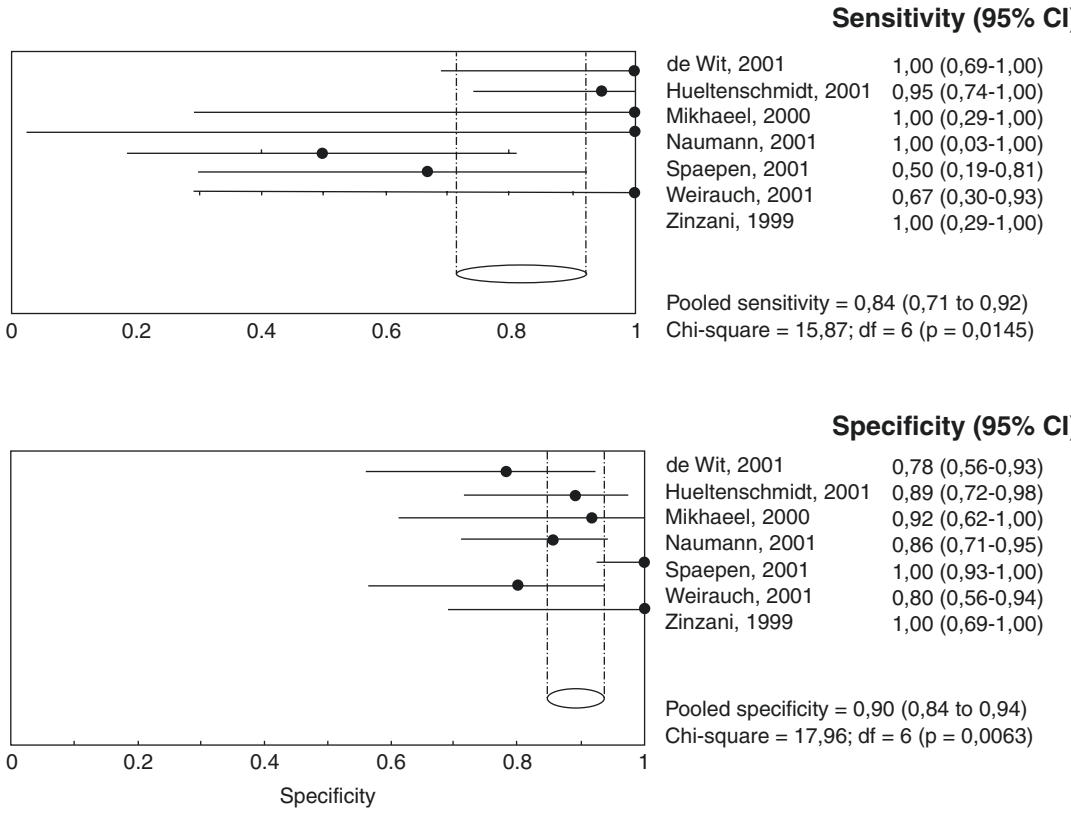


Fig. 7.2 Zijlstra unchanged. (**a**) Sensitivities and 95% confidence intervals for studies assessing the diagnostic accuracy of FDG-PET in patients with HD. (**b**) Specificity and 95% confidence intervals for studies assessing the diagnostic accuracy of FDG-PET in patients with HD. (Asterisk) The diamond represents the 95% CI of the pooled estimate (From Zijlstra 2006, by permission [77])

are most frequent in the anterior mediastinum [63, 65]. The original study by Jerusalem et al. [82] showed the superior accuracy of FDG-PET over CeCT in predicting long-term disease outcome in patients showing persisting FDG uptake. Many reports confirmed the superior performance of functional imaging in this setting. In 2008, Terasawa et al. systematically reviewed all studies published so far on this topic, reporting a pooled sensitivity for HL ranging between 43% and 100%, with a specificity ranging between 67% and 100% [83]. In the pre-PET era, consolidation radiotherapy had been used in advanced-stage HL showing radiological evidence of a residual mass persisting after chemotherapy [2]. The end-of-treatment PET was proposed to deliver consolidation radiotherapy (cRT) only in PET-positive residual masses. As a consequence, the number of patients undergoing cRT at the end of treatment changed from 71% to 11% [22]. In the German Hodgkin Study Group trial HD 15, cRT was administered to patients having FDG-avid residual mass of more than 2.5 cm at the end of chemotherapy. About 30% of the patients showed a residual mass, and in about 10% the residual mass proved FDG avid. Comparing irradiated with non-irradiated patients, the 4-year PFS was 86.2% and 92.6%, respectively ($p = 0.022$). Overall, the NPV at the end of therapy was 94% [22]. Savage et al. reported very similar results in a retrospective analysis of 163 advanced-stage HL patients undergoing cRT avter ABVD chemotherapy only in the case of a residual FDG-avid mass of 2 cm or more at the end of chemotherapy. Patients with a PET-negative scan ($n = 130$, 80%) had a 3-year time to progression far superior to that of patients with a

PET-positive scan (89% vs. 55%, $p = 0.00001$), with no difference between those having bulky or non-bulky disease. The NPV for end-of-treatment PET was 92% [84]. However, NPV at the end-of-treatment PET depends on the efficacy of chemotherapy, being so low as 86% with low-intensity regimen such as VEBEP [85].

7.4.4 Interpretation Criteria

7.4.4.1 Interim PET Scan

Early studies demonstrated that not all interim PET scans could be dichotomized as positive or negative; some patients had "equivocal" or "inconclusive" results showing residual FDG uptake defined as minimal residual uptake (MRU). MRU definition evolved from residual unspecific FDG uptake with intensity equal, or slightly superior to mediastinum [86], to an uptake with higher intensity, equal to that of the liver [79]. This was proposed with the aim to increase the specificity and reduce false-positive results in predicting treatment outcome [87]. These criteria have been generally accepted by imaging specialists and clinicians as a useful tool for visual interim PET assessment in lymphoma and have been incorporated in several guidelines and recommendation by academic institutions [9, 10, 88–90] (Fig. 7.3).

The Deauville five-point scale (5-PS) has been retrospectively and prospectively validated in HL in four different studies [11, 12, 52, 81]. Prospective testing between national imaging core laboratories also showed good interobserver agreement in HL [91]. In standard treatment or treatment intensification planned for interim PET-positive patients, a Deauville score (DS) of 3 represents a complete metabolic response (CMR). DS 3 also proved to be the most reproducible threshold when interpreting PET scans in lymphoma patients [52]. If treatment is to be de-escalated, a more sensitive threshold is preferred to avoid the risk of undertreatment [3, 7]. The use of a higher threshold for a positive interim PET scan was supported by the RATHL trial showing that the DS in PET-negative patients (DS 1 vs. DS 2 vs. DS 3) did not influence PFS, suggesting that DS 3 is likely to represent CMR with standard ABVD treatment [4]. To obtain more stable measures of residual activity in interim PET, the Leipzig/Germany group proposed a semiquantitative method for interim PET reading, using the SUVpeak of the residuum and the SUVmean of the liver rather than SUVmax [92]. Since the residual lesion detected in interim PET is often very small and a VOI of 1 ml too large, the SUVpeak was defined as the average value in the maximum SUV voxel and the three hottest adjacent ones [92].

7.4.4.2 End-of-Treatment PET Scan

The presence of a FDG-avid residual mass at the end of treatment represents a true diagnostic dilemma. As mentioned above, only half of the residual masses at the end of treatment in HL have been considered as a harbinger of persisting disease [93]. Primary mediastinal B-cell lymphoma is a rare disease often presenting in young females with isolated mediastinal bulky lesion and a good treatment outcome [94]. The disease

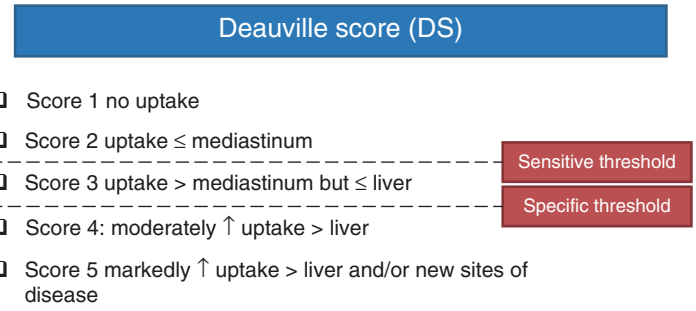


Fig. 7.3 The Deauville 5-point scale (unchanged) (From Meignan M, Leuk Lymphoma 2009, by permission [79]; Barrington S: Eur J. Nucl Med Mol Imaging 2010;37:1824–1833)

is biologically and clinically related to nodular sclerosis HL, where the putative normal cell counterpart is a thymic B cell [95]. End-of-treatment PET scan in this disease is often associated with false-positive results [96, 97]. A 5-PS threshold between 4 and 5 has been proposed as positive scan [98]. Moreover, only the association of 5-PS score 5 in end-of-treatment PET and high baseline total lesion glycolysis (TLG) in baseline PET showed a very poor prognosis [98]. In conclusion, patients with residual FDG uptake in the context of a nodal mass with bulky disease at baseline should undergo biopsy if salvage treatment is considered [99].

7.4.5 Treatment Response Assessment to Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (CPI) are a new class of antineoplastic drugs that proved very active in lung cancer, melanoma, renal carcinoma [100–102], and other neoplastic disorders, including HL [20, 103]. In the last few years, the knowledge on the mechanism of action has been largely unveiled. The activation of the PD-1 receptor on the T-cell surface by its ligand PD-L1 expressed on the surface of the neoplastic cells or macrophages downregulates T-cell function, which normally controls the immune activity [104]. Due to this mechanism of action restoring the immune reactivity of the host against the tumor, the antineoplastic activity of CPIs could be delayed, thus fueling a sustained inflammatory response which persists beyond the drug administration and after treatment end. The following criteria and categories for immune response (IRC) in lymphoma (LYRIC) have been proposed [105]:

1. *Increase in overall tumor burden (as assessed by sum of the product of the diameters [SPD]) of ≥ 50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration [IR(1)]*. A biopsy is advisable, but when this is not possible, a second scan 12 weeks after the initial determination of IR should be planned.
2. *Appearance of new lesions or growth of one or more existing lesion(s) ≥ 50% at any time during treatment, occurring in the context of lack of overall progression (<50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during the treatment [IR(2)]*. Again a biopsy is strongly encouraged: if as expected, the biopsy is negative, the lesion(s) is/are considered negative and should no longer be considered in the following scans.
3. *Increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number [IR (3)]*. Increased immune activity at the site of tumor may manifest as an increase in FDG uptake. Therefore, by itself, changes in uptake should not trigger an assignment of PD with checkpoint inhibitors. Nonetheless, whenever feasible, a biopsy is advised.

Despite an evident bias of subjectivity, a common denominator in these three categories of IR is a "stable" clinical situation of the patient. Moreover, another common recommendation in the follow-up of these three IR is to perform a second PET scan 12 weeks after the first imaging (Fig. 7.4).

7.4.6 PET in Radiotherapy Planning

Radiation therapy in HL is an essential therapeutic tool in combined modality treatment (CMT) of early-stage disease and a useful tool to consolidate chemotherapy treatment in a limited number of advanced-stage patients with a residual mass at the end of chemotherapy. Radiation techniques have benefited from an impressive technological evolution. Extended fields developed for single modality treatment have been replaced by more conformal fields designed for CMT, encompassing the initially macroscopically involved tissue volumes in early-stage disease and bulky masses and/or residual masses after chemotherapy in advanced disease [106–109]. These changes led to dramatic decreases in the volume of normal tissue being irradiated and

a parallel reduction in the risk of serious long-term sequelae of RT. A more accurate geometry for radiation field delineation also demands a higher accuracy of the imaging technique used. As FDG-PET has been shown to be more accurate for HL staging, it is by implication also more precise in defining the initially involved regions to be irradiated in patients with early-stage disease. No diagnostic modality has a 100% overall accuracy, and the delineation of the lymphoma volume must be based on the diagnostic information available, including FDG-PET/CT of both anatomy and physiology of the disease [110–112]. In 2013, the International Lymphoma Radiation Oncology Group (ILROG) identified the residual gross tumor volume (GTV) as the first imaging target to be delineated in post-chemotherapy FDG-PET to be redrawn in the co-registered images of pre-chemotherapy PET scan [113]. Then, clinical target volume (CTV) should be identified by contouring the original GTV in pre-chemotherapy FDG-PET. Finally, especially when the target is moving, the internal target volume (ITV) should be delineated moving from CTV plus a margin taking into account uncertainty in size, shape, and position of the CTV in the patient. The optimal tool to obtain ITV is using a 4D CT simulator and, as a second choice, by fluoroscopy. Margins of 1.5–2 cm in cranio-caudal direction are commonly chosen in the chest or upper abdomen. Finally, the planned target volume (PTV) is calculated to delineate the

IR1: Increase in overall tumor burden (by SPD) of ≥50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration

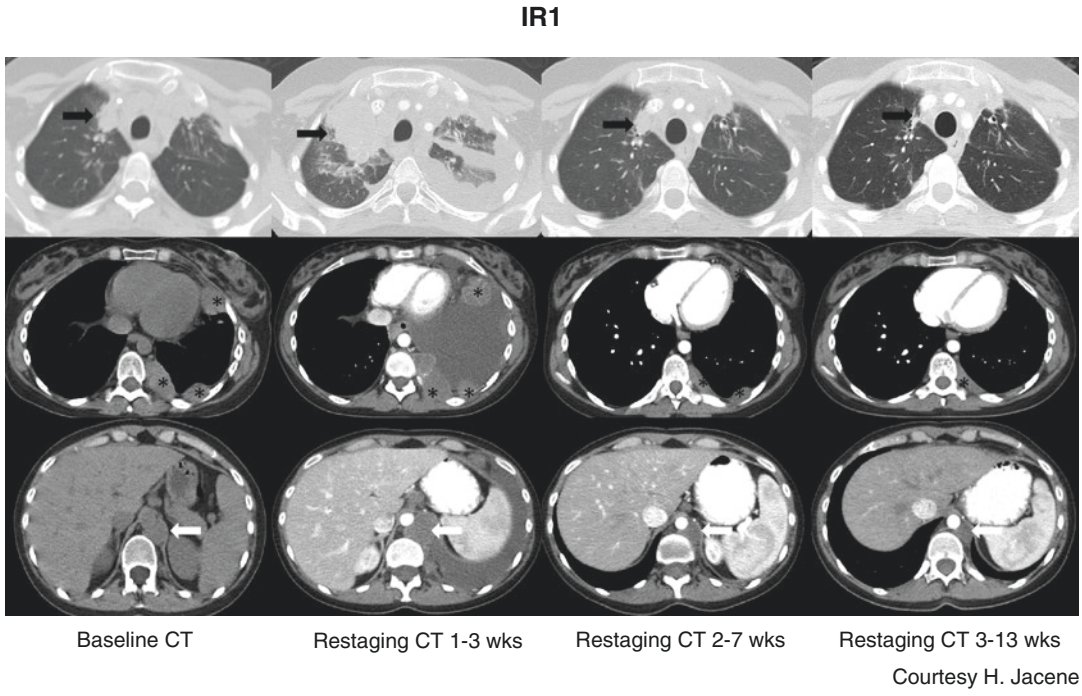
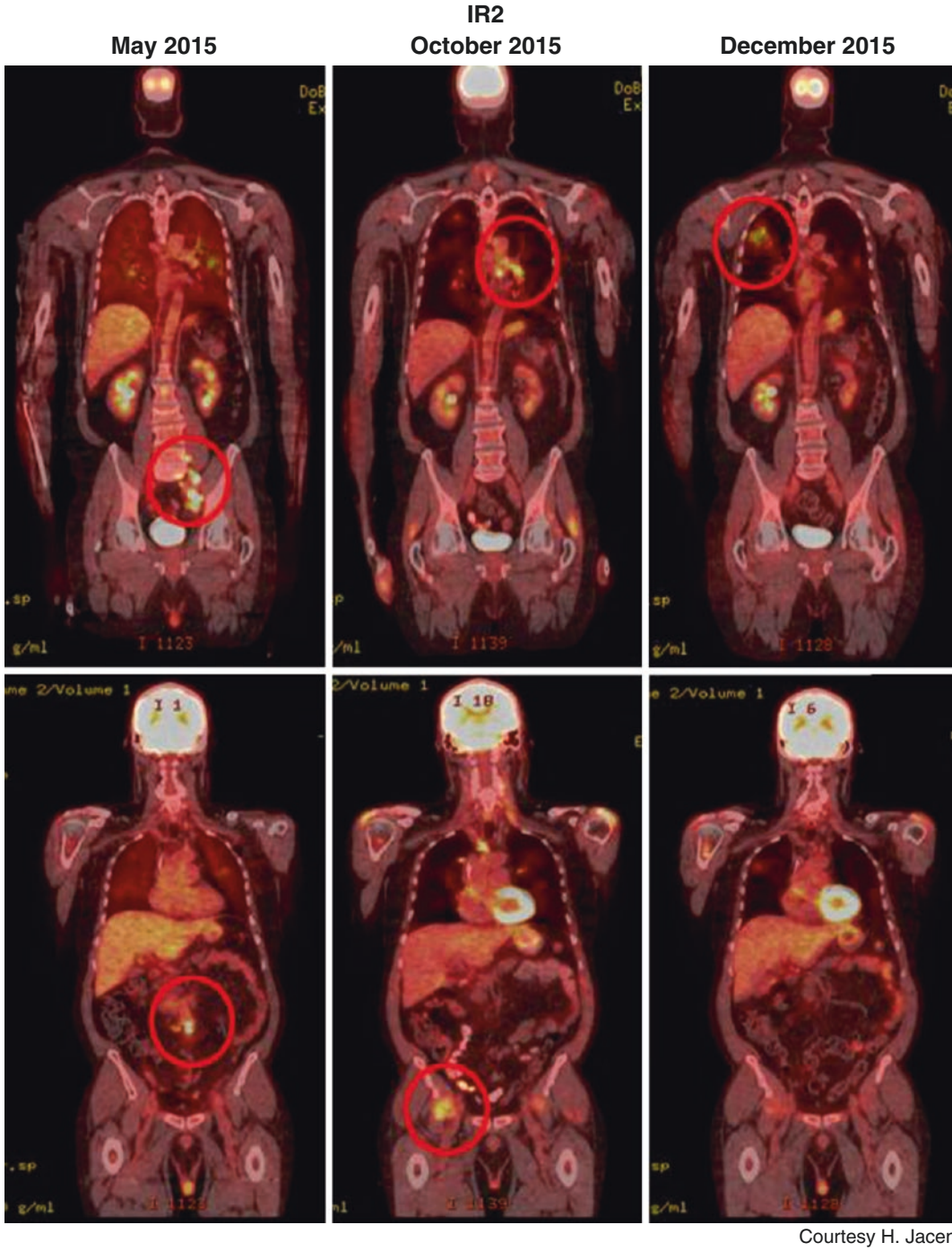


Fig. 7.4 Type 1, type 2, and type 3 IR (indefinite response) according to LYRIC criteria (From Cheson. Type 1, type 2 and type 3 LYRIC type of response. Blood 2016 [105]: courtesy of B. Cheson). IR1: Increase in overall tumor burden (by SPD) of ≥50% of up to six measurable lesions in the first 12 weeks of therapy, without clinical deterioration (Courtesy H. Jacene). IR2: Appearing of new lesions; or growth of oneor more existing lesion(s) ≥50%; at any time during treatment; occurring in the context of lack of overall progression (<50% in increase) of overall tumor burden, by SPD of up to six lesions at any time during the treatment (Courtesy H. Jacene). IR3: Increase in FDG uptake of one or more lesion(s) without a concomitant increase in lesion size or number (Courtesy L. Schwartz)

IR2

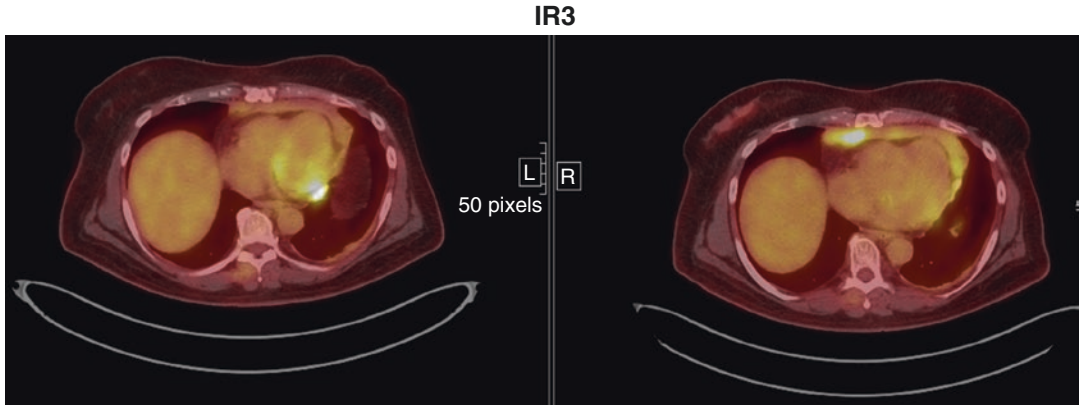
IR2: Appearance of new lesions; or growth of one or more existing lesion(s) of ≥50%; at any time during treatment; occurring in the context of lack of overall progression (<50% increase) of overall tumor burden, by SPD of up to 6 lesions at any time during the treatment.



Courtesy H. Jacene

Fig. 7.4 (continued)

IR3: Increase in FDG uptake of one or more lesion(s) without a concomitant increase in lesion size or number



Courtesy L. Schwartz

Fig. 7.4 (continued)

radiation fields as function of immobilizing devices, body site, and patient cooperation. In early-stage HL undergoing CMT pre-chemotherapy, PET/CT should be acquired with the patient in the same position to be used for RT. Relatively limited clinical data are available on CTV definition by FDG-PET for RT planning in HL [114, 115]. If extended-field irradiation is still used, the impact of FDG-PET is not expected to be very large since additional involvement found on FDG-PET will often be included in large treatment fields anyway [116, 117]. With modern, more conformal radiotherapy, changes due to FDG-PET have been shown to be significant [118, 119].

7.4.7 PET for Response Prediction During Salvage Treatment

High-dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT) remains the best treatment option for relapsed/refractory Hodgkin lymphoma (r/r HL) [120]. More recently, an international consortium modeled r/r HL (the RisPACT consortium) retrospectively identified stage IV, ECOG performance status ≥1, bulky nodal lesion >5 cm at relapse, time to relapse ≤3 months, and an inadequate therapy response, assessed with a CT or PET/CT before ASCT, as the sole risk factors, in multivariate analysis predictive of progression-free survival (PFS) [121]. Different groups [122–124] and a large meta-analysis of the published literature including also non-Hodgkin lymphoma [125] demonstrated that interim PET (iPET) before ASCT in r/r HL had a predictive value (PV) independent from other RF. The impact was similar to that during first-line ABVD treatment, where iPET proved the prognostic marker with the highest PV, irrespective of other RF included in the International Prognostic Score (IPS) [15]. More recently, semiquantitative reading of PET with metabolic tumor volume (MTV) calculation on the scan performed at the time of HL relapse proved to be the strongest predictor of treatment outcome in r/r HL [126]. Curiously, MTV computed on the FDG-PET performed at relapse and interim PET performed immediately before ASCT behaved as independent prognostic factors, and the former improved the PV of the latter. Overall, the two FDG-PET scans performed in different time points during salvage treatment for r/r HL were able to recapitulate 4 out of the 5 RisPACT factors: MTV in baseline PET portrays tumor burden (bulk and stage IV disease), while iPET is able to detect a low chemosensitivity (inadequate response to treatment/chemotherapy resistance and possibly an inadequate immune response by the host) [127]. The 3-year EFS rates for patients with low MTV/negative pretransplant PET, low MTV/positive pretransplant PET, high

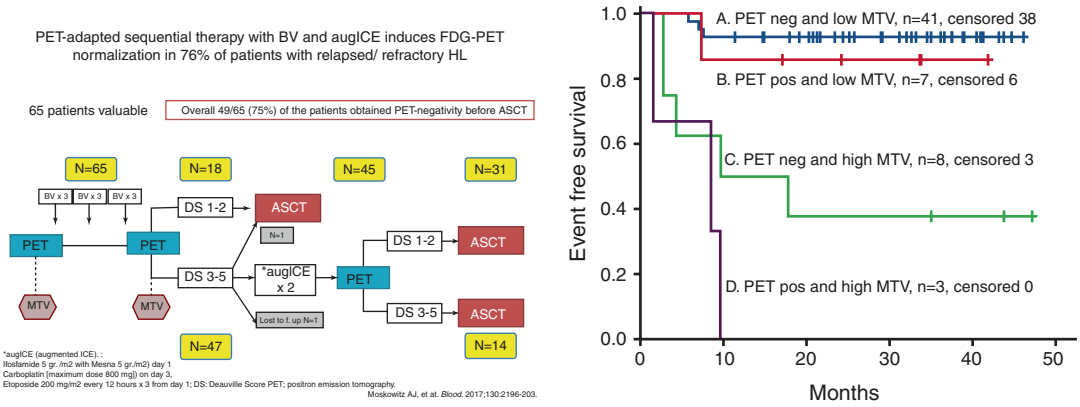


Fig. 7.5 Baseline and interim PET to predict treatment outcome in relapsed/refractory Hodgkin lymphoma (From Moskowitz AJ Blood 2017, by permission [126])

MTV/negative pretransplant PET, and high MTV/positive pretransplant PET were 93%, 86%, 38%, and 0%, respectively ($p < 0.0001$) [126] (Fig. 7.5).

7.4.8 PET for Follow-Up of HL Patients in Complete Remission

The impact of surveillance imaging tests (CT, FDG-PET/CT) during follow-up of lymphoma patients in CR after treatment is still a matter of debate. In general, the probability of detecting relapse during monitoring for disease recurrence depends on the probability of relapse of the disease in the population being tested, as well as the sensitivity, specificity, and the frequency of the test [128]. The prevalence of relapse in a HL patient in complete remission at the end of treatment is rare, corresponding to one event per 68 visits in HL [129]. Moreover, the risk of relapse could depend on a number of clinical parameters associated with disease relapse as follows: (1) the presence of clinical symptoms, (2) poor chemosensitivity of the tumor at interim evaluation, (3) the preferred anatomical pattern of recurrence of a given lymphoma subtype, as well as (4) a residual mass at the end of treatment [130]. Up to 80% of relapses in HL are associated with clinical symptoms [129, 131]. Zinzani et al. investigated the role of surveillance FDG-PET performed every 6 months for 4 years after CR [132]. Overall, 778 scans were evaluated in a cohort of 160 HL patients. In 11/778 scans (1.4%), PET was classified as positive, mainly in the first 18 months after CR. All these patients underwent a confirmatory biopsy: 6/11 were proven positive, mostly in patients having an interim-positive PET scan. A total of 51 relapses in 160 HL patients were detected: all 51 by PET/CT, 37 by CT, and 35 by clinical symptoms. However, 778 PET/CT scans were needed to detect 14 relapses earlier than CT or other methods. Jerusalem et al. performed FDG-PET every 4–6 months for 3 years in 36 HL patients who were in CR after ABVD for a total of 139 scans. Six false-positive studies, and no false-negative studies, were found. In the five positive studies, FDG-PET preceded the relapse at a median of 3.5 [1–9] months [133]. In 2012, El-Galaly et al. published a retrospective study in a cohort of 299 HL patients in CR after ABVD, in which surveillance PET scan was used in asymptomatic patients (routine scans $n = 211$) or for patients suspected of harboring an impending relapse (clinically indicated, $n = 88$). The true positive rates of routine and clinically indicated scans were 5% and 13%, respectively. The overall positive and negative predictive values were 28% and 100%, respectively. The estimated cost per routinely diagnosed relapse was 50,778 US $ [134]. In conclusion, surveillance FDG-PET cannot be recommended as a routine follow-up procedure for HL patients in complete remission after first-line treatment; instead, this

should be considered in rare cases of patients with high risk of relapse without signs or symptoms of disease.

7.5 PET Response-Adapted Therapy

7.5.1 Early-Stage HL

More than 90% of early-stage HL patients are cured with standard therapy. These patients still have a reduced life expectancy due to treatment-related morbidity including second cancers and cardiopulmonary disease. In fact, early-stage HL patients more often die from late effects of treatment than from the disease itself [135]. A number of trials have investigated such PET-response-adapted therapy in early-stage HL. The UK National Cancer Research Institute (NCRI) Lymphoma Group RAPID trial for early-stage patients as well as the German Hodgkin Study Group (GHSG) HD16 randomized trial investigated non-inferiority of reducing treatment intensity by omitting radiotherapy interim PET-negative early-stage patients. The experimental arms of EORTC/GELA/FIL H10 study also omitted radiotherapy in interim PET-negative patients while escalating from standard ABVD to more intensive BEACOPPesc followed by radiotherapy in PET-positive patients. Both the RAPID trial and the H10 trial failed to demonstrate non-inferior PFS in the chemotherapy-only arms. In the UK RAPID study, patients who were PET negative after three cycles of chemotherapy were randomized to either radiotherapy or no further treatment (NFT). At a median follow-up of 3 years, the PFS difference in the RAPID trial was 3.8% (95% CI, 8.8–1.3) favoring the radiotherapy arm, thus failing to meet the predefined margin of non-inferiority of 7%. There was no difference in overall survival (OS) between the two treatment arms [3]. The European H10 trial stratified patients in favorable and unfavorable subgroups, according to standard risk factors for early-stage HL [7]. All patients had an FDG-PET after two cycles of chemotherapy (PET2). In the experimental arms, PET2-negative patients were given chemotherapy alone, but the chemotherapy only arms were stopped prematurely after a futility interim analysis predicted failure of meeting the primary endpoint, which was PFS non-inferiority [136]. The final analyses confirmed a loss of disease control when radiotherapy was omitted, even though the difference in PFS was only clearly clinically relevant in patients without risk factors [7]. In the GHSG HD16 study for patients with early-stage disease and no risk factors, patients were randomized to either standard therapy with 2 × ABVD + 20 Gy radiotherapy or an experimental arm where PET-negative patients after 2 × ABVD would receive no further treatment. After a median follow-up of 47 months, the estimated 5-year PFS for early PET-negative patients was 93.4% (90.4–96.5) with standard treatment and 86.1% with chemotherapy only. The hazard ratio was 1.78 with a 95% CI ranging from 1.02 to 3.12, including the non-inferiority margin of 3.01. The PFS difference resulted from a significant increase in disease recurrences with infield recurrence rates of 2.1% vs. 8.7% (p = 0.0003); there was no relevant difference regarding outfield recurrences (3.7% vs. 4.7%, p = 0.55). There was no difference in the estimated 5-year overall survival in the per-protocol population (98.1% in the standard arm vs. 98.4% in the chemotherapy-only arm) [137].

In the H10 study, PET2-positive patients in the experimental arm (including both favorable and unfavorable risk groups) had their treatment intensified with a shift to two cycles of more intensive chemotherapy (BEACOPP escalated) followed by radiotherapy. In the PET2-positive patients, PFS of patients with a BEACOPP-intensified chemotherapy was significantly better when compared with the standard arm where patients were treated with less intensive chemotherapy followed by radiotherapy (5-year PFS 90.6% vs. 77.4%, HR 0.42 with 95% CI 0.23–0.74) [7]. This difference was mainly due to improved PFS of patients in the unfavorable risk group who received intensified chemotherapy. Even without knowing the results of the German HD16 study, we can conclude from the RAPID and H10 studies that omitting radiotherapy in good-risk (PET2-negative) patients results in a modest loss of disease control (PFS), while there is no difference in OS.

7.5.2 Advanced-Stage HL

Around 70% of advanced-stage HL patients can be cured with six cycles of ABVD with or without consolidation radiotherapy, which is the standard first-line therapy in most centers. BEACOPPesc cures 85–90% of patients if given upfront, but concern regarding acute toxicity and second neoplasias is the reason why a number of centers are reluctant to use this regimen as standard therapy [138]. Numerous trials have investigated PET-response-adapted therapy for advanced-stage HL patients. Three non-randomized trials used early treatment intensification with BEACOPPesc (The Italian GITIL HD 0607, the US SWOG S0813 and the UK RATHL trial) or even high-dose chemotherapy with autologous stem cell support (The Italian HD0801 FIL trial) in patients who were still PET positive after two cycles of ABVD. The randomized German HD18 trial tested abbreviation on BEACOPPesc therapy based on PET results after two therapy cycles. The French AHL 2011 trial was also a BEACOPPesc-based randomized trial with treatment modifications based on PET after both two and four cycles.

The UK RATHL study included 1214 patients with stage IIB–IV or stage IIA with high-risk features who received two cycles of ABVD followed by FDG-PET. PET2-negative patients (Deauville scores 1–3) were randomized to either continued ABVD (total of six cycles) or treatment without bleomycin (AVD), for 4 cycles. The analyses of the PET2-negative patients showed no difference in PFS between the two randomization arms (3-year PFS 85.7% vs. 84.4%) [4]. Even though in the primary analysis the results fell short of the specified non-inferiority margin, an updated analysis showed that with extended follow-up the study had met its primary endpoint of PFS non-inferiority [139].

PET2-positive patients received more intensive chemotherapy with an additional four cycles of BEACOPP14 or BEACOPPesc, resulting in a 3-year PFS of 68%, comparing favorably with historical controls from observational studies in which ABVD was continued in PET2-positive patients [4, 12, 30]. The Italian single-arm GITIL/FIL HD0607 (stage IIB–IV patients) study showed similar results from escalation to eBEACOPP in PET-positive patients after two cycles of ABVD (3-year PFS 60%). They also showed no improvement of outcomes from consolidative radiotherapy to initially bulky masses (>5 cm) in patients who were PET2 negative and remained posttreatment PET negative [17]. In the German HD18 study, all patients with advanced-stage HL had two cycles of BEACOPPesc followed by FDG-PET. Patients in the standard arm received eight cycles of BEACOPPesc, but half way during the study, the duration of standard treatment was abbreviated to six cycles as a result of the analysis of the German HD15 study. In the experimental arm, PET2-negative patients (Deauville 1–2) only received an additional two cycles of BEACOPPesc. The final analysis showed that in PET2-negative patients, a total of four cycles was non-inferior to six cycles in terms of 5-year PFS (90.8% vs. 92.2%) and importantly was associated with significantly less acute and late toxicity [140]. PET2-positive patients continuing eBEACOPP still had very high 3-year PFS of 87.6% (95% CI 83.0–92.3), illustrating that the positive predictive value of interim FDG-PET depends on the treatment setting. A subsequent analysis showed no differences in outcome between patients in the standard arm who had a Deauville score of 1–2 and those with a Deauville score of 3 (the latter would in many other studies be considered PET negative, but in HD18 regarded as PET positive). This indicates that abbreviation of BEACOPPesc therapy in early PET-negative patients should be done in those having a PET2 Deauville score of 3 as well as in patients with Deauville score of 1 and 2 [141]. The French AHL2011 study aimed to assess whether interim FDG-PET could identify good-risk patients to be given de-escalation treatment BEACOPPesc upfront. A total of 823 patients were randomized to the standard arm (n = 413) and the experimental arm (n = 410). After a median follow-up of 50.4 months, the 4-year progression-free survival (PFS) for the experimental arm was 87.1% and for the standard arm 87.4% with no difference in OS, demonstrating that treatment intensity can be safely reduced from BEACOPPesc to ABVD in PET2-negative patients [142].

Thus, in advanced-stage HL, early interim PET can be used to de-escalate therapy such as reducing the number of BEACOPPesc cycles, reduction of intensity from BEACOPPesc to ABVD as well as omission of bleomycin from ABVD in PET2-negative patients. At the same time, intensification to BEACOPPesc should be considered with insufficient initial PET response to ABVD.

7.5.3 Post-chemotherapy PET/CT-Driven Consolidation Radiotherapy

In advanced HL, radiotherapy is used less frequently than in early-stage HL and usually only to residual masses. CT cannot discriminate between a residual mass with viable lymphoma cells and a residual mass consisting only of fibrotic tissue. However, since PET/CT cannot detect microscopic disease, it was necessary to perform studies to investigate whether a PET-negative residual mass requires radiotherapy or not. The mature results of the German HD15 trial shed light on this for patients treated with BEACOPP. In the HD15 study, consolidation radiotherapy was given only to those patients having a PET-positive single residual mass of more than 2.5 cm, which was encompassable in a single field of radiotherapy. The remaining majority of patients who did not receive radiotherapy had a relapse-free survival of 94% after 1 year, indicating that radiotherapy can be safely omitted in advanced-stage HL patients who are PET negative after the end of BEACOPPesc [22, 143]. A retrospective analysis from the British Columbia Cancer Agency addressed the same situation for patients treated with ABVD. The authors reported a 10-year experience with advanced-stage HL patients having residual masses >2 cm after chemotherapy undergoing PET/CT (n = 163). Only patients with a positive posttreatment PET/CT received radiotherapy. At the end of treatment, 316 patients had residual masses larger than 2 cm undergoing PET/CT. Of those, 264 (83.5%) were FDG-PET negative, none of whom received RT, and 52 (16.5%) were FDG-PET positive, of whom 79% (n = 41) received consolidative RT (30–35 Gy). With a median follow-up for living patients of 4.6 years (range 0.6–13.5 years), the 5-year freedom from treatment failure (FFTF) for the whole cohort was 83%, and the 5-year OS was 94.5%. Not surprisingly, patients with a negative posttreatment FDG-PET had a superior 5-year FFTF compared to those with a positive scan (89% vs. 56%, respectively). In the posttreatment FDG-PET-negative group, there was no difference in outcome comparing bulky (n = 112) and non-bulky (n = 152) subgroups (5-year FFTF 89% vs. 88.5%, respectively). Similarly, when the analysis was restricted to FDG-PET-negative patients with a bulky mediastinal mass at diagnosis (n = 102), outcomes were excellent (5-year FFTF 89%; 5-year OS 96%) [84]. These results support the omission of radiotherapy in advanced-stage HL patients who achieve a PET-negative remission after six cycles of chemotherapy.

7.5.4 PET/CT-Adapted Therapy in Relapsed HL

For HL patients in first relapse, a number of risk factors predict outcome after high-dose chemotherapy with autologous stem cell support (HD + ASCT) [121]. Two important factors are the duration of remission prior to relapse and the response to induction therapy. A number of studies have shown that FDG-PET performed after induction therapy and before HD + ASCT can predict the long-term remission after salvage [144–146]. These studies report a poor long-term PFS in patients who are FDG-PET positive after induction chemotherapy (31–41%), compared to a PFS of 73–82% in patients who reach a PET-negative remission before HD + ASCT. A study from the Memorial Sloan Kettering Cancer Center investigated a PET-guided approach where FDG-PET-positive patients after the standard induction (ICE, ifosfamide, carboplatin, etoposide) instead of proceeding to HD + ASCT were given a non-cross-resistant regimen consisting of four biweekly doses of gemcitabine, vinorelbine, and liposomal doxorubicin (GVD) before HD + ASCT. Patients who were FDG-PET

positive after ICE but became FDG-PET negative after GVD had similar outcomes compared to those who were PET negative after ICE [147].

A number of studies demonstrated a high prognostic value of pretransplant FDG-PET/CT before alloSCT with reduced intensity [148–150]. Two studies suggest that FDG-PET/CT may have a role in guiding the use of donor lymphocyte infusions after allogeneic stem cell transplantation [151, 152].

7.6 Toward Revised Criteria for PET Scan Interpretation

Juweid et al. first demonstrated that PET-based response improved predictability compared to criteria relying on CT. They demonstrated that in patients with diffuse large B-cell NHL and a residual mass posttreatment, a lack of FDG avidity correlated closely with a CT-based CR for the end-of-treatment evaluation [153]. These observations were subsequently confirmed, leading to the incorporation of PET into standardized response criteria for patients with DLBCL and HL [78]. These initial studies of PET used visual assessment using the mediastinal blood pool as the comparator and formed the basis of the recommendations of the International Harmonization Project in lymphoma [78]. Efforts toward a more reliable and reproducible approach resulted in the 5-point Deauville criteria which are more accurate with greater interobserver concordance and a higher positive predictive value (PPV) [11]. One consequence of this improvement was the Lugano classification currently considered the standard for staging and response assessment for all FDG-avid lymphomas [9, 10].

7.6.1 Qualitative vs. Semiquantitative Assessment

7.6.1.1 From Anatomical to Functional Imaging

In 1999, the National Cancer Institute-sponsored Working Group (NCI-WG) published the first uniformly adopted response criteria for lymphoma [154]. These included standardized definitions for complete response (CR) and partial response (PR), stable disease (SD), progressive disease (PD), and relapsed disease (RD). Since these recommendations were based on CT scanning, they included the category of complete remission unconfirmed (CRu), first introduced in the Cotswold classification [24], referring to patients with a persistent mass with size reduction following treatment which, represented fibrosis, rather than viable lymphoma.

PET scans were initially considered as an adjunct to lymphoma assessment in about 1990. Their added value was first demonstrated by Juweid et al. [153]. They compared the outcome of 53 patients with diffuse large B-cell lymphoma using either the NCI-WG response criteria alone or with the incorporation of PET. Progression-free survival was similar regardless of whether the patient had a CR or PR based on CT criteria, as long as the mass was not FDG avid. Thus, not only was the accuracy of response assessment improved with PET, but the misleading term CRu was eliminated as a response category.

Along with the validation of the above observations, numerous other studies demonstrated the superior sensitivity and specificity of PET compared with CT mandated revised response criteria. Thus, in 2007 the International Harmonization Project published recommendations that incorporated PET [78]. These were primarily for HL and DLBCL as data with FDG-PET in other histologic subtypes were limited.

In the ensuing years following publication of the 2007 criteria, a large body of data demonstrated the role of FDG/PET in follicular lymphoma (FL) as well as other histologies [155]. Whereas PET interpretation in the 2007 criteria was purely visual, using mediastinal blood pool as the reference standard, the newly created Deauville 5-point scale (D5-PS) used the hepatic blood pool and was more reproducible [79]. In 2014, the Lugano classification was published recommending FDG PET/CT as standard for staging of FDG-avid histologies [9, 10]. Several studies in HL demonstrated the improved sensitivity of FDG/PET compared with bone marrow biopsies [31, 52, 57, 156]. Thus, in the Lugano classification, trephine biopsies were no longer required in the routine staging of HL. The Lugano

classification also recommended the D5PS for interpretation of FDG/PET for assessment of response to treatment assessment. The change from the binary IHP criteria to the five-point DS is associated with greater interobserver reproducibility and provides greater flexibility to modify the threshold between a good and a poor response according to the clinical context and/or the proposed treatment strategy.

The DS is now uniformly adopted and is of particular importance in risk-adapted therapeutic strategies. The group that requires particular attention are the DS5 patients whose outcome differs significantly even from DS4 [4] in advanced disease, but has been yet demonstrated in those with limited-stage disease.

7.6.1.2 Toward New Criteria for Response Assessment of New Drugs

The availability of newer effective treatment led to issues in interpretation of response and disease progression due to the occurrence of flare reactions. The most notable examples are immunomodulatory agents that stimulate the immune system resulting in a flare reaction, particularly lenalidomide [157–160]. Similar effects were observed for rituximab [161, 162], brentuximab vedotin [163], ibrutinib [164], and idelalisib [165], respectively. In HL, the use of checkpoint inhibitors can induce a flare reaction that may be confused with progressive disease [20]. This potential clinically significant problem led to publication of the lymphoma response to immunomodulatory therapy (LYRIC) criteria [105] (see Chap. 4). These recommendations use a provisional term of indeterminate response to categorize various types of flare reactions. Thus, patients in whom a flare reaction is considered may remain on treatment until progressive disease is confirmed by biopsy or by continued growth, or evidence of deterioration.

7.6.1.3 Biomarker Integration in Response Criteria

Despite the sensitivity of PET-CT scans, the negative predictive value remains imperfect. An increasingly recognized problem is that relapse occurs not infrequently, even in patients considered to be in a CMR following therapy. In the RAPID trial [3], patients with stage I/IIA non-bulky disease underwent PET after three cycles of ABVD. Those with a negative PET were randomized to IFRT or no further therapy. In patients considered in mCR, there was an apparent correlation between the maximum transverse diameter of the tumor and the likelihood of recurrence, with a threshold of 5 cm. Thus, assays that are able to detect minimal residual disease may be a useful adjunct, not only in response assessment but also in distinguishing a flare reaction from progressive disease. Circulating DNA assays have been used in patients with NHL to predict outcome and are approved by the FDA [166]. Only recently has this technology been applied to HL. Van Eijndhoven et al. [167] suggested that classical HL-related miRNA levels in circulating EVs may reflect the presence of tumor tissue and may provide a marker for therapy response and relapse monitoring in HL patients. Rossi et al. [168] using a sensitive next-generation sequencing technique demonstrated the potential for monitoring patients with HL lymphoma.

In a study of 102 Hodgkin lymphoma patients treated with ABVD, interim PET, pretreatment CD68+ cell counts, and the presence of B symptoms were independently associated with PFS [169]. Therefore, the evaluation of CD68+ cell counts and B symptoms at diagnosis was suggested to help identify low-risk patients regardless of a positive interim PET result. Agostinelli et al. [170] provided evidence for an interaction between the microenvironment and PET. Although PET after two cycles of therapy predicts outcome in HL, 10–15% of patients still relapse. When interim PET after two cycles was combined with pretreatment environmental markers including PD-1 and CD68 in Micro Environment cells and STAT-1 in HRS cells in a Classification and Regression Tree (CART) analysis, PET2-negative patients could be distinguished into three risk groups with markedly different outcomes.

7.6.2 Interim PET

The use of quantitative techniques has been explored in DLBCL to improve on the accuracy

of visual assessment. Change in the maximum SUV (ΔSUVmax) in tumor before and after treatment has been evaluated as a measure of response. Lin et al. [171] and Itti et al. [172] performed receiver operator curve (ROC) analysis in 92 patients with DLBCL who underwent PET scan after two cycles of therapy, and 80 patients were scanned after four and identified the optimum thresholds for percentage change in SUVmax for predicting event-free survival (EFS). The ΔSUVmax better predicted PFS, compared with standard visual analysis. Biggi et al. [173] provided data from a retrospective analysis to suggest that incorporating semiquantitative analyses with visual interpretation improved predictive value of interim and end-of-treatment PET. Unfortunately, despite the fact that other groups have also reported that ΔSUVmax predicts response, the thresholds vary widely among studies. Thus, it is not clear that this technique is ready for general application until there is improved consistency in scanning protocols, matching conditions for serial scans, as well as proper calibration and scanner maintenance. The optimum cutoff is also likely influenced by timing, with a tendency for a higher cutoff later during treatment. Clinical correlation is also critically important.

7.6.3 End-of-Treatment PET

As first reported by Juweid et al. [153] and further recommended in the Lugano classification [9, 10], PET-CT is the standard of care for remission assessment in FDG-avid patients. PET allows for better discrimination between fibrosis and residual tumor, reducing the implementation of additional therapy. The high-level accuracy for PET was reported in patients with advanced HL following ABVD [174]. Another example is the German HD15 trial in which patients with a residual mass of at least 2.5 cm underwent PET [22]. If negative, they received no further therapy. Patients with a positive scan underwent radiation therapy. The outcome of the group with a residual mass that was not FDG avid was similar to those without a residual mass. Whether the size of the residual mass is clinically important is controversial. In a subsequent subset analysis of the German HD 15 trial [175]), those with a positive end-of-treatment PET and a decrease in the size of the residual mass <40% had a particularly poor outcome with a relapse rate in the first year of 23.1% compared with 5.3% for those with a greater decrease.

For patients with a residual mass following treatment of HL and for whom additional therapy is being considered, whether a biopsy is recommended is controversial as it is often falsely negative in HL due to the effects of treatment and sclerosis of the tumor.

7.7 FDG-PET/MRI

In 2014, a preliminary report was published comparing PET/MRI and PET/CT in a head-to-head for tumor staging in a cohort of 50 patients affected by miscellaneous cancers undergoing PET/CT with a non contrast-enhanced low-dose CT for attenuation correction at 120 KeV with 10 mA, followed 20 min later by PET-MRI [176]. All patients underwent whole-body PET/CT after a single intravenous injection of PET tracers ^{18}F-FDG, ^{68}Ga-DOTATATE, or ^{18}F-fluoro-ethyl-choline (^{18}FFECH) according to a standard clinical protocol performed on an integrated 64-slice PET/CT scanner (Discovery VCT; GE Healthcare). PET/MRI imaging was performed using a Siemens 3T Biograph mMR system with an integrated PET system within the MR gantry, which allows simultaneous PET and MR acquisitions without having to reposition the patient. Two hundred twenty-seven FDG-avid lesions were found: 225 were detected on PET/CT, and all the 227 on PET/MRI. Overall, anatomic localization was superior in 5.1% of the cases in PET/MRI modality compared with PET/CT; this was attributed to the established superior soft tissue contrast seen in head and neck, pelvis, and colorectal cancer patients. More recently, advances in magnetic resonance imaging (MRI) technology allowed the introduction of "functional" MRI, such as whole-body diffusion-weighted MRI (WB-DW-MRI). The latter could improve the sensitivity of tumor staging by standard MRI, thanks to a higher tumor-to-

background contrast, and of tumor restaging, thanks to a different apparent diffusion coefficient of the necrotic post-therapy tissue vs. that of the viable, pre-therapy, tumor lesion [177]. Herrmann et al. prospectively evaluated the overall accuracy of FDG-PET/CT, FDG-PET/MRI, and WB-DW-MRI for lymphoma staging and restaging in a cohort of 61 patients, including 21 cases of HL [178] undergoing sequential scanning with these three imaging techniques [178]. A total of 82 examinations were performed: 14 for staging and 68 for restaging, during (n = 14) or after chemotherapy (n = 19) and during follow-up (n = 35). Most examinations were performed in HL (n = 28) or diffuse large B-cell lymphoma (DLBCL; n = 26). FDG-PET/CT was used as reference method for assessing the performance of the other two techniques. One hundred thirteen lesions were found in lymphoma staging: FDG-PET/MRI detected all of them, while WB-DW-MRI detected only 64.6% of the lesions. FDG-PET/CT and FDG-PET/MRI detected the same number of lesions during interim (n = 16), end-of-therapy (n = 12), and surveillance (n = 47) scanning. On the other hand, WB-DW-MRI detected 56.3%, 50.0%, and 78.7%, respectively. The authors concluded that FDG-PET/CT and FDG-PET/MRI had a comparable diagnostic performance, while WB-DW-MRI could be preferred during patient follow-up as the latter had a comparable sensitivity to FDG-PET/CT or FDG-PET/MRI in detecting residual, persisting disease.

7.8 Future Perspectives

7.8.1 Other Tracers

FDG is a glucose analogue, and FDG uptake reflects the level of glucose metabolism in the tissue. However, like other cancers, lymphoma is characterized by deregulated cell cycle progression, and most anticancer drugs are designed to inhibit cell proliferation. Thus, a tracer enabling imaging of cell proliferation could be useful for both initial characterization and treatment monitoring of the disease. FDG uptake is somewhat correlated with cell proliferation, but this correlation is weakened by a number of factors, including FDG uptake in nonmalignant lesions as a result of inflammation or infection. The nucleoside [^{11}C]thymidine was the first PET tracer to specifically address cell proliferation. Early studies suggested that [^{11}C]thymidine could determine both disease extent and early response to chemotherapy in aggressive NHL patients [179, 180]. However, the short 20-min half-life of ^{11}C along with rapid in vivo metabolism limited its clinical application. The thymidine analogue 3′-deoxy-3′-[^{18}F]fluorothymidine (FLT) offers a more suitable half-life of 110 min and is stable in vivo [181]. A pilot study of seven patients showed that FLT-PET can sensitively identify lymphoma sites and distinguish aggressive from indolent NHL [182, 183], although less sensitive than FDG [184]. Furthermore, preclinical studies suggested a potential of FLT for imaging in early response to treatment in lymphoma [185]. Increased uptake of amino acids reflects the increased transport and protein synthesis of malignant tissue [186]. This observation provides the rationale for PET imaging of amino acid metabolism with the labeled amino acids L-[methyl-^{11}C]methionine (MET) and O-2-[^{18}F]fluoroethyl-L-tyrosine (FET). Nuutinen et al. [187] studied 32 lymphoma patients and found MET-PET to be highly sensitive for the detection of disease sites, although there was no correlation between MET uptake and patient outcome. Kaste et al. [188] evaluated pediatric patients with lymphoma using 11C-methionine and compared it directly with FDG PET-CT for staging and follow-up. Whereas the results were fairly synchronous, 11C-methionine had the disadvantage of limited abdominal utility because of its uptake in normal structures. Furthermore, no advantage has been demonstrated over FDG-PET [189].

Rylova et al. [190] studied immune-PET imaging of CD30-positive lymphomas using ^{90}Zr-desferrioxamine-labeled CD30-specific AC-10 antibody in a preclinical model and suggested that this technique might be of value in Hodgkin lymphoma and other CD30-expressing tumors. Clinical trials have not been reported. Thus, at the present time, 18-FDG remains the preferred tracer for imaging patients with lymphoma.

7.8.2 Quantitative Methods for PET Reading (SUV, MTV, TLG)

7.8.2.1 Semiquantitative Assessment

Whereas the DS relies on the qualitative assessment of FDG uptake, Standardized Uptake Value (SUV), is the most widely used method of PET interpretation in HL, and more semiquantitative measures have been explored. The SUV is the most widely used parameter for quantitative analysis. It is readily available and well established in routine clinical work. Other investigators evaluated the SUVmax, which is the uptake in the single voxel exhibiting the highest tracer uptake. The SUVmax is easily available, has good inter-reader reproducibility, and is relatively unaffected by partial volume effects. SUVmean is the mean uptake in a larger user-defined region. Rossi et al. [191] conducted a retrospective analysis of 59 patients with HL who underwent PET after two cycles of anthracycline-based chemotherapy. The DS was compared with the ΔSUV comparing PET-0 with PET-2. A good response was considered a ΔSUV of at least 71%. Using the DS, 78% were considered to have a negative scan, seven of whom failed treatment for a NPV of 85%. The ΔSUVmax was greater than 71% in 83% of patients, six of whom failed treatment with a NPV of 88%. On the other hand, the PPV was superior for the ΔSUVmax at 70% vs. 46% using the DS. The ΔSUVmax reclassified 46% of the DS-positive patients as negative. Moreover, the ΔSUVmax was more accurate at predicting 4-year PFS 82% vs. 30%. Unfortunately, the ΔSUV is not yet ready to be adopted in general practice. This method of interpretation is not standardized, with different cutoffs in the various published studies. Further studies should clarify the value compared with standard interpretation.

7.8.2.2 Metabolic Tumor Volume

A number of prognostic scoring systems are used by various investigators in patients with HL. Most of these include factors that are surrogates for tumor burden. The first attempt to approach the total tumor burden (TB) was made by Specht et al. [192] evaluating 290 patients with limited-stage HL. Data were supplied by the Danish National Hodgkin Study, with an index combining the tumor size of each involved region with the number of involved regions, sex, and histologic subtype to identify patients at a particularly poor risk following radiotherapy or chemoradiotherapy. Subsequently, other systems have been proposed using functional imaging. PET-CT affords the opportunity to provide a better assessment of tumor burden by measuring the total metabolic tumor volume (TMTV), which is related to both the tumor size and the activity of tumor and microenvironment cells. For these reasons, baseline TMTV has been suggested by several investigators to be a new risk factor to stratify early-stage patients. A high TMTV at baseline predicts a lower survival in early-stage HL [193, 194]. Using PET-CT, Cottereau et al. [60] evaluated the TMTV in 258 evaluable, high-risk, early-stage HL patients, treated on the H10 trial, 101 with favorable and 157 unfavorable disease. TMTV accurately predicted PFS and OS with 86% and 84% specificity, respectively. Indeed, TMTV identified 4 risk groups and was more accurate than baseline staging systems from the European Organization for the Research and Treatment of Cancer (EORTC), the German Hodgkin Study Group, the NCCN Network, and the Groupe d'Etude des Lymphomes de l'Adulte. The German Hodgkin Study Group evaluated 310 patients who underwent PET for staging and calculated MTV by four different methods [195] and found all predicted outcomes.

Moskowitz [126] et al. reported a phase II, risk-adapted study in patients with relapsed or refractory HL. Transplant eligible patients received two or three cycles of brentuximab vedotin; those who became PET negative went on to ASCT. Those with residual disease received augmented ifosfamide, carboplatin, and etoposide (ICE) prior to ASCT. Three-year overall survival and event-free survival (EFS) were 95% and 82%, respectively. Factors predicting favorable outcome were low baseline metabolic tumor volume (<109.5 cm^3) and relapsed disease, which was associated with a 100% likelihood of 3-year EFS. For patients who underwent ASCT, bMTV and pre-ASCT PET were independently prognos-

tic. The 3-year EFS for pre-ASCT PET-positive patients with low bMTV was 86%. Thus, bMTV improved the predictive power of pre-ASCT PET. In the future, consideration for ASCT should include such factors, to treat those patients most likely to benefit and to exclude those unlikely to do so.

The use of interim PET remains controversial. It appears to permit escalation of treatment toward improved outcome in PET-positive patients HL, as well as a reduction in treatment for those whose scan is interpreted as negative. Although PET-2 is the most common time point for an interim study, other data suggest that PET as early as after the first cycle may be preferred. Hutchings et al. found a very high prognostic value of PET after one cycle of chemotherapy and a higher negative predictive value after one cycle than after two cycles of chemotherapy [66]. The authors concluded that PET after one cycle should be the preferred method for PET-response-adapted strategies designed to select patients candidate to a less intensive or a de-escalated treatment. Kostakoglu et al. has come to a similar conclusion [14]. However, earlier studies may be associated with a higher false positive rate [14]. Thus, at the present time, two cycles is the current standard.

7.9 General Recommendations for the Use of PET in HL

Cheson et al. [9] recommended PET-CT as part of routine staging and restaging of patients with HL in the Lugano classification. A contrast-enhanced CT is not required unless measurement of a mass is critical to developing a treatment strategy. When used for initial staging, ample data support that a bone marrow aspirate and biopsy are no longer required. Interim PET may also be a valuable adjunct in Hodgkin lymphoma, as described above. A restaging study is best performed 6–8 weeks following the completion of standard induction therapy, with no contrast-enhanced CT indicated as whether there is evidence of persistent disease or not is what is critical. No additional scans are needed for surveillance unless there is clinical evidence supporting disease recurrence. PET-CT provides important guidance for patients who relapse and are being considered candidates for intensive therapy with a stem cell transplant.

Overall, PET-CT plays a major role in risk-adapted approaches as part of initial treatment, during interim evaluation, and in conjunction with other factors for patients being considered for various salvage strategies.

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Prognostic Factors

8

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_8

Abbreviations

ABVD	Adriamycin, bleomycin, vinblastine, dacarbazine
ASCT	Autologous stem cell transplant
BEACOPPesc	Bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisolone, escalated
BNLI	British National Lymphoma Investigation
BV	Brentuximab vedotin
CALGB	Cancer and Leukemia Group B
cfDNA	Cell-free DNA
CRP	C-reactive protein
CS	Clinical stage
EBMT	European Society for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EN	Extranodal
EORTC	European Organization for Research and Treatment of Cancer
ESR	Erythrocyte sedimentation rate
FDG	2-[18F]fluoro-2-deoxy-D-glucose
FF2F	Freedom from second failure
FFP	Freedom from progression
GELA	Groupe d'Etudes des Lymphomes de l'Adulte
GHSG	German Hodgkin Lymphoma Study Group
HDCT	High-dose chemotherapy
HL	Hodgkin lymphoma
HRS	Hodgkin-Reed-Sternberg
IPS	International Prognostic Score
LDH	Lactate dehydrogenase
LMM	Large mediastinal mass
LP	Lymphocyte predominant
MHC	Major histocompatibility complex
MOPP	Mechlorethamine, vincristine, procarbazine, prednisolone
MTV	Metabolic tumour volume
NCI-C	National Cancer Institute of Canada
NCI-US	National Cancer Institute of the United States
NS	Nodular sclerosis
OS	Overall survival
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PR	Partial remission
r/r	Relapsed or refractory
RT	Radiation therapy
SWOG	Southwest Oncology Group
TAM	Tumour-associated macrophages
TARC	Thymus and activation regulated chemokine
TNF	Tumour necrosis factor
TTR	Time to relapse

8.1 Historical Perspective

The concept that Hodgkin lymphoma (HL, then called Hodgkin's disease) passes through successive clinical stages with increasing spread of the disease and progressive worsening of prognosis was developed early on [1]. Different staging classifications were proposed based on the anatomic extent of disease [2–8]. A consensus was reached at the Workshop on the Staging of Hodgkin's Disease at Ann Arbor in 1971 [9], and the Ann Arbor staging classification was universally adopted. It still remains the basis for the

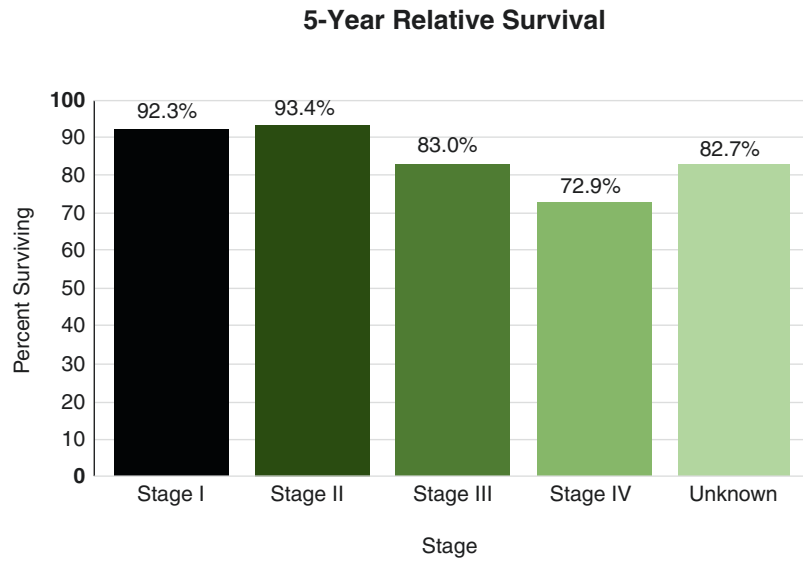


Fig. 8.1 Five-year relative survival according to Ann Arbor stage for patients in the US National Cancer Institute's Surveillance, Epidemiology, and End Results (*SEER*) program treated in the period 1975–2015 (Reprinted with permission from Noone et al. [18])

evaluation of patients with HL, and its prognostic significance has been documented in numerous studies of patients treated with different treatment modalities [10–17]. Five-year relative survival according to Ann Arbor stage for patients treated between 1975 and 2015 from the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program is shown in Fig. 8.1 [18].

However, the extent of disease varies within the Ann Arbor stages leading to variations in prognosis. A modification of the Ann Arbor classification was proposed at the Cotswold meeting, incorporating a designation for number of sites and bulk [19]. This modification has not been universally adopted. An update of the staging system was introduced in 2014 with the Lugano classification [20]. Therein a single nodal mass of 10 cm or greater than a third of the transthoracic diameter at any level of thoracic vertebrae as determined by CT was retained as the definition of bulky disease. PET/CT was designated as the preferred method of staging, obviating the need for bone marrow biopsies.

Numerous other prognostic factors for different Ann Arbor stages, disease presentations, treatment approaches, and outcomes have been introduced, and varying combinations of these factors are currently being used by different centres and study groups.

8.2 Prognostic Factors

8.2.1 Definition and Use

Prognostic factors are variables measured in individual patients that offer a partial explanation of the outcome heterogeneity of a given disease [21]. They are important in clinical practice for allocating patients into different risk groups, for selection of treatment strategy, and as an aid in patient counselling [22]. However, it is important to realise that prediction is very uncertain for the individual patient. Statements of probability can be made, but even these will be more accurate for groups of patients than for individuals [23]. Prognostic factors can also be used in the design of clinical trials to define eligibility criteria and strata to ensure comparability of treatment groups [21–24]. However, prognostic factors are rarely sufficiently explanatory to justify the comparison of treatments by use of non-randomised data [25, 26].

8.2.2 Types of Prognostic Factors

Prognostic factors are divided into tumour-related factors, host-related factors, and environment-related factors [22]. Tumour-related factors

include those directly related to the presence of the tumour or its effect on the host, reflecting tumour pathology, anatomic extent, or tumour biology. Host-related factors include factors that are not directly related to the tumour but which may significantly influence outcome, such as demographic characteristics and co-morbidity. Environment-related factors include factors outside the patient, such as socio-economic status and access to and quality of health care.

The values of prognostic factors are generally assumed to be known from the outset, before start of treatment, so-called fixed covariates. However, other important prognostic variables may only be known later, such as time to response, toxicity of treatment, and the value of presumed markers. These are time-dependent covariates. They may be important for answering biological questions, but they should not be applied for adjustment for treatment comparison, as they are themselves affected by treatment [21–23].

8.2.3 Different End Points

Different outcomes may be of interest in analyses of prognostic factors. Overall survival and progression-free survival are usually analysed, but others may be relevant, e.g. disease-free survival for early-stage patients as nearly all patients achieve remission. For each end point, there must be clear information on the point in time from which it is measured and the clinical characteristics of events and censoring. International guidelines have been published [27].

8.2.4 Types and Analyses of Prognostic Studies

Three different study phases of prognostic factors have been proposed, beginning with phase I early exploratory analyses to identify potential markers and generate hypotheses for further investigation. Phase II studies are exploratory studies attempting to use values of a proposed prognostic factor to discriminate between high- and low-risk patients. Phase III studies are large, confirmatory studies based on prespecified hypotheses involving one or a few new factors, and the purpose of these studies is to determine how much the new factor adds to the predictive power of already accepted factors [24, 28].

A useful prognostic factor must be significant, independent, and clinically important [29]. Many variables may be prognostic in univariate analysis. However, different variables are likely to be interrelated. The important question is whether a particular variable adds useful information to what is already known. Multiple regression analysis is commonly employed to determine whether a variable has independent significance when other known variables are taken into account. This kind of analysis may form the basis for the development of a prognostic model and a risk score or risk groups [28]. The Cox proportional hazards regression model is most commonly used when time-to-event outcomes are of interest [30]. The selection of variables for the final model is usually done by stepwise selection. By play of chance, different factors may be selected in different studies. An important additional analysis for a new marker is therefore to determine its prognostic ability in a model including all previously defined prognostic factors [28, 31]. Differences may also be due to small sample size, different assay techniques, different cut points for variables, inclusion of different subsets of patients, and different study end points.

8.2.5 Predictive Factors

Predictive factors are patient characteristics that identify subgroups of patients with different outcomes as a consequence of a given treatment. Hence a predictive factor identifies subgroups of treated patients having different outcomes, whereas a prognostic factor identifies subgroups of untreated patients having different outcomes. A factor that is predictive of outcome after one particular treatment may not be predictive for another treatment.

8.3 Prognostic Factors across Stages

Most important prognostic factors in HL, irrespective of stage, are correlated with and provide indirect measures of the patient's total tumour burden. The total tumour burden is the most important prognostic factor, rendering most other prognostic factors insignificant in multivariate analysis. This was demonstrated by semi-quantitative methods, based on a combination of the number of involved lymph node regions and the volume of disease in individual regions, in patient materials treated even before staging with CT scans was introduced [32–39]. When patient materials staged with CT scans became available, it became possible to directly contour and quantitate the total tumour volume in each individual patient, and the pivotal prognostic role of the total tumour burden was confirmed [40–46]. However, these methods for estimating the total tumour burden were too laborious to be implemented into clinical practice.

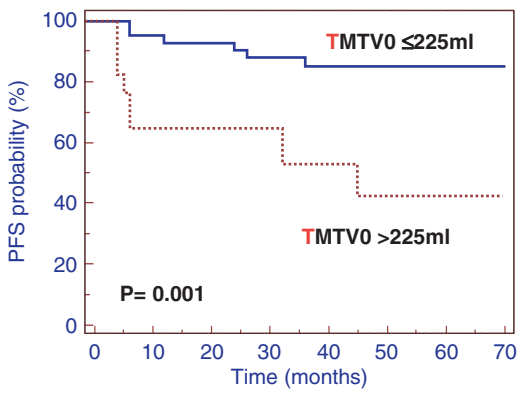
HL is a highly FDG-avid tumour, and the total volume of the PET-positive lymphoma tissue (the metabolic tumour volume) is highly correlated with the total tumour burden. Hence, studies are now demonstrating the prognostic relevance of the metabolic tumour volume [47–51]. The preferred method for measuring the baseline metabolic tumour volume has not yet been agreed [52–55]. Hopefully this problem will be solved soon, resulting in a simple method that will allow measuring the total metabolic tumour volume. This should be closely related to the total tumour burden and become a practical and clinically useful method for dividing patients with HL into prognostic subgroups (Fig. 8.2).

8.4 Early-Stage Hodgkin Lymphoma

From early studies in Hodgkin lymphoma, it was evident that the number of involved regions and size of mediastinal disease, B symptoms, histological subtype, age, gender, ESR, haemoglobin, and serum albumin were prognostically significant [14, 56–65]. Table 8.1 lists the established

Table 8.1 Prognostic factors in early-stage HL

Tumour burden
Number of involved lymph node regions
Large tumour mass, particularly mediastinal
B symptoms
Histological subtype
Age
Gender
Erythrocyte sedimentation rate (ESR)
Haemoglobin
Serum albumin
(early interim FDG-PET scan)



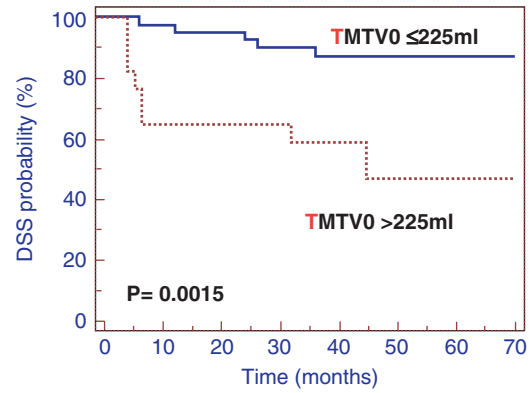


Fig. 8.2 Progression-free (PFS) and disease-specific survival (DSS) for 59 patients with all stages of HL divided into low and high total metabolic tumour volume, i.e. < or >225 ml (Reprinted with permission from Kanoun et al. 2014 [49])

prognostic factors in early-stage HL. Based on the most important factors, different centres and groups divided early-stage patients into favourable and unfavourable. Table 8.2 shows the factors and risk groups defined by some of the major groups. Although the factors included in these risk group definitions are fairly similar, the risk group definitions vary making comparisons between patient materials difficult.

Treatment of early-stage patients is tailored according to prognostic subgroups. Thus, in many studies patients are selected, making the detection of prognostic factors difficult. Most of the important prognostic factors are correlated providing indirect measures of the patient's total tumour burden [36, 39, 62].

Functional imaging with FDG-PET has become an important part of staging and treatment evaluation of lymphomas. An early interim FDG-PET scan after one or two cycles of chemotherapy has been shown to be highly predictive of outcome after combined modality treatment [66–71]. However, in early-stage disease, there are many false-positive results, the predictive value depends on the chemotherapy regimen used, and the majority of the patients with interim PET positivity were cured with combined modality therapy, yielding a positive predictive value of only 15% [72]. The negative predictive value is very high in early-stage disease, which would be expected in a disease with a very good prognosis. In fact, because over 90% of patients with early-stage disease are cured with standard treatment, the added information from a negative interim PET scan is actually very limited [73, 74]. The early interim FDG-PET scan may be regarded as an in vivo test of the chemosensitivity of disease. As the result of the scan is not known at the outset, there is a methodological problem with this test. Strictly speaking, outcome according to the result of an early interim FDG-PET scan should only be measured from the time when it is available, and it should be regarded more as a predictive factor indicating the sensitivity to a particular treatment rather than as a usual prognostic factor.

From a clinical point of view, it would be better to predict the outcome with a given regimen up front rather than having to initially administer possibly ineffective or too intensive treatment. The total metabolic tumour volume (MTV) as a surrogate for the total tumour burden seems promising in this respect. Furthermore, recent research into molecular abnormalities in either tumour cells or non-malignant background cells has demonstrated numerous biomarkers, some of which will hopefully allow individualization of treatment up front [75–91]. However, for a new prognostic factor to be proven useful, it needs to be demonstrated to show independent significance when the already known factors, in particular the total tumour burden, are taken into account.

The standard treatment for early-stage disease is combined modality treatment. Recently, chemotherapy alone has been used, resulting in a moderate increase in the risk of relapse. Prognostic factors in this group of patients have not been analysed in detail as large cohorts of patients with reasonable follow-up are not yet available.

8.5 Advanced-Stage Hodgkin Lymphoma

Patients presenting in stage III/IV are universally considered as advanced-stage requiring systemic treatment, eventually followed by consolidative RT in selected cases. Patients with stage IIB and additional risk factors such as extranodal disease (EN) or a large mediastinal mass (LMM) are additionally regarded advanced-stage by some study groups or centres for the purpose of first-line therapy.

Large data sets are important to reliably assess the independent contributions of single routinely documented clinical prognostic factors and two very large data sets resulted from international cooperation: The International Database on Hodgkin's Disease set up in 1989 combined >14,000 individual patient data across all stages from 20 study groups in the MOPP era [14]. In 1995, the International Prognostic Factors Project on advanced Hodgkin lymphoma combined data of 5141 advanced-stage patients mainly treated with doxorubicin-containing regimen [92]. More

Table 8.2 Criteria for favourable vs. unfavourable early-stage HL as defined by different centres and cooperative study groups

	GHSG	EORTC	NCI-C and ECOG	Stanford
Risk factors	(a) Large mediastinal mass (b) Extranodal disease (c) ESR ≥ 50 without B symptoms or ≥30 with B symptoms (d) ≥3 nodal areas	(a) Large mediastinal mass (b) Age ≥ 50 years (c) ESR ≥ 50 without B symptoms or ≥with B symptoms (d) ≥4 nodal areas	(a) Histology other than LP/NS (b) Age ≥ 40 years (c) ESR ≥ 50 (d) ≥4 nodal areas	(a) B symptoms (b) Large mediastinal mass
Favourable	CS I–II without risk factors	CS I–II (supradiaphragmatic) without risk factors	CS I–II without risk factors	CS I–II without risk factors
Unfavourable	CS I or CS IIA with ≥1 risk factors CS IIB with (c) or (d) but without (a) and (b)	CS I–II (supradiaphragmatic) with ≥1 risk factors	CS I–II with ≥1 risk factors	CS I–II with ≥1 risk factors

GHSG German Hodgkin Study Group, *EORTC* European Organization for Research and Treatment of Cancer, *NCI-C* National Cancer Institute of Canada, *ECOG* Eastern Cooperative Oncology Group

recent studies focussed on disease activity measured by interim and/or end-of-treatment PET to further individualize treatment.

8.5.1 Pretreatment Prognostic Factors in Advanced-Stage Hodgkin Lymphoma

The most important patient-related prognostic factor for overall survival (OS) in advanced-stage HL is age [93–97]. Elderly patients (>60 years) are often excluded from clinical trials [98]. Prevalence of co-morbidity is associated with age and treatment-related mortality is increased [99]. In patients up to 65 years, age >45 years is an independent prognostic factor for freedom from progression. The impact of age is amplified in overall survival as compared to progression-free survival due to compromised results of salvage treatment in elderly relapsed patients [100]. Male gender is another independent, although quantitatively moderate, adverse patient-related prognostic factor within advanced stages [14, 92, 101, 102].

In terms of disease-related factors, tumour burden either quantified from conventional or PET imaging is a main determinant of prognosis [39–41, 62, 103]. As previously outlined, MTV is increasingly being recognised as pre-therapeutic prognostic factor but still rarely measured routinely. Stage IV marks dissemination of the disease to extranodal sites and is independently prognostic within advanced-stage disease [14, 92]. A particularly bad prognosis for bone marrow, lung, or liver involvement could not be confirmed. It thus remains controversial whether certain disease locations or the number of involved extranodal sites carries independent prognostic value within stage IV disease.

Several haematological and biochemical laboratory parameters form a cluster of interrelated prognostic indicators that mirror both tumour burden and inflammatory processes [75]. These factors include decreased serum albumin and haemoglobin levels as well as an elevated ESR, LDH, C-reactive protein (CRP), and alkaline phosphatase, which are correlated with one other as well as with the presence of B symptoms and tumour burden. Leukocyte and lymphocyte counts form a second correlation cluster of laboratory parameters; in addition, leucocytosis and lymphocytopenia have an independent prognostic impact [92].

A plethora of biological parameters such as levels of cytokines released by HRS cells, soluble forms of membrane-derived antigens, and cell-free tumour DNA have been investigated for prognostic value not confined to advanced-stage disease. Many of these studies were done in rather small data sets, and findings are often not yet integrated with other clinical or imaging factors in multivariate analysis. The soluble form of the CD30 molecule (sCD30) is released by HRS cells and is detectable in the serum of virtually all untreated patients. It maintains independent prognostic significance in multivariate analysis in moderately sized data sets [78, 104–106]. The thymus and activation-regulated chemokine (TARC or CCL117) plays a role in the pathogenesis of HL and correlates with disease burden and outcome [107]. A correlative analysis of the recent randomized phase III ECHELON-1 trial comparing ABVD and BV-AVD could not confirm a prognostic role for sCD30 or TARC since neither of the two parameters correlated with early or end-of-treatment response nor PFS [108]. The relevance of cytokine levels such as IL-1RA, IL-2R, IL-6, IL-10, or tumour necrosis factor (TNF) requires further investigation [78, 109, 110] as does the role of elevated β_2-microglobulin [111]. Circulating cell-free tumour DNA (cfDNA) recently gained attention across various tumour types since it potentially allows minimally invasive monitoring of disease activity over the course of treatment as well as genetic assessment of the malignancy [112]. After a proof-of-concept study for HL was published [113], very recent studies highlight the prognostic potential of cfDNA, especially in correlation with disease status by PET [114, 115].

Focussing on tumour architecture and composition, several histopathological markers in tumour tissue either expressed by HRS or reactive bystander cells were identified. High density of CD68+ macrophages has been shown to be adversely prognostic with ABVD treatment [89,

116]. Tumour-associated macrophages (TAM) together with cells involved in a TH1 immune response possibly create an inflammatory environment favouring rapid lymphoma proliferation. A recent analysis revealed frequent 9p24.1 amplifications in advanced-stage cHL which were associated with poorer PFS in ABVD-treated patients [117]. In order to obtain a method usable in clinical practice, a 23-gene expression signature was shown to be predictive in advanced-stage ABVD-treated patients [88]. However, further validation in clinical trials including PET-adapted or BEACOPP-based therapy is required.

8.5.2 Interim PET as Prognostic Factor in Advanced-Stage Hodgkin Lymphoma

An early interim FDG-PET scan after two cycles of chemotherapy (PET-2) has been shown to be highly predictive of outcome in advanced-stage HL a decade ago [68, 118–120]. In a large study of advanced-stage patients treated with ABVD, the prognostic value of PET-2 completely overshadowed the role of the International Prognostic Score (IPS) [121]. Figure 8.3 shows PFS according to the IPS and the PET-2 result.

Within the last years, individualized treatment guided by PET-2 was investigated in several phase III trials. Within the UK-led RATHL trial, PFS and OS were superior in PET-2-negative patients as compared to PET-2-positive patients, despite de-escalation from ABVD to AVD or escalation from ABVD to $BEACOPP_{escalated}$, respectively [122]. In PET-2-negative patients, only stage IV disease and the IPS but no other factors such as bulky disease, PET score by Deauville, or B symptoms retained prognostic significance for PFS. In contrast, PET-2 status was not prognostic for PFS in the GHSG HD18 trial [123] as shown in Fig. 8.4.

Neither addition of rituximab to $BEACOPP_{escalated}$ in the PET-2-positive patient nor reduction from 6–8×$BEACOPP_{escalated}$ to 4×$BEACOPP_{escalated}$ did relevantly change PFS or OS for these different treatment arms (Fig. 8.5) [123]. Similar observations were made in the French AHL2011 trial, which investigated de-escalation to 4xABVD in PET-2-negative patients after 2×$BEACOPP_{escalated}$ [124]. These findings underline the poor positive predictive value of a positive PET-2 in patients initially treated with $BEACOPP_{escalated}$. On the other hand, the improved negative predictive value of a negative PET-2 in this group of patients has to be compared to those initially treated with ABVD.

Of note, post-hoc analyses of the UK RATHL trial showed very good inter-observer comparability, highlighting the feasibility of utilizing PET-2-guided therapy in routine clinical care [125] .

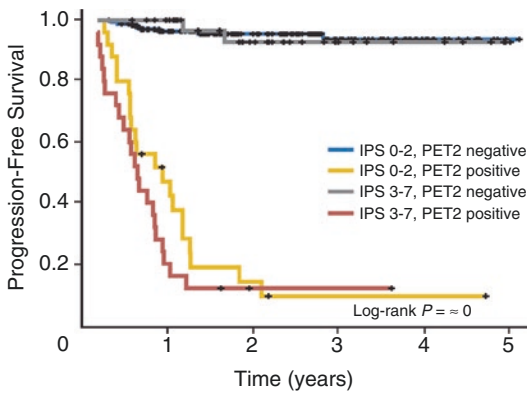


Fig. 8.3 PFS in 260 patients with advanced-stage disease according to the IPS and PET-2 status after 2×ABVD (Reprinted with permission from Gallamini et al. [121])

8.5.3 Prognostic Indices in Advanced-Stage Hodgkin Lymphoma

Prognostic indices for advanced HL are clinically important to select patients prior to initiation of first-line treatment who may be over- or under-treated by standard therapeutic approaches.

Over the last decades, several groups developed prognostic indices or scores based on a few hundred cases trying to define high-risk groups. Most scores combined age, disease extent, and laboratory markers, but only a prognostic model for OS developed by Gobbi et al. based on the following seven factors received

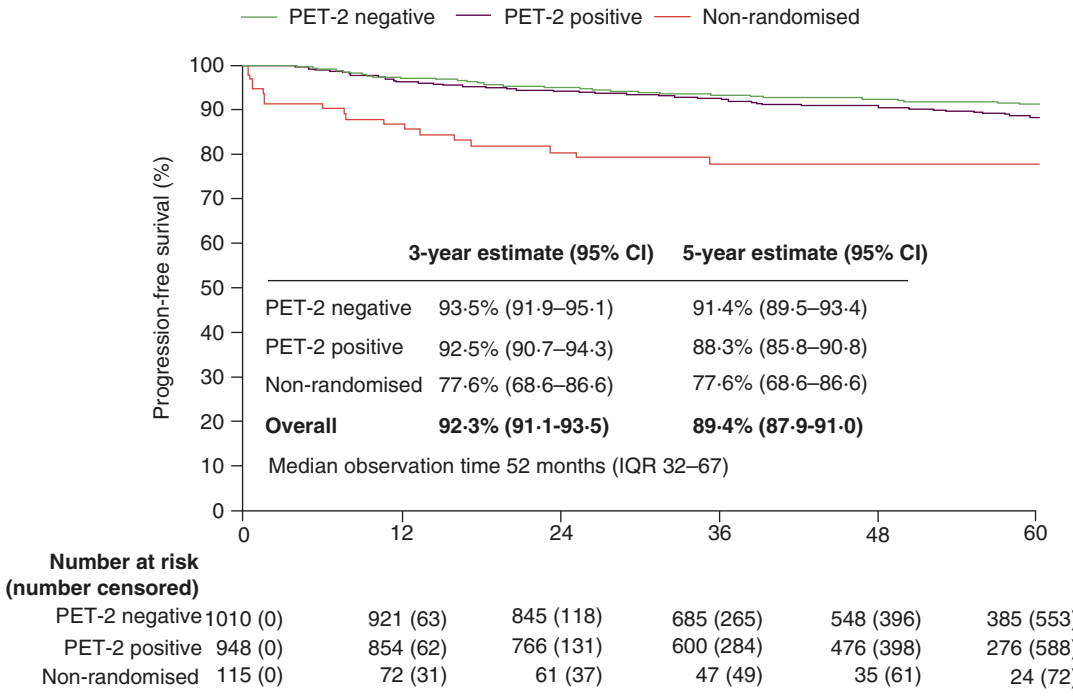


Fig. 8.4 PFS according to PET-2 status after 2×BEACOPP$_{escalated}$ in 2073 patients with advanced-stage treated within the HD18 trial (Reprinted with permission from Borchmann et al. [123])

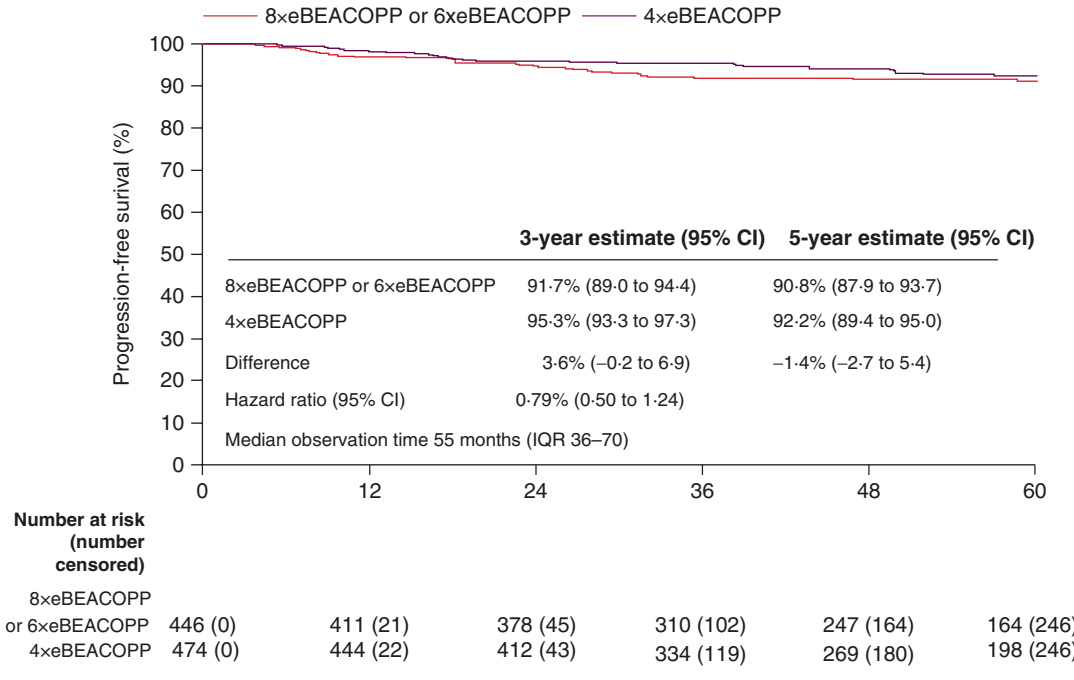


Fig. 8.5 PFS in 920 PET-2-negative patients treated with a total of 6–8× vs. 4×BEACOPPescalated in the HD18 trial (Reprinted with permission from Borchmann et al. [123])

general acceptance: stage, age, histology, B symptoms, serum albumin, sex, and involved area distribution (infradiaphragmatic disease or >3 supradiaphragmatic areas) [101].

Some years later, the International Prognostic Factors Project on advanced-stage HL focussed on FFP [92]. Individual patient data were collected from 23 centres and study groups including 5141 advanced-stage HL patients who were treated mainly with doxorubicin-containing chemotherapy with and without radiotherapy. A prognostic score was developed from this data set in patients up to 65 years of age. The score is a simple count of seven binary adverse prognostic factors (Table 8.3):

This prognostic model, termed the "International Prognostic Score" (IPS), predicts 5-year tumour control rates in the range of 45–80%. Each additional factor reduces the prognosis by about 8%. Figure 8.6 shows the FFP according to the number of adverse prognostic factors.

Since its publication, the IPS has performed reasonably well in independent data sets [126–131], including patients treated with intensified BEACOPP chemotherapy, where outcome uniformly improved in all IPS groups with persisting but quantitatively reduced differences [126, 130].

Comparison of several prognostic models [94, 128] revealed that none of the models including the IPS are able to select either a very low-risk group (e.g. <10% failure rate) or a substantial very high-risk group (>50%). The prognostic models thus discriminate only between low-risk and high-risk patients (e.g. IPS ≤2 vs. IPS >2). A more recent analysis verified the prognostic value of the original IPS-7 in patients treated with either ABVD or Stanford V within the multicentre US E2496 trial, though with narrowed prognostic range. Based on the three prognostic factors age, stage, and haemoglobin identified by multivariable analysis, a simple IPS-3 with better discrimination for freedom from progression and overall survival (OS) was developed (Fig. 8.7) [132].

Several authors tried to extend the IPS beyond advanced stages. The IPS works nicely to predict outcome after autologous haematopoietic stem cell transplantation [133]. It appears to be moderately predictive in early and intermediate stages, extending the factor stage IV to include any extranodal disease [57, 134].

Table 8.3 Adverse prognostic factors incorporated in the International Prognostic Factors Project score for FFP in advanced-stage HL

Age ≥ 45 years
Male sex
Stage IV disease
Haemoglobin <10.5 g/dl
Serum albumin <4.0 g/dl
Leucocytosis ≥15 × 10^9/l
Lymphocytopenia <0.6 × 10^9/l or <8% of white blood cell count

8.6 Prognostic Factors in Relapsed or Refractory Hodgkin Lymphoma

8.6.1 Patients Treated for r/r HL with Conventional Treatment

Patients relapsing after initial treatment with chemotherapy only or combined modality therapy, whether for limited or advanced disease, historically had a poor prognosis with conventional chemotherapy, obtaining durable remissions in only 10–30% of cases [135–140]. In this setting, the extent and duration of an initial remission (i.e. time-to-relapse, TTR) is the most important prognostic factor for outcome after relapse. Patients who never achieve a remission (i.e. refractory or primary progressive disease) have an extremely poor prognosis, while patients who relapse within or after 12 months of completion of therapy have an intermediate or relatively good prognosis, respectively [135–138, 140, 141]. But even for the latter, long-term outlook is poor with historic conventional chemotherapy and dismal in patients with second or higher relapse [142–144]. Figure 8.8 shows survival curves for patients relapsing after initial chemotherapy divided into these three prognostic groups [145].

In addition to TTR, the extent of disease at relapse is also independently significant for

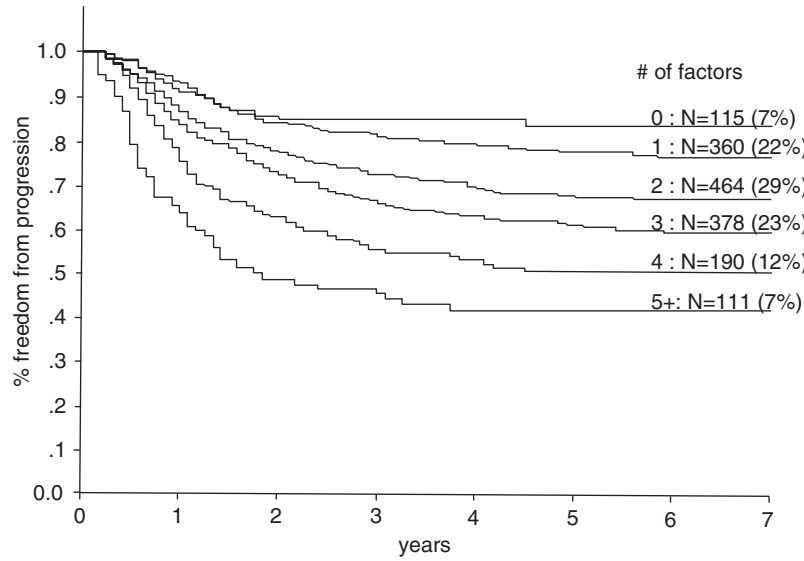


Fig. 8.6 Freedom from progression according to the number of adverse prognostic factors (see Table 8.3) for 1618 patients with advanced-stage HL in the International Prognostic Factors Project (Reprinted with permission from Hasenclever and Diehl [81])

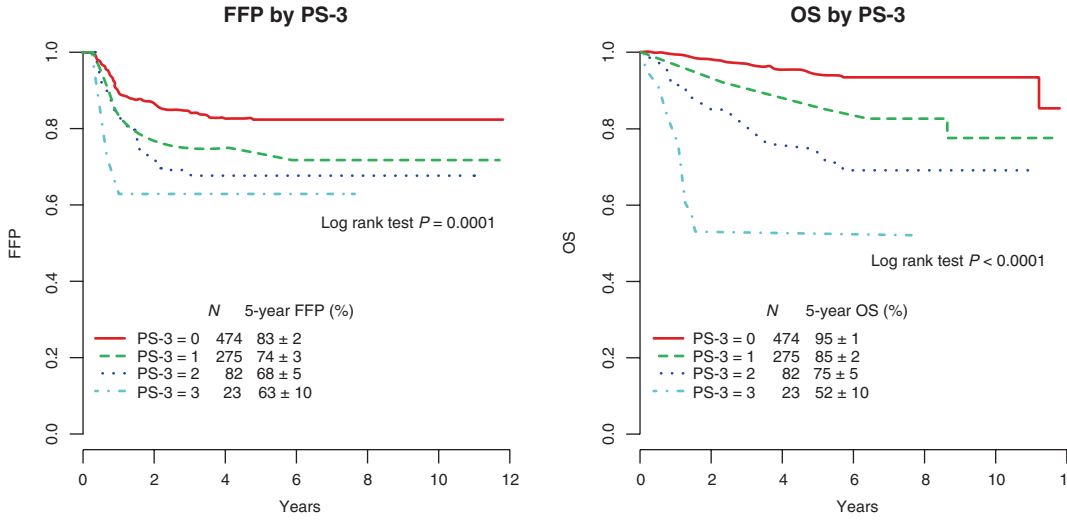


Fig. 8.7 FFP and OS according to IPS-3 among 854 patients with advanced-stage HL in the E2496 trial (Reprinted with permission from Diefenbach et al. [132])

prognosis. Advanced stage, extranodal disease, and more than three involved sites at relapse are adverse prognostic factors [100, 135, 136, 140, 146]. Age, performance status, histology other than nodular sclerosis, B symptoms at relapse, and a low haemoglobin have also been shown to be significant [100, 135, 137, 138, 140, 141, 146]. Prognostic factors which have been shown to be independently significant for outcome after HL relapse treated with conventional chemotherapy are summarised in Table 8.4.

A subgroup of patients with relapsed or refractory HL (r/r HL) have anatomically limited disease. For selected patients in this subgroup, RT with or without additional chemotherapy offers some chance of durable remission [138, 147–150]. Prognostic factor analyses indicate that patients suitable for this kind of relapse treatment are those relapsing exclusively in supradiaphragmatic nodal sites, with no B symptoms at relapse, and after a disease-free interval of >12 months [147, 148, 151]. In patients with

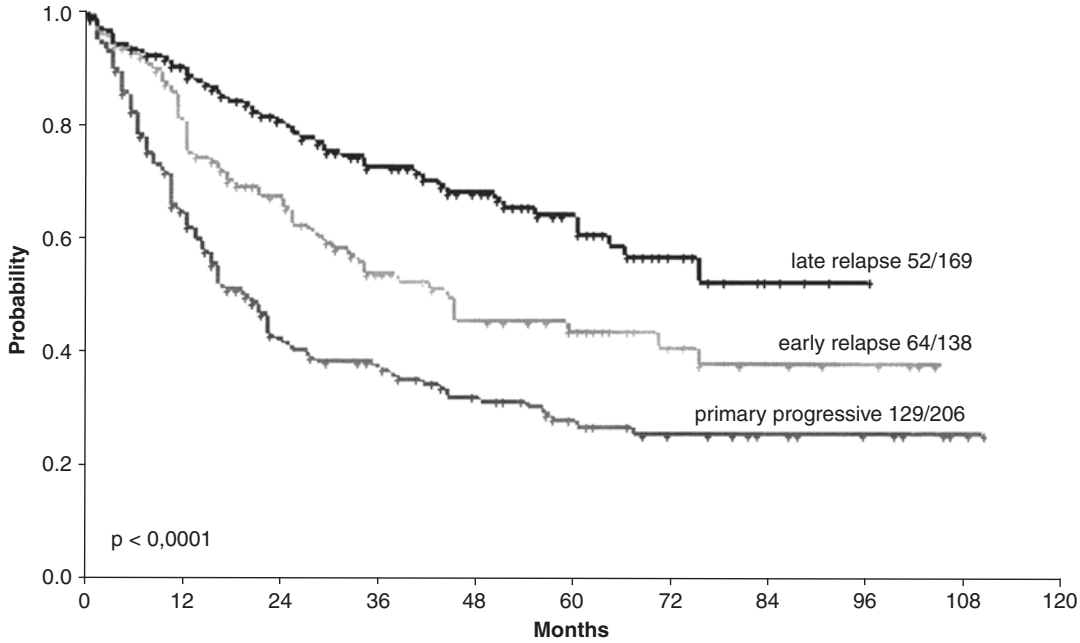


Fig. 8.8 OS of patients with primary progressive, early relapse, or late relapse of HL, treated in GHSG trials from 1988 to 1999 primarily with conventional salvage (Reprinted with permission from Josting and Schmitz [145])

Table 8.4 Independent prognostic factors for outcome in r/r HL treated with conventional chemotherapy

Extent and durability of first remission (TTR)
Extent of disease at relapse (relapse stage, extranodal relapse, ≥3 sites of relapse)
B symptoms at relapse
Haemoglobin at relapse
Histology
Age
Performance status

these favourable characteristics, durable remission with RT may be achieved in up to 50% of cases.

8.6.2 Treatment with High-Dose Chemotherapy and Autologous Stem Cell Transplantation

High-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) is superior to conventional chemotherapy in r/r HL [152, 153]. Hence, it is the preferred treatment in relapsed eligible patients and current standard of care. Similar to treatment with conventional chemotherapy, a number of prognostic factors were identified decades ago and are still independently significant for outcome. The chemosensitivity of the disease is extremely important. Thus, the response to initial or salvage therapy, the duration of initial remission, and the number of prior failed regimens have been shown to be associated with outcome [154–161]. Evaluation of response to salvage treatment before HDCT by PET further refines prognostication [162–167].

The disease burden before transplantation is another important prognostic factor, and measures reflecting tumour burden such as stage of disease and bulky or extranodal disease at salvage have been shown to be independently significant [145, 154, 161, 168]. B symptoms, low haemoglobin, and elevated serum LDH at relapse are also significant [154, 157, 162, 169, 170]. A poor performance status is an important adverse prognostic feature [155, 159, 171], whereas age has not been significant in most series, probably due to the fact that most patients are relatively young as required by the intensive HDCT + ASCT approach [161, 172–176]. Of note, paediatric patients have the same outcome as adults [177].

Table 8.5 Independent prognostic factors for outcome after HDCT + ASCT in r/r HL

Chemosensitivity of HL
Response to initial or salvage therapy
Duration of initial remission (TTR)
Number of failed prior regimens
FDG-PET after salvage and before HCT + ASCT
Disease burden before salvage
Stage of disease in r/r HL
Bulky disease in r/r HL
Extranodal r/r HL
B symptoms at r/r HL
Haemoglobin at r/r HL
Serum lactate dehydrogenase (LDH) at r/r HL

The seven factors included in the IPS for advanced-stage HL have also been examined in r/r HL and are at least partially applicable [133, 178]. The prognostic factors known to be independently significant for outcome after high-dose chemotherapy and stem cell transplantation are shown in Table 8.5.

For patients with disease recurrence after ASCT, prognosis was poor historically. Refractory disease at second-line treatment and short disease-free interval after ASCT are very poor prognostic factors [179–182].

8.6.3 Patients' Prognostic Indices or Scores in r/r HL Treated with Novel Agents

Over the last years, several studies aimed at combining individual risk factors in prognostic scores developed by multivariable analyses to improve clinical applicability.

An early prognostic score based on the equally weighted three clinical risk factors haemoglobin <10.5 g/dl and <12.0 g/dl in female and male patients, respectively, clinical stage III/IV, and TTR <12 months was established by an analysis of 422 patients relapsing after treatment in GHSG trials between 1988 and 1999. Four-year FF2F was estimated at 65%, 35%, and 25% for low-, intermediate-, and high-risk patients, respectively [183]. In a more recent analysis of the European HDR2 trial, only stage IV disease but not stage III or III/IV at relapse retained prognostic significance; 3-year PFS was estimated at 81% and 14% for the most favourable and unfavourable risk groups with zero or all three risk factors, respectively [184].

Based on EBMT registry data and the four factors Karnofsky performance score < 90%, chemotherapy resistance prior to ASCT, ≥3 chemotherapies pre-ASCT, and extranodal disease, a different risk score was proposed and externally validated. Four-year PFS for the low-, intermediate-, and high-risk group were 71%, 60%, and 42%, respectively [185].

In a very recent international effort, a simple externally validated prognostic score in contemporarily treated patients within or outside clinical trials was developed [171]. Equal weighting of the five factors stage IV disease, TTR ≤ 3 months, ECOG performance status ≥ 1, bulk ≥ 5 cm, and inadequate response to salvage chemotherapy (i.e. <PR or PET positivity) thereby resulted in optimal prognostication of both PFS and OS after ASCT (Fig. 8.9).

8.6.4 Prognostic Factors for Treatment with Novel Agents in r/r HL

The anti-CD30 antibody-drug conjugate brentuximab vedotin (BV) was one of the first drugs in decades approved for the treatment of r/r HL based on acceptable toxicity and high response rates in the pivotal phase II trial [186]. Subgroup analyses according to potential risk factors did not reveal any unfavourable risk groups in terms of response rates or PFS. A recent trial investigating BV as salvage therapy prior to ASCT identified MTV in addition to refractory disease as relevant prognostic factors for event-free survival (EFS) in multivariable analysis [50]. When administering BV as consolidative therapy after ASCT, a sustained 5-year PFS benefit compared to placebo was seen across risk groups with a pronounced difference in patients with any ≥2 risk factors from a variety of potential single risk factors [187].

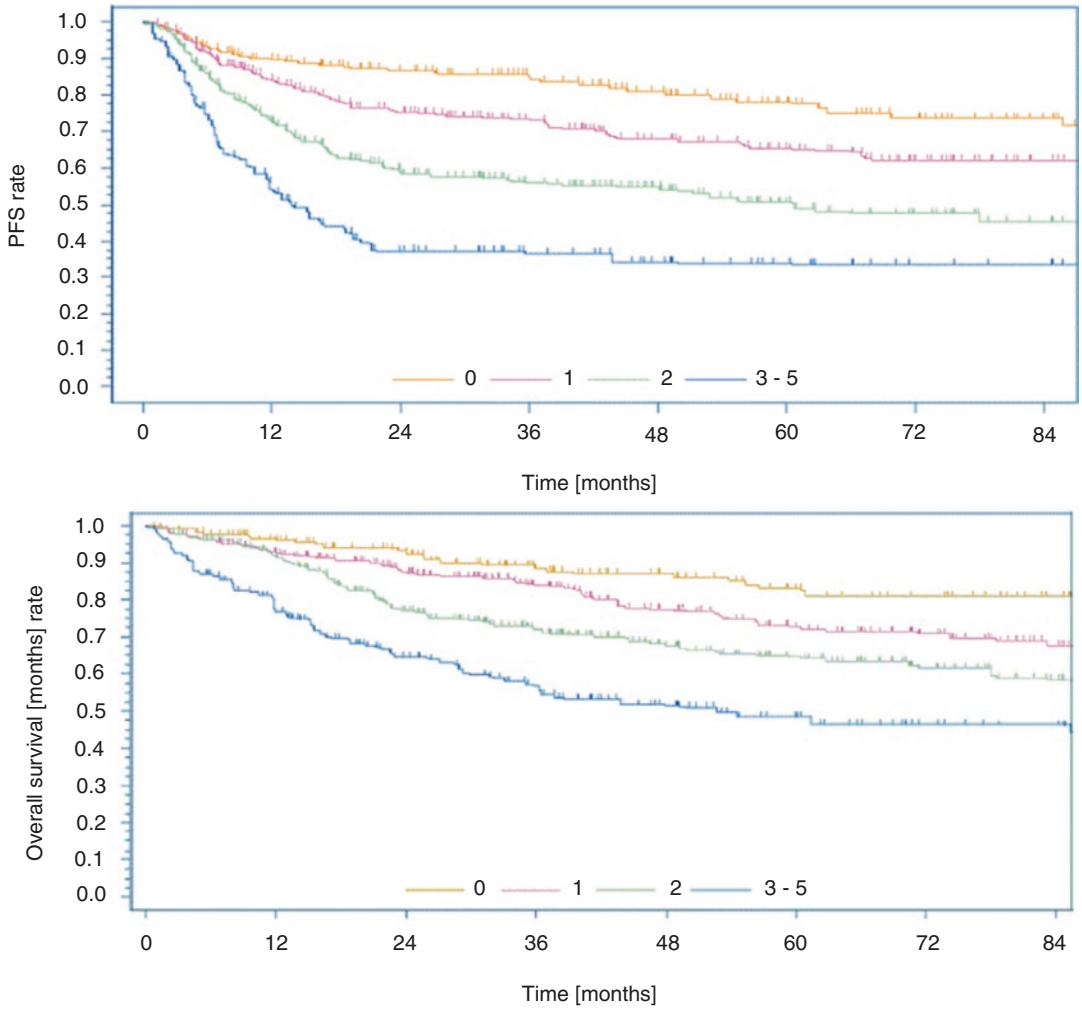


Fig. 8.9 PFS and OS after ASCT for r/r HL according to the number of risk factors present (Adapted with permission from Bröckelmann et al. 2017 [171])

More recently, the anti-PD1 antibodies nivolumab and pembrolizumab were approved for r/r cHL due to high response rates and exceptional tolerability in the pivotal phase II trials [188, 189]. Across both trials, also heavily pretreated patients with unfavourable disease characteristics responded to therapy and achieved relatively long PFS. Exploratory analyses in r/r cHL patients treated with nivolumab revealed 9p24.1 alterations in virtually all patients and a correlation of PFS with the 9p24.1 genetic categories (e.g. amplification or copy gain) as well as PD-L1 expression by the HRS cells. In addition, sustained MHC class II expression on HRS cells was associated with superior response rates and PFS in patients treated >12 months after ASCT. As expected, patients achieving a PR or CR had superior PFS to non-responders [190].

8.7 Conclusion and Future Aspects

As demonstrated above, a large number of variables have been shown to possess prognostic significance in HL, both at initial presentation and at relapse or progression. Most of these variables are correlated with the total tumour burden,

which has hitherto been too cumbersome to measure for use in clinical practice. However, the metabolic tumour volume, measured by FDG-PET, is highly correlated with the total tumour burden and may become an important and clinically useful prognostic tool in the future. Today, treatment is tailored to risk groups defined by prognostic factors, with less intensive therapies for patients with favourable disease in order to reduce toxicity and increasing treatment intensity for patients with unfavourable characteristics with the aim of increasing cure rates. Different centres and groups use slightly differing criteria for initial treatment selection, which makes direct comparisons challenging and some form of international harmonisation desirable. Early interim functional imaging by FDG-PET as a marker for treatment sensitivity allows individualized treatment in routine clinical care of advanced-stage HL. In early-stage disease, its role is less clear. Molecular abnormalities in either tumour cells or their microenvironment as well as circulating cell-free DNA may potentially prove to be powerful prognostic markers. Integration of these biomarkers will hopefully enable refined therapeutic approaches better tailored to individual disease activity and risk of treatment failure. With the advent of novel agents, drug-specific prognostic or predictive factors are of increasing interest to stratify treatments and minimize potentially harmful and expensive exposure.

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9 Principles of Radiation Therapy for Hodgkin Lymphoma

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_9

Abbreviations

3DCRT	Three-dimensional conformal radiotherapy
ABVD	Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine
AP-PA	Opposed anterior and posterior fields
ASCT	Autologous stem cell transplantation
ASH	American Society of Hematology
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, procarbazine, prednisone
BV	Brentuximab vedotin
CR	Complete response
CT	Computed tomography
CTV	Clinical target volume
CVRT	Consolidation volume radiation therapy
DIBH	Deep-Inspiration Breath Hold
EBVP	Epirubicin, bleomycin, vinblastine, dacarbazine
EFS	Event-free survival
EORTC	European Organisation for Research and Treatment of Cancer
FFTF	Freedom from treatment failure
GELA	Groupe d'Études des Lymphomes Adultes
GHSG	German Hodgkin Study Group
HL	Hodgkin lymphoma
IFRT	Involved-field radiation therapy
IMRT	Intensity-modulated radiation therapy
INRT	Involved-node radiation therapy
ISHL11	International Symposium on Hodgkin Lymphoma 2018 meeting
ISRT	Involved-site radiation therapy
LPHL	Lymphocyte-predominant HL
MOP-BAP	Mechlorethamine, vincristine, prednisone, bleomycin, doxorubicin, procarbazine
MOPP	Mustargen, vincristine, procarbazine, prednisone
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximum tumor dimension

NCCN	National Comprehensive Cancer Network
OS	Overall survival
PET	Positron emission tomography
PTV	Planning target volume
RT	Radiation therapy
STLI	Subtotal lymphoid irradiation
TLI	Total lymphoid irradiation
TSH	Thyroid-stimulating hormone

9.1 Principles of Radiation Therapy of Hodgkin Lymphoma

Radiation therapy (RT) is a major component of the successful treatment of Hodgkin lymphoma (HL). For decades, RT was used alone to cure the majority of patients with HL, and it is still the most effective single agent in the oncologic armamentarium for this disease [1]. RT alone remains the treatment of choice for patients with early-stage lymphocyte-predominant HL (LPHL) and for selected patients with classic HL who have contraindications to chemotherapy [2].Currently, most patients with HL are treated with combined-modality programs in which RT is given as consolidation after chemotherapy. As the role of RT has transformed over the years from a single modality into a component of combined-modality therapy, the classic principles of RT fields, dose, and technique have fundamentally changed.

The following principles guide the current strategy of using RT in HL:

1. RT as part of a combined-modality program is radically different from the large-field, high-dose RT that was used as a single modality in the past. Both the volume treated and the dose required are significantly reduced following chemotherapy as compared to when RT was used alone. In addition, the planning and delivery of RT has improved substantially over the last two decades and continues to improve.
2. Adding RT to chemotherapy improves disease control and allows the administration of shorter and less toxic chemotherapy regimens for all stages of HL. In early-stage HL, multiple randomized studies have shown that the omission of RT results in inferior progression-free survival even after chemo-intensification.
3. Modern RT for HL treats only involved sites to reduced doses and is both better tolerated and associated with significantly lower risk for long-term morbidities than the large-field, high-dose RT used as a single modality in the past [3].

9.2 The Evolution of Radiotherapy for HL

RT has been used in the management of HL since shortly after the discovery of X-rays [4, 5]. Initially, it was used for local palliation, but careful study by pioneers in the field including Rene Gilbert and Vera Peters demonstrated that more aggressive treatment with higher doses and larger fields resulted in the cure of many patients, especially those who presented with limited disease [6, 7]. At Stanford, Henry Kaplan, advantaged by access to the medical linear accelerator, refined the RT concepts and together with Saul Rosenberg advocated strongly for the curative potential of RT [8]. RT as a single modality remained the standard therapy for patients until effective chemotherapy was developed in the second half of the twentieth century. The success of chemotherapy along with the awareness of adverse late events linked to RT initially led to a decrease in its use, but the eventual realization that its judicious application in lower doses and to more tailored fields could enhance curability and allow a meaningful decrease in chemotherapy doses led to the development of combined-modality programs.

The RT of modern combined-modality therapy programs includes the use of very limited treatment volumes and the employment of advanced techniques that improve conformity and dose homogeneity. In contrast to RT fields of the past, which were based upon bony landmarks, these field reductions require detailed clinical information to delineate the target accurately. Both pre- and post-chemotherapy imaging are

essential to define the tumor volume and the integration of computed tomography (CT), and positron emission tomography (PET)/CT treatment planning further improves accurate RT volume design. A margin of safety to address subclinical disease and random and systematic positioning error is still necessary in treatment setup, but techniques to minimize inaccuracies in treatment planning and delivery continue to develop.

The current recommended RT volume is involved-site radiation therapy (ISRT), which uses pre- and post-chemotherapy CT imaging to tailor the radiation volumes to include only the initially involved lymph node sites and residual CT abnormalities. ISRT represents a significant reduction from the previous customary involved-field RT, which was based on bony landmarks visualized on 2D imaging. Involved-node radiation therapy (INRT) is an even more restricted form of ISRT and is recommended only when detailed pre-chemotherapy imaging in the treatment position is available [9]. The volumes for ISRT and INRT were designed to be smaller than the classic IFRT fields that encompassed the entire predefined anatomical regions. Recommendations for ISRT and INRT design have been established, and INRT has already been incorporated in combined-modality clinical trials in the European Organisation for the Research and Treatment of Cancer (EORTC) and the German Hodgkin Study Group (GHSG) [10]. Recommendations for ISRT design have recently been established by the International Lymphoma Radiation Oncology Group (ILROG), and ISRT has been incorporated into pediatric and adult guidelines and clinical trials in North America and Europe [2, 11, 12].

9.3 Indications for Radiation Therapy in HL

It is important to distinguish between classic HL and nodular lymphocyte-predominant HL (LPHL). The management of each entity is different. Most patients with stage I–II LPHL may be treated with radiation alone with curative intent, whereas combined-modality therapy is the standard approach for the majority of patients with classic HL.

9.3.1 Lymphocyte-Predominant HL

Over 75% of patients with LPHL present with stage IA or IIA disease. In this setting, the disease is commonly limited to one peripheral site (neck, axilla, or groin), and involvement of the mediastinum is extremely rare. The National Comprehensive Cancer Network (NCCN) guidelines [2], the German Hodgkin Lymphoma Study Group (GHSG), and the European Organisation for Research and Treatment of Cancer (EORTC) currently recommend limited radiation (IFRT or ISRT) as the treatment of choice for early-stage LPHL. Since the mediastinum is rarely involved, it does not need to be prophylactically treated, thus avoiding the site most responsible for radiation-related short- and long-term side effects. In a recent retrospective study of 131 patients with stage IA disease, 98% of patients obtained a complete response (CR), 98% after extended-field RT alone, 100% after involved-field RT alone, and 95% after combined-modality therapy [13]. With a median follow-up of 43 months, only 5% of patients relapsed and only three patients died. Toxicity of treatment was generally mild and was the greatest in association with combined-modality therapy. Two other studies from the Peter MacCallum in Australia and the Dana-Farber Cancer Institute in Boston supported the adequacy of limited-field RT for LPHL and suggested a reduced risk of second tumors compared to extended-field RT [14, 15].

Although there has not been a prospective study comparing extended-field RT, which was commonly used in the past, and IFRT/ISRT, retrospective data suggest that the more limited fields are adequate [15, 16]. The radiation dose recommended is 30–36 Gy, with the higher dose reserved for bulky sites.

9.3.2 Classic Hodgkin: Stage I–II

Over the last two decades, the treatment of stage I–II classic HL has changed markedly. Combined-modality therapy consisting of short-course chemotherapy, most often ABVD, followed by reduced-dose IFRT/ISRT carefully directed only to the involved lymph node(s) has replaced RT

alone as the treatment of choice. Combined modality is the standard treatment for favorable and unfavorable presentations of stage I–II disease in Europe, including the EORTC and GHSG. In the United States, chemotherapy followed by ISRT is the preferred treatment recommended by the NCCN guidelines [2]. Several randomized studies have demonstrated that excellent results in stage I–II HL may be obtained with combined-modality treatment that includes only IFRT and that more extensive fields of total or subtotal lymphoid irradiation (STLI and TLI) are not required [17].

The strategy to reduce the number of chemotherapy cycles and/or the radiation dose was tested by two large-scale randomized noninferiority studies conducted by the GHSG. In the HD10 study, 1370 patients with early *favorable* HL were randomly assigned in a 2 × 2 factorial design to receive either four or two cycles of ABVD followed by 30 or 20 Gy IFRT. The 8-year freedom from treatment failure (FFTF) and overall survival (OS) for all patients were 87% and 95%, respectively. Most importantly, there were no significant differences between patients receiving the minimal treatment of ABVD x two cycles followed by IFRT of only 20 Gy and patients receiving more chemotherapy and/or more RT [18]. Patients with unfavorable early-stage HL were randomized on the GHSG HD11 to receive either four cycles of ABVD or four cycles of baseline BEACOPP, followed by IFRT of either 30 or 20 Gy. Five-year FFTF and OS for all patients were 85% and 94.5%, respectively. There was no difference in FFTF when BEACOPP × 4 cycles was followed by either 30 or 20 Gy, and similar excellent results were obtained with ABVD × 4 cycles and IFRT of 30 Gy. Patients who received ABVD×4 cycles and only 20 Gy had a FFTF that was lower by 4.7%, but OS was similar in all treatment groups [19]. Finally, the EORTC H9U study investigated three different chemo regimens all followed by consolidative 30–40 Gy IFRT. The results showed that ABVD × 4 cycles and BEACOPP × 4 cycles were not inferior to ABVD × 6 cycles with 5-year EFS of 86%, 89%, and 90%, thus leading to the conclusion that ABVD × 4 cycles followed by IFRT yields high disease control in early unfavorable HL [20]. These large trials of the GHSG and the EORTC have established combined-modality therapy with reduced-field RT as the treatment of choice for patients with stage I–II disease.

Recently, trials utilizing results of interim PET scans that were performed after two or three cycles of ABVD to identify possible patients who may be treated with chemotherapy alone have been reported [21–23]. In the UK RAPID trial, researchers tested a chemotherapy-alone treatment program for patients with favorable stage I–II HL who had a negative PET, defined strictly as Deauville 1–2 only, after three cycles of ABVD. They found that ABVD × 3 cycles was inferior to combined-modality therapy in a per-protocol analysis in which randomized groups were analyzed as treated; progression-free survival was significantly better for patients who received consolidative RT (HR 2.36 in favor of IFRT, $p = 0.02$) [23]. Most recently, in data presented at the International Symposium on Hodgkin Lymphoma 2018 meeting (ISHL11) in Cologne, Germany, additional analysis of the UK RAPID study found that as maximum tumor diameter (MTD) increased, so did the risk of relapse, specifically in patients who did not receive RT. For patients with an MTD < 5 cm, 5-year event-free survival was 93.6% where as it was 79.3% in patients with an MTD ≥ 5 cm (HR 1.23 [95% CI: 1.01–1.48], $p = 0.04$) [24]. Similarly, a chemotherapy-alone approach has been proven inferior by the EORTC H10 trials for patients with favorable and unfavorable stage I–II HL. In the EORTC H10F and H10U trials, the ABVD-alone arms for patients who were PET-negative (Deauville <3) after ABVD × 2 cycles were terminated early due to an excess number of events when radiation therapy was not incorporated into the therapy even though RT omission was compensated for by an intensification in the number of cycles of ABVD [22]. In the final analysis of the favorable subset of H10, ABVD with INRT resulted in a 5-year PFS of 99.0%, while ABVD alone resulted in a 5-year PFS of only 87.1%. Similarly, in the unfavorable subset, noninferiority also could not be demonstrated with chemotherapy alone as the 5-year PFS was 92.1% in the combined-modality arm and 89.6% in the

chemotherapy-alone arm. Thus, H10 concluded that combined modality with ABVD and INRT remained the standard of care for patients with either favorable or unfavorable stage I–II HL [25].

Most recently, the GHSG presented the results of HD16 at the ISHL11 and the American Society of Hematology (ASH) 2018 meetings. Patients with early-stage favorable HL were randomized to either a standard arm of ABVD × 2 cycles followed by 20 Gy IFRT versus an experimental arm of no further therapy if they were PET-negative, defined as Deauville 1–2, at the end of two cycles of ABVD. The initial analysis, which included Deauville 1–3 patients, showed the omission of RT resulted in inferior outcomes for these favorable-risk patients with a 5-year estimated PFS of 93.4% in the combined-modality arm and 86.1% in the chemotherapy-alone arm. The difference of −7.3% [95% CI: −13.0%, −1.6%] could not exclude the prespecified non-inferiority margin of 3.01%, and thus, combined modality with ABVD × 2 cycles followed by 20 Gy of radiation remains the standard of care for patients with early-stage favorable HL [26].

Finally, the UK RATHL trial, though advertised as a trial for advanced-stage HL, actually was comprised of approximately 50% of patients with stage II disease [27]. This included patients with B symptoms, large mediastinal adenopathy, or >2 sites of disease. Patients with a negative interim PET (Deauville <4) were treated with ABVD or ABVD/AVD chemotherapy alone, without RT. The 3-year PFS was a respectable 90.0%, and the authors conclude that this is acceptable. However, patients on the H10U trial who were treated with just four cycles of ABVD followed by consolidative RT had a 3-year PFS of 95% (Table 9.1).

Thus, we have learned from GHSG HD8 that reducing the irradiated volume from the extended-field RT that was used in the era before adequate systemic therapy to involved-field RT does not result in inferior outcomes. We have also learned from GHSG HD10 and HD11 that combined modality with reduced dose and reduced-volume RT after systemic therapy results in excellent outcomes for patients with early-stage HL. Finally, we may conclude from the UK RAPID, EORTC H10, and GHSG HD11 trials that the omission of RT results in inferior outcomes and combined modality remains the standard of care. This conclusion has been further bolstered by a recent systematic review, in which combined-modality treatment was found to improve tumor control and overall survival in patients with early-stage

Table 9.1 Summary of trials for stage I–II Hodgkin lymphoma in the PET era (Courtesy of Dr. Richard Hoppe, Stanford University, United States of America)

Study	Definition of PET negative	Total chemo	PFS (%) (years)	PFS diff	OS	Notes
NCIC CTG HD.6 [28]	CT CR/cru	CR/cru ABVD × 4	95 (5)		94 (12)	Excludes B sx, bulk
		PR ABVD × 6 (5)	81.0 (5)			
RAPID [23] (per protocol)	*D* < 3	ABVD × 3	97.1 (3)	6.3	97.1 (3)	Excludes B sx, bulk
		ABVD × 3 + RT	90.8 (3)			
EORTC/GELA/FIL H10F [25]	*D* < 3	ABVD × 4	87.1 (5)	11.9	100 (5)	EORTC favorable
		ABVD × 3 + RT	99.0 (5)		99.6 (5)	
EORTC/GELA/FIL H10U [25]	*D* < 3	ABVD × 6	89.6 (5)	2.5	98.3 (5)	EORTC unfavorable
		ABVD × 4 + RT	92.1 (5)		96.7 (5)	
GHSG HD16 [26]	*D* < 3	ABVD × 2 + RT	93.4 (5)	7.3	98.1 (5)	GHSG favorable
		ABVD × 2	86.1 (5)		98.4 (5)	
Israeli [29]	*D* < 4	ABVD × 2–4 + RT	98.5 (5)	9.9		
		ABVD × 4–6	88.6 (5)			
CALGB/Alliance 50604 [30]	D < 4	ABVD × 4	92.0 (3)			Non-randomized
RATHL [27]	D < 4	A(B)VD × 6	90.0 (3)			B sx, bulk, > sites

Hodgkin lymphoma [31, 32]. We acknowledge there may be select early-stage HL patients for whom a chemotherapy-alone approach may be preferred. A commonly cited example is a young woman who would likely receive a large volume of radiation to breast tissue due to her anatomy or localization of disease in the mediastinum and axillae. It is our recommendation that these patients are discussed in a multidisciplinary conference prior to the start of treatment and that patients are made aware of all possible treatment options so that their preferences may be considered.

9.3.3 Stage III–IV HL

Although the role of consolidative RT after induction chemotherapy in stages III–IV remains controversial, RT is often added in patients who present with bulky disease or who do not have a clear complete remission after chemotherapy [33]. The results of prospective studies testing the concept have been conflicting. A meta-analysis of several randomized studies demonstrated that the addition of radiotherapy to chemotherapy reduces the rate of relapse but did not show survival benefit for combined modality compared to chemotherapy alone [34]. Unfortunately, nearly all studies that addressed the question of adding RT in stage III–IV disease were conducted in the pre-PET era. With interim PET imaging, it is possible that a more selective use of RT would prove its benefit.

For historical context, we will briefly discuss three main pre-PET era studies. The EORTC 20884 trial was a randomized study that evaluated the role of IFRT in patients with stage III–IV Hodgkin disease who obtained a CR after MOPP/ABV chemotherapy [35]. Patients received six or eight cycles of MOPP/ABV (number of cycles depended upon the response). Patients who did not achieve a CR (40%) based upon CT imaging only were not randomized but were all assigned to receive IFRT. Among the 333 randomized patients, the 5-year overall survival rates were 91% (no RT). Among the partial responders after six cycles of MOPP/ABV, the addition of IFRT yielded overall survival and event-free survival rates that were similar to those obtained among patients who achieved a CR to chemotherapy. This suggests a key role for consolidative RT in stages III–IV when patients fail to achieve a complete response to chemotherapy. Unfortunately, MOPP/ABV is toxic and has been abandoned for use in North America. A more modern randomized study evaluated the role of consolidation RT after CR to chemotherapy used ABVD × 6 cycles, which is the most common regimen currently used for advanced-stage HL. This trial was conducted at the Tata Medical Center in India. It included patients of all stages, but nearly half were stages III–IV. A subgroup analysis of these patients showed a statistically significant improvement of both 8-year event-free survival (EFS) and 8-year overall survival with added RT compared to ABVD alone (EFS 78 vs. 59%; $p < 0.03$ and OS 100 vs. 80%; $p < 0.006$) [36]. Finally, a secondary analysis of the UKLG LY09 study evaluated the effect of consolidation RT following different chemotherapy regimens in advanced-stage patients. Although more patients with bulky disease and partial response were in the RT group, PFS and overall survival were significantly better for 43% of the patients who received RT in this study. Subgroup and multivariate analysis confirmed this benefit from additional RT [37].

The first study to incorporate PET imaging in an attempt to define the more selective use of RT was the GHSG HD15 trial. In this trial, patients with advanced disease were treated with different schedules of BEACOPP chemotherapy. Following completion of chemotherapy, patients with residual disease greater than 2.5 cm underwent PET imaging. If the PET scan was negative, patients received no further therapy. If the PET scan was positive, the patients received 30 Gy of consolidative RT. Although the group with a positive PET scan had a worse PFS than the PET-negative group (86.2% vs. 92.6%), the results in the PET-positive group were actually quite good for this subset of poor-prognosis patients, supporting the use of RT for patients in PR by PET following completion of chemotherapy [38]. Another recent trial evaluated the role of RT

among stage IIB–IVB patients who had interim and end-of-treatment PET-negative disease [39]. The GITIL/FIL HD 0607 trial randomized patients who had nodal disease >5 cm to receive no further treatment or consolidative RT to the initially bulky sites following ABVD × 6 cycles. With a median follow-up of 3.6 years, there was no significant difference in PFS (93% vs. 97% at 3 years, $p < 0.3$) or OS (99% vs. 100%, $p < 0.08$). The RT question was not addressed for patients who failed to achieve a complete metabolic response following the completion of chemotherapy. Finally, the US Intergroup trial S0816 treated patients with chemotherapy alone, including chemotherapy escalation for patients who had an interim-positive PET [40]. Among patients who had an end-of-treatment positive PET, the 2-year PFS was only 30.6%. Although no RT was utilized for these patients, an analysis was completed assuming patients who met the GHSG HD15 criteria were irradiated [41]. Assuming a modest 50% local control for RT, this would have boosted the likely PFS from 30.6% to 42.8%. Assuming a more likely 80% local control for RT, this would have boosted the 2-year PFS to 50.2%.

In summary, the data from the EORTC 20884 and GITIL/FIL HD 0607 suggest a limited role for RT among patients who achieve a complete response to chemotherapy. In contrast, the EORTC 20884, GHSG HD15, and special analysis of the US Intergroup S0816 trial all suggest that patients who fail to achieve a CR to chemotherapy are very likely to be benefited by the incorporation of RT. Some patients may benefit simply from consolidative RT at the conclusion of chemotherapy, while others may benefit from its inclusion in an overall salvage treatment program.

9.3.4 RT in Salvage Programs for Refractory and Relapsed HL

High-dose therapy supported by autologous stem cell transplantation (ASCT) has become a standard salvage treatment for patients with HL who relapse or remain refractory to primary therapy. Many of these patients have not received prior RT or have relapsed at sites outside the original radiation field. These patients could benefit from integrating RT into the salvage regimen.

Poen and colleagues from Stanford analyzed the efficacy and toxicity of adding cytoreductive or consolidative RT to 24 of 100 patients receiving high-dose therapy [42]. When involved sites were irradiated in conjunction with transplantation, no in-field failures occurred. While only a trend in favor of IFRT could be shown for the entire group of transplanted patients, analysis restricted to patients who had no prior RT or those with relapse stages I–III demonstrated significant improvement in freedom from relapse. Fatal toxicity in this series was not influenced significantly by IFRT. Similar improvements in outcomes by the addition of RT have been demonstrated in multiple other series including studies from the University of Rochester [43] and the University of Torino [44]. At MSKCC, a program that integrated RT into the high-dose regimen for salvage therapy was developed and included accelerated hyperfractionated irradiation (twice daily fractions of 1.8 Gy each) to start after the completion of reinduction chemotherapy and stem cell collection and prior to the high-dose chemotherapy and stem cell transplantation [45–47]. Patients who had not been previously irradiated received involved-field RT (18 Gy in 5 days) to sites of initially bulky (>5 cm) disease and/or residual clinical abnormalities, followed by total lymphoid irradiation (TLI) of 18 Gy (1.8 Gy per fraction, bid.) during an additional 5 days. Patients who had prior RT received only involved-field RT (when feasible) to a maximal dose of 36 Gy. A recent report detailed the outcomes of 186 patients treated from 1985 to 2008. The 10-year OS and EFS were 56% [48]. The authors concluded that this was a safe and effective salvage strategy. A report on the quality of life and treatment-related complications of this program disclosed only a small number of late complications [49].

ILROG has published consensus guidelines regarding best practice for inclusion of RT in salvage treatment programs for Hodgkin lymphoma [50]. This report details the patient variables that

affect selection of salvage treatment, including intensity of prior therapy, extent of relapse, whether disease is chemorefractory, and how radiation can best be incorporated into effective salvage therapy.

9.4 Radiation Fields and Volumes: Principles and Design

In the past, radiation-field design attempted to include multiple involved and uninvolved lymph node sites. The large fields known as *mantle*, *inverted Y*, and *TLI* were synonymous with the radiation treatment of HL. These fields are no longer in use.

IFRT encompasses a significantly smaller volume and was incorporated into many clinical trials of the past two decades. Extending this concept further, even more limited radiation volumes termed involved-node radiation therapy (INRT) and involved-site radiation therapy (ISRT) have been introduced into combined-modality programs and endorsed by guideline groups as the new standard RT volumes for HL [9, 10]. Even when radiation is used as primary management for LPHL, the treatment volumes should be limited to the involved site or to the involved sites and immediately adjacent the lymph nodes.

The terminologies that define radiation volumes may be confusing and create difficulties in comparing treatment programs. However, general definitions and guidelines are now available and should be followed [9]. The following are definitions of types of radiation fields and volumes that have been used in HL.

9.4.1 Extended-Field Radiation Therapy

This field includes the involved lymph node group *plus* the adjacent clinically uninvolved region(s). For extranodal disease, it includes the involved organ plus the clinically uninvolved lymph node region. It was common during the era of treatment with RT alone to treat large fields encompassing multiple lymph node regions, both involved and uninvolved. The field design that includes all of the supradiaphragmatic lymph node regions was referred to as the *mantle* field. The field that includes all lymph node sites below the diaphragm (with or without the spleen and called after its shape) is the *inverted Y*. When all the major lymph node regions above and below the diaphragm were irradiated, this was referred to as *total lymphoid irradiation* (Fig. 9.1). If the pelvic nodes were not included, this was referred to as *subtotal nodal irradiation*. Extended fields are rarely used in modern treatment of HL.

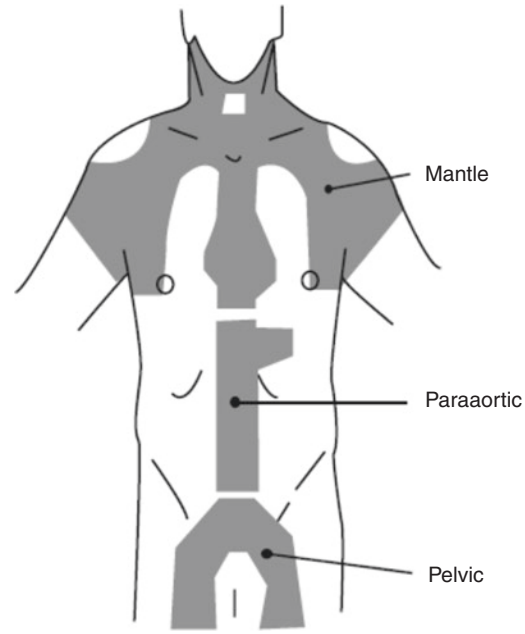


Fig. 9.1 Illustration of extended RT fields used in the past

9.4.2 Involved-Field Radiation Therapy

These fields are limited to the clinically involved lymph node *regions* [51]. It was influenced by lymphoid regions that were defined in the Ann Arbor staging system for Hodgkin's disease [52]. For extranodal sites, the field includes the organ alone (if no evidence for lymph node

involvement). IFRT was commonly employed in clinical trials during the past two decades, but fields have now become even smaller as 3D cross-sectional imaging has become widely available. The new volumes based on CT-based simulation are *involved-node radiation therapy (INRT)* and *involved-site radiation therapy (ISRT).*

9.4.3 Involved-Site Radiation Therapy (ISRT): The New Standard Volume for HL

The International Lymphoma Radiation Oncology Group (ILROG) now recommends the use of ISRT to treat HL [9]. ISRT has already been adopted as the standard volume by several organizations including the NCCN [2]. In the majority of cases, assuming the same clinical presentation and response, ISRT is smaller than IFRT and more precise as treatment volumes are determined by modern cross-sectional imaging such as CT and PET-CT rather than by standard bony landmarks of the involved location as seen on 2D imaging. The concept of ISRT was developed as an extension of the INRT concept that was conceived earlier [10]. In comparison to INRT, ISRT allows for more flexibility and use of clinical judgment when the strict criteria for INRT pre-chemotherapy imaging cannot be met. Indeed, in the majority of practices, pre-resection or pre-chemotherapy precise imaging is not available in the radiation treatment position. ISRT accounts for this deficiency. INRT is fundamentally a more optimal case of ISRT when accurate pre-chemotherapy imaging allows for tighter margins around the original volumes. Finally, unlike IFRT, which uses predetermined anatomical regional "borders" determined by bony landmarks that are easy to visualize during conventional 2D simulation, which has now been replaced by CT or PET/CT simulation, ISRT and INRT incorporate the current concepts of volume determination as outlined in the ICRU Report 83 [53]. The modern RT treatment volumes are based on defining a gross tumor volume (GTV), a clinical target volume (CTV), and a planning target volume (PTV). The PTV is then used to define beam coverage.

9.4.3.1 ISRT When RT Is the Primary Treatment

RT as single modality in HL is relevant for stage I–II lymphocyte-predominant Hodgkin lymphoma (LPHL). It may also be relevant in selected cases of early-stage classic HL in patients who are not candidates for primary chemotherapy due to serious comorbidities. In most clinical situations that require RT as the primary modality, the GTV should be readily visualized during simulation. In this situation, the clinical target volume (CTV) should be more generous since microscopic or subclinical disease is more likely to be present without chemotherapy.

9.4.3.2 ISRT When RT Is Part of Combined-Modality Treatment

RT is often part of the treatment program for early-stage classic HL following adequate systemic chemotherapy. RT improves freedom from treatment failure and progression-free survival even in patients with a negative interim PET [22, 23, 26,] and allows for a reduced number of chemotherapy cycles [18]. In a recent systematic review, combined-modality treatment was found to improve tumor control and overall survival in patients with early-stage Hodgkin lymphoma [29]. In select patients with advanced-stage disease, localized RT may be used for residual sites of lymphoma after full course of chemotherapy [39]. The GTV may be markedly affected by prior systemic chemotherapy, and it is therefore particularly important to review the pre-chemotherapy imaging and to define the pre-chemotherapy volume on the

simulation CT study as "pre-chemotherapy GTV" as well as the post-chemotherapy remaining CT and/or PET abnormality as "post-chemotherapy" GTV.

9.4.4 Involved-Node Radiation Therapy (INRT): A Special Case of ISRT

INRT was originally developed and implemented by the EORTC to replace IFRT in prospective randomized studies (EORTC/GELA/IIL H10). It mandated accurate PET/CT information prior to chemotherapy and in a position similar the subsequent post-chemotherapy radiation therapy treatment position. The INRT technique reduces the treated volume to a minimum, but in order to be safe, optimal imaging both before and after chemotherapy is needed [9, 38]. INRT represents a special case of ISRT, where pre-chemotherapy imaging is ideal for post-chemotherapy treatment planning (Fig. 9.2). PET/CT up front for staging purposes is mandatory as it has been demonstrated that PET/CT is the most accurate imaging method for determining disease extent in HL [39]. In order to enable image fusion of the pre-chemotherapy and the post-chemotherapy planning images, the pre-chemotherapy PET/CT scan should be acquired with the patient in the treatment position and using the same breathing instructions that will be used later for RT. Ideally, the patient should be scanned on a flat couch top, with the use of appropriate immobilization devices and using markers at skin positions which are visible in the imaging. During or following the completion of chemotherapy, a response assessment using PET/CT or contrast-enhanced CT should be performed. A planning CT scan is acquired with the patient in the same position as in the pre-chemotherapy CT scan. This highly conformal treatment technique has been shown to be safe, provided strict adherence to the principles above is maintained [54–56].

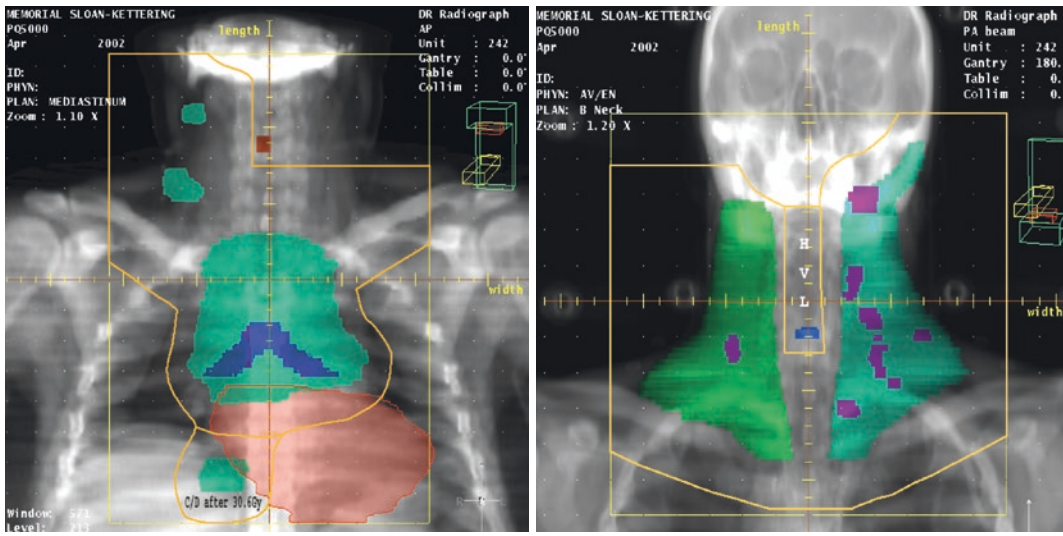


Fig. 9.2 Involved-node radiation therapy. Single lymph node in the left lower neck prior to chemotherapy (left) and following chemotherapy (right). The border of the field encompasses the original volume of the node and not of the whole unilateral neck (as in IFRT approach) (Courtesy of Dr. Theodore Girinsky, Institute Goustave-Roussy, France)

9.4.5 Volume Definitions for Planning ISRT and INRT

These principles apply regardless if RT is used as primary treatment or as part of combined modality and are relevant to both involved-site radiation therapy (ISRT) and involved-node radiation therapy (INRT). The only difference between ISRT and INRT is the quality and accuracy of the pre-chemotherapy imaging, which determines the margins needed to allow for uncertainties in the contouring of the clinical target volume (CTV).

9.4.5.1 Volume of Interest Acquisition

Planning RT for lymphoma is based on obtaining a three-dimensional (3D) simulation study using either a CT simulator, a PET/CT simulator, or an MRI simulator. If PET and/or CT information has been obtained separately or prior to simulation, it is possible to transfer the data either manually or electronically into the simulation CT data. Ideally, any imaging studies that provide planning information should be obtained in the treatment position and using the planned immobilization devices.

9.4.5.2 Determination of Gross Tumor Volume (GTV)

Pre-chemotherapy (or Presurgery) GTV

Any abnormalities on imaging studies obtained prior to any intervention that might have affected lymphoma volume should be outlined on the simulation study, as these volumes should (in most situations) be included in the CTV.

No Chemotherapy or Post-chemotherapy GTV

The primary imaging of untreated lesions or post-chemotherapy residual GTV should be outlined on the simulation study and is always part of the CTV.

9.4.5.3 Determination of Clinical Target Volume (CTV)

CTV encompasses in principle the original (prior to any intervention) GTV. Yet, normal structures such as the large vessels, lungs, kidneys, and muscles that were clearly uninvolved should be excluded from the CTV based on clinical judgment. In outlining the CTV, the following points should be considered:

(a) Quality and accuracy of imaging and transfer of volumes to simulation images.
(b) Concerns of changes in volume since imaging.
(c) Patterns of spread.
(d) Potential subclinical involvement.
(e) Adjacent organs constraints.

If separate nodal volumes are involved, they can potentially be encompassed in the same CTV. However, if the involved nodes are >5 cm apart, they can be treated with separate volumes using the CTV-to-PTV expansion guidelines as outlined further.

9.4.5.4 Determination of Internal Target Volume (ITV)

ITV is defined in the ICRU Report 62 [54] as the CTV plus a margin that accounts for uncertainties in size, shape, and position of the CTV within the patient. The ITV is mostly relevant when the target is moving with respiration, most commonly in the chest and upper abdomen. The optimal way to manage respiratory motion is to use 4D-CT simulation to understand target movement and to generate accurate ITV margins or to use breath-hold techniques. Alternatively, the ITV may be determined by fluoroscopy or estimated by an experienced clinician. In the chest or upper abdomen, margins of 1.5–2 cm in the superior-inferior direction may be necessary. In sites such as the neck, which are well immobilized and unlikely to change shape or position during or in between treatments, outlining the ITV is not required.

9.4.5.5 Determination of Planning Target Volume (PTV)

PTV is the volume that considers the CTV (or ITV, when relevant) and also accounts for setup uncertainties in patient positioning and alignment of the beams during treatment planning and through all treatment sessions. The practice of determining the PTV varies across institutions.

The clinician and/or treatment planner adds the PTV and applies standard margins that depend on estimated setup variations that are a function of immobilization device, body site, and patient cooperation. While standard patient setup has historically been done based on skin marks and weekly portal films, daily image-guided RT (IGRT) has allowed for reduction in PTV margins. The smaller margins are a function of more certainty with setup, which can ultimately help reduce the radiation dose to the normal structures. IGRT can include daily orthogonal KV images or cone beam CT scan (KV or MV). In general, PTV expansions can range from 0.3 to 1.0 cm depending on the location and use of IGRT.

9.4.6 Determination of Organs at Risk (OAR)

The OARs are normal structures that, if irradiated, could result in significant morbidity including acute toxicity, such as pneumonitis and esophagitis, and late toxicity, such as hypothyroidism, cardiac toxicity, and second cancers. OARs may influence treatment planning or the prescribed dose. They should be outlined on the simulation study. Dose-volume histograms (DVH) and normal tissue complication probability (NTCP) should be calculated by the planner and the plan vetted by the clinician in consideration of this information. Of note, the general principle with regard to OARs in HL should always be ALARA—as low as reasonably achievable—and should depend on the disease distribution, planned treatment volume, and total dose.

9.4.6.1 Lung

A major concern for patients with HL and mediastinal disease who receive RT is pneumonitis with grade 3 pneumonitis rates as high as 7% reported by the MD Anderson Cancer Center (MDACC) following IMRT. This is especially true if given as part of second-line therapy and transplant. The MDACC group evaluated factors predictive of grade 1–3 pneumonitis (14% overall) and found the risk of radiation pneumonitis increases with mean lung dose >13.5 Gy, $V_{20} > 30\%$, $V_{15} > 35\%$, $V_{10} > 40\%$, and $V_5 > 55\%$. Of note, the strongest predictor was V_5 with $V_5 > 55\%$ associated with a risk of pneumonitis of almost 35% [57].

9.4.6.2 Heart

Multiple studies have explored the relationship of heart dose and cardiac toxicity and death among HL survivors. Cardiac toxicity may be due to pericarditis, arrhythmia, coronary artery disease, valvular disease, and cardiomyopathy/congestive heart failure. Dosimetric factors have been identified that have been associated with increased risk of cardiac toxicity. Van Nimwegen et al. reported on a cohort of HL survivors from the Netherlands and found a mean heart dose correlated well with coronary heart disease, demonstrating an excess relative risk of 7.4% per Gy mean heart dose [58]. A statistically significant increased risk of coronary heart disease was demonstrated among patients getting a mean heart dose as low as 5–14 Gy (RR 2.31) compared with a mean heart dose of 0 Gy. This risk was even higher for mean heart dose of 15 Gy or higher (RR 2.83 for 15–19 Gy, 2.9 for 20–24 Gy, and 3.35 for 25–34 Gy).

A recent analysis of 24,214 5-year survivors of childhood cancer in the Childhood Cancer Survivor Study provided substantial insights into the relationships between radiation and risk of long-term cardiac disease. Mean heart doses >10 Gy were associated with increasing cardiac disease risk in a dose-response manner. Volumes of the heart receiving radiation also were correlated with cardiac risk; children receiving a V_5 of >50% had a 1.6-fold increased risk of late cardiac disease. Those receiving at least 20 Gy to any part of the heart also were at increased risk. Current recommendations are to keep the mean heart dose as low as possible with stricter goals to try and keep the mean heart dose <15 Gy in adults and <10 Gy in pediatrics whenever possible. Rarely, should mean heart doses greater than 20 Gy be used, unless patients are being treated definitively in the salvage setting [59].

While mean heart dose may be appropriate for radiation evaluation for IFRT, it is unclear whether it is as important when more conformal techniques

are being used, which can redistribute the dose [60]. Recent studies have demonstrated radiation dose relationships with specific cardiac substructures. For example, Van Niwmegen demonstrated a relationship between heart failure and mean dose to the left ventricle [56]. Among patients treated with anthracyclines, the 25-year cumulative risk of heart failure was 11.2% for mean LV dose <15 Gy, 15.9% for 16–20 Gy, and 32.9% for greater than or equal to 21 Gy. Another study by Cutter et al. demonstrated 30-year cumulative risks of valvular heart disease of 3%, 6.4%, 9.3%, and 12.4% for mean valvular dose of <30, 31–35, 36–40, and >40 Gy [61]. Based on this data, we would recommend keeping the mean valve dose <30 Gy, mean left ventricle dose <15 Gy, and ideally <5 Gy.

9.4.6.3 Thyroid

While hypothyroidism is a common late toxicity, it can be easily managed with thyroid supplementation medication. Cella et al. demonstrated a dose volume effect with 11.5% of patients with hypothyroidism with a $V_{30} < 63\%$ vs. 71% for patients with V_{30} greater than or equal to 63% [62].

9.4.6.4 Second Cancers

The primary cause of death among long-term survivors of HL is second cancers. The most common among survivors are breast cancer, thyroid cancer, sarcomas (bone and soft tissue), and lung cancer. Risk modeling has identified linear dose risks for all these cancers, except for thyroid cancer.

Breast cancer is the most concerning second cancer among female survivors receiving radiation. While smaller treatment fields have greatly reduced the risk of second breast cancers, consideration of breast dose is important in minimizing the risk for all patients. Travis et al. demonstrated that radiation doses >4 Gy were associated with increased risk of secondary breast cancer with increasing dose further increasing the risk. In fact, the relative risk was 1.8 and 4.1 for breast dose of 4–6.9 and 7–23.1 Gy, respectively [63]. Therefore, it is important to keep the mean breast dose as low as possible and try to minimize the breast V_4 to as low as possible.

Lung cancer is an aggressive second cancer that will often result in death for a HL survivor. Fortunately, the risk can greatly be mitigated for nonsmokers. However, among smokers, this risk is increased significantly with the addition of lung irradiation. Travis et al. demonstrated among HL survivors that lung dose of >5 Gy had a relative risk of 5.9 compared with lung dose <5 Gy for developing a second lung cancer [64]. Similar to concerns of pneumonitis, lung V_5 should be evaluated with attempts to keep as low as possible.

Secondary sarcomas have also been found to increase with higher radiation doses to the body. Tukenova et al. demonstrated increased risk (12.5) for dying from a secondary sarcoma when the calculated integral dose was >150 J [65].

Thyroid cancers do not have a linear dose-risk relationship with radiation. Bhatti et al. demonstrated a relative risk increase in secondary thyroid cancers of 8.5 with doses of 5–10 Gy, 10.6 for 10–15 Gy, 13.8 with 15–20 Gy, and 14.6 for 20–25 Gy, with relative risks then declining with doses >25 Gy [66].

9.4.7 Consolidation Volume Radiation Therapy (CVRT)

As systemic therapies continue to improve, further reductions in RT volumes may be possible. Currently, there are ongoing studies looking at modifications in systemic therapy to include brentuximab vedotin (BV) and/or checkpoint inhibitors, such as pembrolizumab and nivolumab [67, 68]. One recent reported study from Memorial Sloan Kettering Cancer Center (MSKCC) demonstrated a favorable response to BV-AVD × 4 cycles followed by ISRT [69]. Consolidation volume radiation therapy (CVRT), which treats only residual CT abnormalities in patients who achieve a CR by PET, is currently being tested after BV-AVD × 4 cycles [70].

9.5 Dose Considerations and Recommendations

Although doses in the range of 40–44 Gy were at one time recommended for the definitive treatment of HL, these recommendations have been modified over time, both in the context of

combined-modality therapy for cHL and the treatment of patients with LPHL. The radiation dose is typically delivered in 1.8–2.0 Gy fractions. If significant portions of lung or heart are included, the dose per fraction can be reduced to 1.5 Gy. The available data indicate that the choice of fractionation is not critical for tumor control and that a schedule with minimal risk of damage to normal structures should be selected.

The GHSG evaluated dose in patients with stage IA–IIB disease without risk factors in a randomized trial of 40 Gy extended-field radiation alone vs. 30 Gy extended-field radiation with a boost of 10 Gy to the involved site of disease [71, 72]. There was no significant difference in outcome between the two arms of the study indicating that 30 Gy is sufficient for clinically uninvolved areas when RT is used alone. The optimum dose for clinically involved sites of disease with RT alone has not been tested in a randomized trial.

More relevant to current practice is the determination of the adequate radiation dose after treatment with chemotherapy. In many early studies, radiation doses were kept at approximately 40 Gy even after achieving a CR to chemotherapy; others reduced the dose in advanced disease when combined with five cycles of chemotherapy to 20–24 Gy with excellent overall results [73]. Studies of combined modality in advanced stage also used reduced doses of RT for patients who achieved a CR to chemotherapy and higher doses (approximately 30 Gy) for patients in PR. The pediatric groups addressing the concern of radiation effects on skeletal and muscular development also effectively reduced the dose of RT after combination chemotherapy to 21–24 Gy [74]. However, recent reports have demonstrated that >90% of all relapses occur in field, suggesting higher doses may be appropriate for pediatrics in certain cases [75].

Several recent studies addressed the adequacy of low-dose IFRT following chemotherapy. A study conducted by the EORTC/GELA [76] randomized patients with favorable early-stage HL to 36, 20, or no IFRT after achieving a CR to six cycles of EBVP. Because an excessive number of relapses occurred in the no-RT arm, this arm was closed early. There was no difference in EFS at 4 years between patients receiving IFRT 36 Gy (87%) vs. 20 Gy (84%). A GHSG randomized study (HD 10) addressed the radiation dose question after short-course chemotherapy [18]. Patients with favorable stages I–II were randomized to receive either four or only two cycles of ABVD followed by IFRT of 30 or 20 Gy. At a median follow-up of 7 years, there was no difference in FFTF among the four arms. FFTF at 5 years was 93.4% in patients treated with 30 Gy (91.0–95.2%) and 92.9% in those receiving 20 Gy (90.4–94.8%). These results, taken together with the better tolerability and the lack of inferiority in secondary efficacy endpoints, led to the conclusion that 20 Gy IFRT, when combined with even only two cycles of ABVD, is equally effective to 30 Gy IFRT in this very favorable group of patients [15]. The GHSG HD11 study targeted patients with unfavorable early stage and randomized them to either ABVD × 4 cycles or BEACOPP × 4 cycles; either program was followed by either 20 or 30 Gy to the involved field. Five-year FFTF and OS for all patients were 85% and 94.5%, respectively. There was no difference in FFTF when BEACOP × 4 cycles was followed by either 30 or 20 Gy, and similar excellent results were obtained with ABVD × 4 cycles and IFRT of 30 Gy. Patients who received ABVD × 4 cycles and only 20 Gy had FFTF that was lower by 4%. OS was similar in all treatment groups [19]. These results suggest that 30 Gy should remain the standard IFRT dose following ABVD in unfavorable early-stage HL [77].

For patients with early-stage LPHL, no advantage has been shown for doses over 30–35 Gy [15].

For patients with residual lymphoma after chemotherapy, the residual mass may represent a more refractory disease, and increasing the dose to the CTV to 36–40 Gy should be considered.

9.5.1 The Significance of Reducing the Radiation Dose

Recent studies clearly indicate that the risk of secondary solid tumor induction is radiation dose related. This was carefully analyzed for secondary breast and lung cancers as well as for other tumors [63, 64, 78, 79]. While it will take more years of careful follow-up of patients in randomized studies to display the full magnitude of risk tapering by current reduction of radiation volume and dose,

recent data suggest that this likely to be the case. In a Duke University study, two groups of patients with early-stage HL were treated with different radiation approaches over the same period. One group received RT alone, given to extended fields with a median dose of 38 Gy; the second group received chemotherapy followed by involved-field low-dose (median of 25 Gy) RT. While 12 patients developed second tumors in the first group and 8 of them died, no second tumors were detected in the second group. The median follow-up was 11.7 and 8.1 years, respectively [80]. Similar observations with an even longer follow-up were made by the Yale group [81]. In a study that used data-based radiobiological modeling to predict the radiation-induced second cancer risk, lowering the dose from 35 to 20 Gy and reducing the extended field to IFRT reduced lung cancer risk and breast cancer risk by 57% and 77%, respectively [82].

Finally, a study by a French Collaborative Lymphoma group (GOELAM) randomized patients with favorable stage I–II HL to receive a conservative RT dose of 40 Gy to involved sites and 30 Gy to adjacent site control arm or in the "experimental arm" to receive only 36 Gy and 24 Gy to the adjacent sites after ABVD × 3 cycles [83]. Surprisingly, the 10-year incidence of severe or fatal complications was nil in the experimental arm but reached 15.5% in the control arm ($p < 0.003$) and 11.1% in the historical controls that received the higher dose. The 10-year FFTF and overall survival rates were similar for the 89 patients in the experimental arm (88.6% and 97.8%, respectively), for the 99 patients in the conservative arm (92.6% and 95%, respectively), and for the 202 patients in the historical control group (91.9% and 92.9%, respectively).

9.5.2 Dose Recommendations

Radiation alone (as primary treatment for LPHL) using ISRT

- Clinically involved and adjacent uninvolved nodes: 30–36 Gy.

Radiation alone (as primary treatment for cHL [uncommon])

- Clinically involved sites: 36 Gy at a minimum.
- Clinically uninvolved sites: 30 Gy.

Radiation following chemotherapy in a combined-modality program

- Patients in CR after chemotherapy: 20–30 Gy.
  - For pediatric or adolescent patients: 15–24 Gy.
  - In some programs of short chemotherapy for bulky or advanced-stage disease (e.g., Stanford V), the recommended RT dose is 30–36 Gy.
- Patients in PR after chemotherapy: 30–40 Gy.

9.6 New Aspects of Radiation Volume Definition and Treatment Delivery

The abandonment of large-field irradiation for most patients with HL permits the use of more conformal RT volumes and introduction of other innovative RT techniques. The change in the lymphoma RT paradigm coincided with substantial improvement in imaging and treatment planning technology that has revolutionized the field of RT. The integration of fast high-resolution computerized tomography into the simulation and planning systems of radiation oncology has changed how treatment volumes and relationship to normal critical structures are determined and planned. In the recent past, tumor volume determinations were made with fluoroscopy-based simulators that produced often poor-quality imaging requiring wide "safety margins" that detracted from accuracy and sparing of critical organs. Most modern simulators are in fact high-resolution CT scanners with software programs that allow accurate conformal treatment planning and provide detailed information on the dose volume delivered to normal structures within the treatment field and the homogeneity of dose delivered to the target. More recently, these simulators have been integrated with a PET scanner that provides additional tumor volume information for consideration during radiation planning.

9.6.1 New Technologies

Intensity-modulated RT (IMRT), tomotherapy, and volumetric modulated arc therapy (VMAT) are advanced systems for photon delivery. These modalities redistribute the radiation to provide high-dose conformality of the target area, but with less conformality in the low-dose region. They also allow for accurately enveloping the tumor with either a homogenous radiation dose ("sculpting") or delivering higher doses to predetermined areas in the tumor volume ("painting"). In the treatment of lymphoma, there are several clinical situations where highly conformal photon techniques provide a benefit. In the mediastinum, a review article of comparison studies showed that IMRT compared with conventional 3D-conformal radiation techniques reduced the mean heart dose on average by 1.44 Gy, mean esophagus dose by 1.4 Gy, and lung V_{20} by 11% [84]. Highly conformal photon techniques can also be useful in the treatment of very large or complicated tumor volumes in the abdomen and head and neck lymphomas. IMRT also allows re-irradiation of sites prior to high-dose salvage programs that otherwise will be prohibited by normal tissue tolerance, particularly of the spinal cord (Figs. 9.3a–d and 9.4a–c).

In general, when using highly conformal photon techniques for mediastinal disease, treatment planning generally tries to avoid equally spaced beams or continuous arcs around the patient in an effort to avoid some of the low-dose bath, especially to the lungs and breasts. MD Anderson Cancer Center has described both the butterfly IMRT technique and the rainbow IMRT technique as ways to optimize the IMRT beam arrangement in mediastinal lymphoma. In the butterfly technique, three anterior and two posterior beams are used to reduce excess exposure to heart, lungs, and spinal cord. In the rainbow technique, one anterior-posterior (AP) beam and four anterior obliques at 0°, 20–30°, 40–60°, 300–320°, and 335–345° are used for patients with only anterior mediastinal disease [85, 86]. Similarly, the University of Torino evaluated optimized VMAT plans that include non-coplanar partial arcs [87, 88]. Early clinical data has begun to emerge from the use of IMRT for mediastinal lymphoma demonstrating similar disease control to 3DCRT treatment [78, 89]. While most have shown little to no pneumonitis with these techniques, MDACC did report a 15% grade 1–3 pneumonitis risk including 6.9% grade 3 rate [58].

9.6.2 Deep Inspiration Breath Hold

An additional technique that can be used to try and further minimize heart and lung dose for mediastinal lymphoma patients and can be used with 3DCRT, IMRT, or proton therapy is deep inspiration breath hold (DIBH). DIBH is a simple technique which the patient inhales deeply and holds this breath during treatment. DIBH can optimize the internal anatomy by pulling the heart caudally while allowing the disease to be irradiated to remain more superiorly by the great vessels for patients with superior mediastinal disease. This allows for more cardiac sparing for these patients. DIBH also immobilizes the disease in the mediastinum, which controls respiratory motion and eliminates the need for an ITV. Finally, it expands the total lung volume, which results in an overall decreased dose to the lungs [90].

Petersen et al. conducted a prospective phase II study of DIBH among patients with mediastinal lymphoma among 19 patients. In the study, the mean lung dose was reduced on average by 2 Gy with DIBH and mean heart dose by 1.4 Gy. Another study by Charpentier et al. reported on 47 patients undergoing DIBH, where the mean lung dose was reduced by approximately 1.5 Gy and mean heart dose reduced by 2.5 Gy [91]. While DIBH appears beneficial for disease located in the superior mediastinum, the benefit is not as obvious for patients with lower mediastinal disease that extends to the level of the heart [92]. This was seen in a study by Paumier et al. who demonstrated a mean heart dose reduction of 50% for patients with upper mediastinal disease, while it was only 8–9% and not significant for lower mediastinum. Similarly, the mean lung dose was reduced by 26% for upper mediastinal disease, but only 18% reduction for lower mediastinal disease [93] (Fig. 9.5).

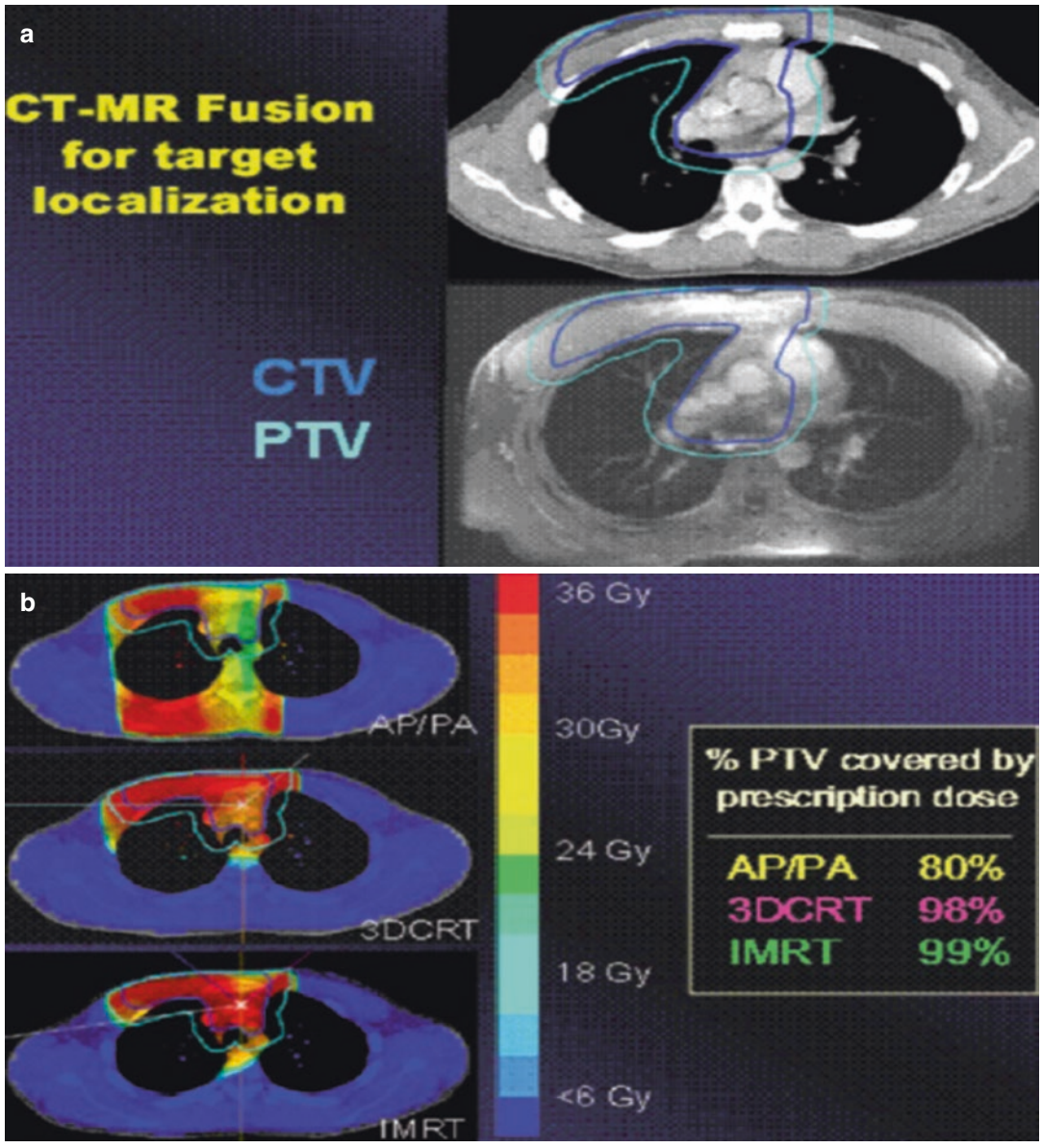
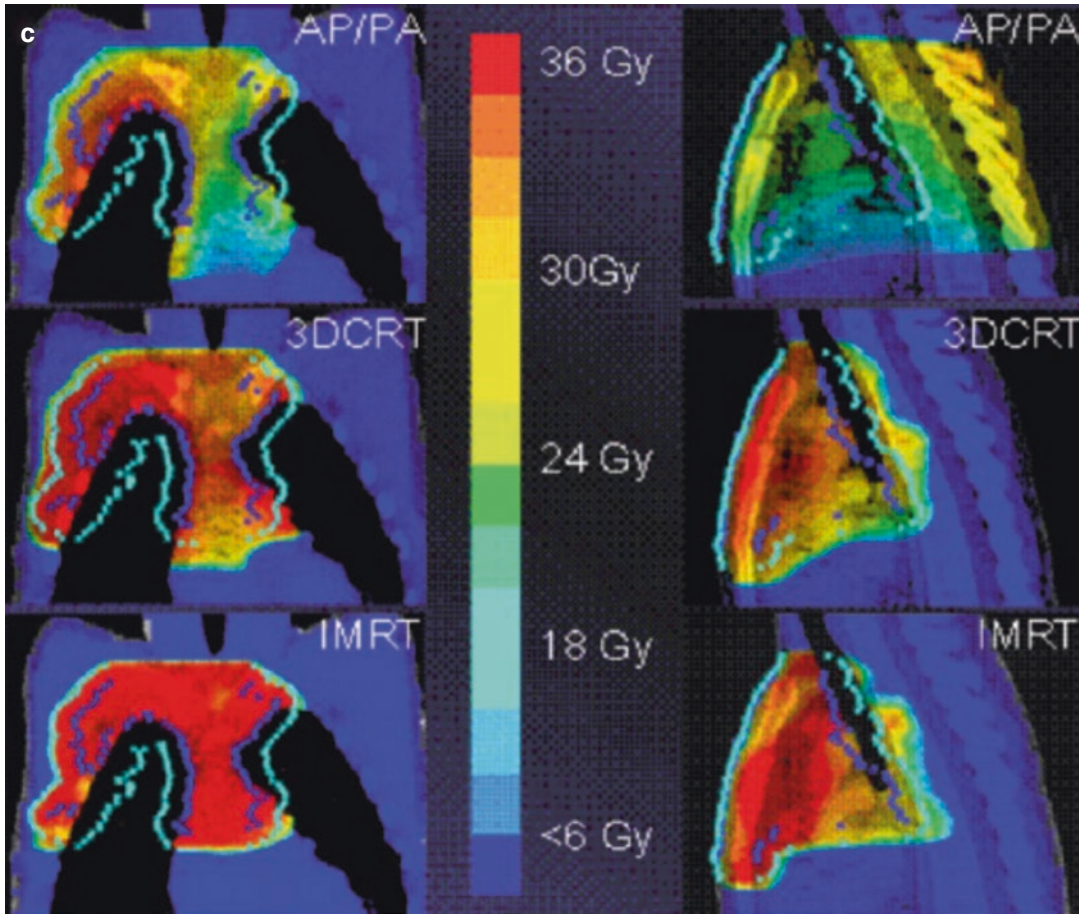


Fig. 9.3 (**a**) CT-MR fusion for target localization of HL involving the mediastinum and right chest wall. *CTV* clinical treatment volume, *PTV* planning treatment volume. (**b**, **c**) Treatment plans comparing AP/PA, 3DCRT, and IMRT. *PTV* planning treatment volume, *AP/PA* opposed anterior and posterior fields, *3DCRT* three-dimensional conformal radiation therapy, *IMRT* intensity-modulated radiation therapy. (**d**) Comparison of lung complication probability of different plans



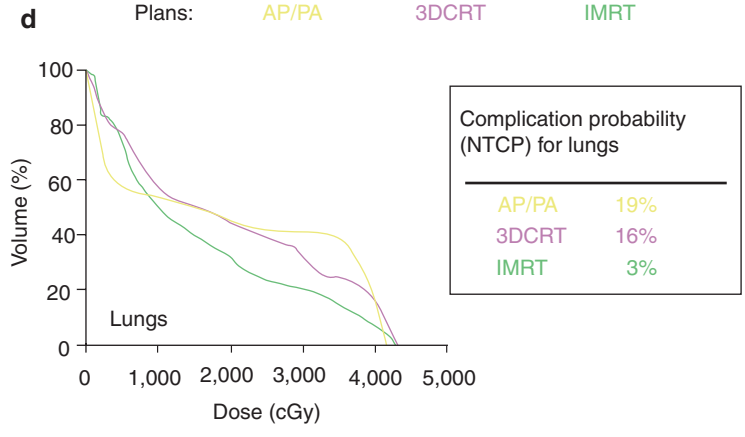


Fig. 9.3 (continued)

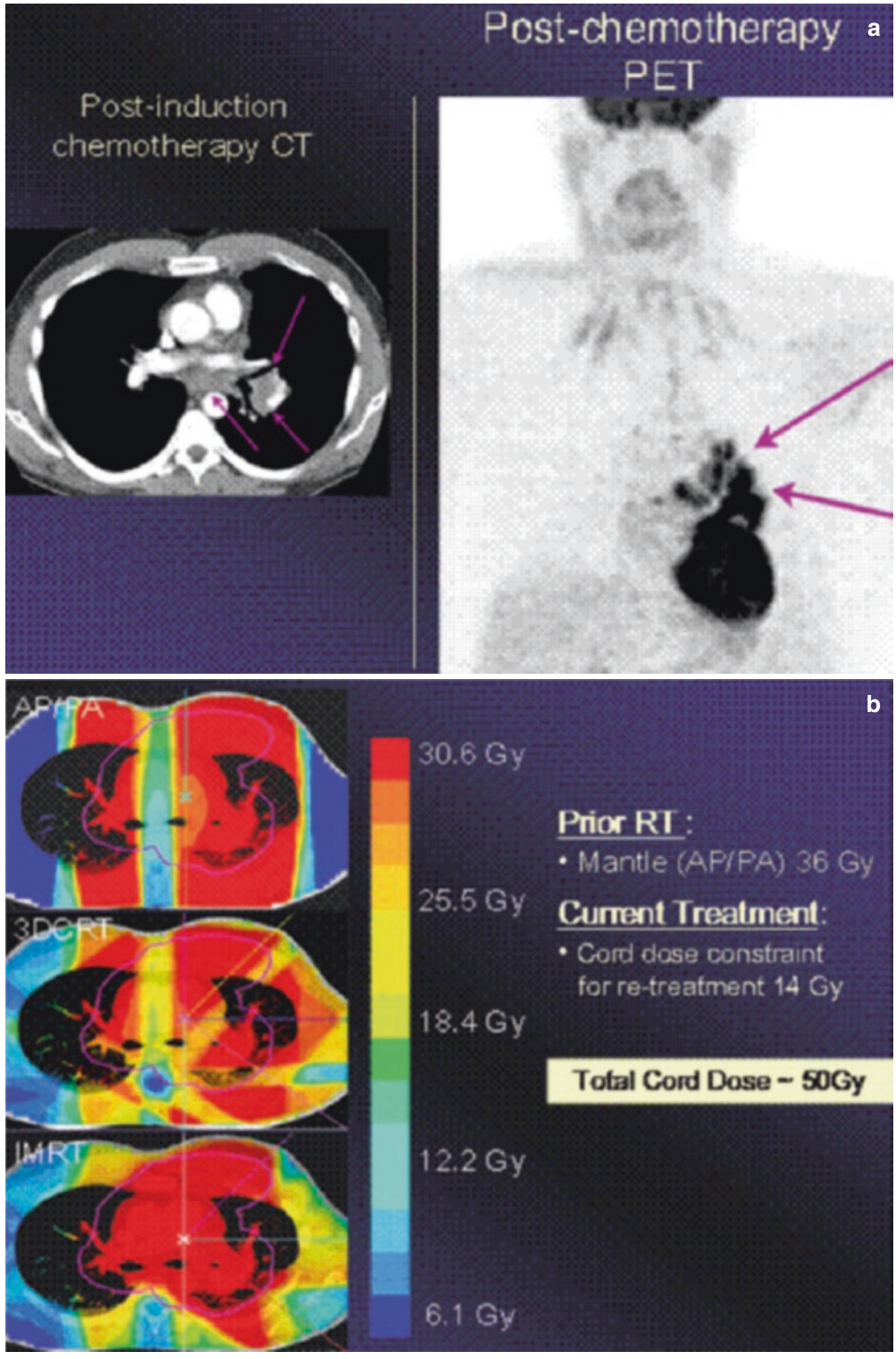


Fig. 9.4 (**a**) Use of IMRT for re-irradiation of a patient relapsing after ABVD and mantle-field irradiation to 36 Gy. (**b**, **c**) Treatment planning options for re-irradiation. *AP/PA* opposed anterior and posterior fields, *3DCRT* three-dimensional conformal radiation therapy, *IMRT* intensity-modulated radiation therapy

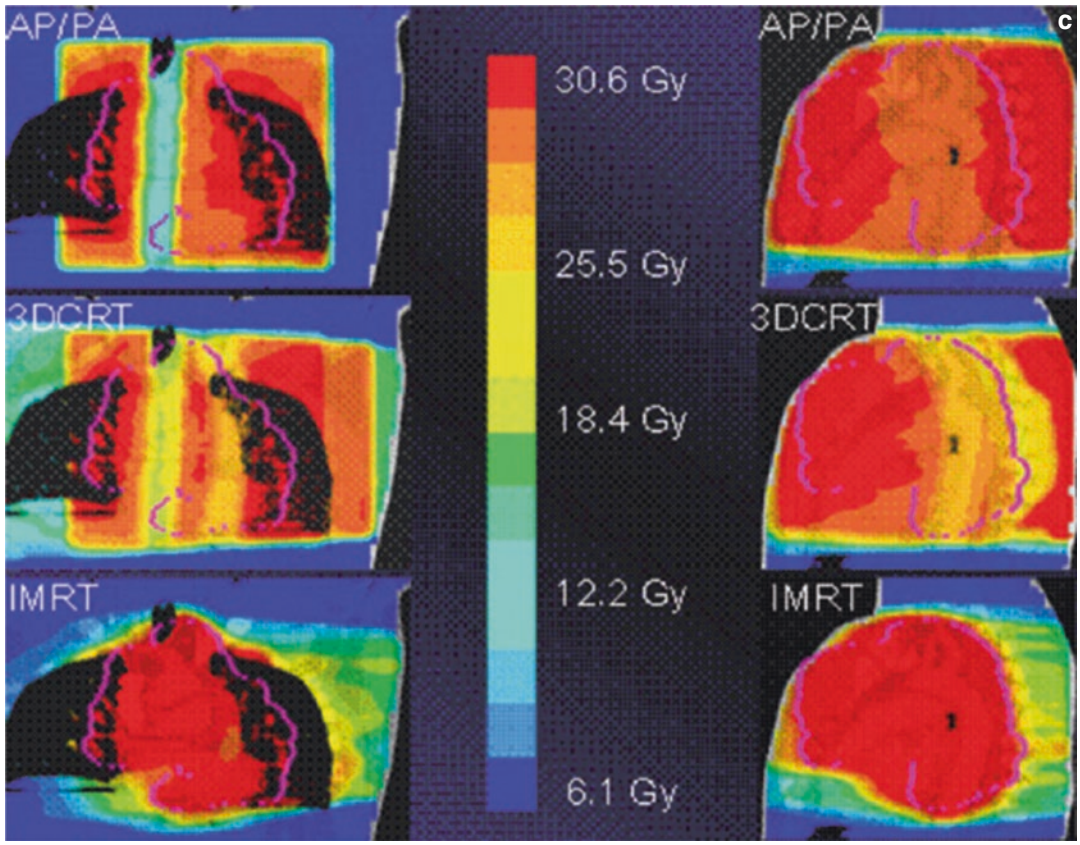


Fig. 9.4 (continued)

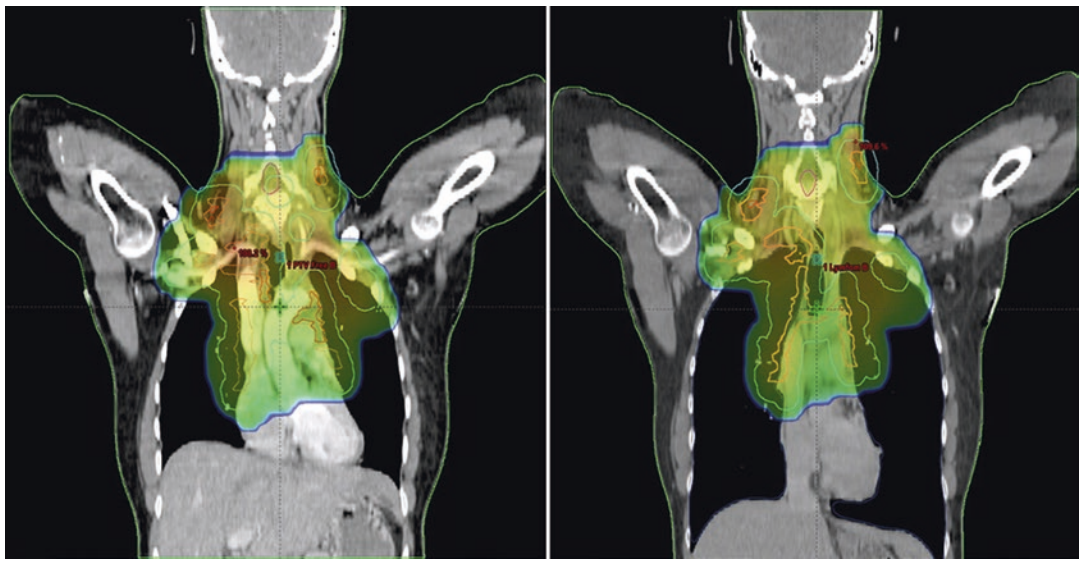


Fig. 9.5 An example case in which the use of DIBH increases total lung volume and pulls the heart caudally, thus decreasing dose to lung and heart without compromising coverage (Courtesy of Lena Specht, MD PhD, Rigshospitalet, University of Copenhagen, Denmark)

9.7 Proton Therapy

Another technical advance is the use of particle therapy (protons). Protons have the advantage of a more defined depth of penetration than photons, which eliminates the "exit dose" of photons. Proton therapy may be helpful in the mediastinum, in select cases where significant sparing of OARs including the heart, lungs, and esophagus cannot be achieved with IMRT [56]. In a review article of several dosimetric studies comparing highly conformal photon techniques with proton therapy, on average proton therapy reduced the mean heart dose by 2.24 Gy, breast by 2.45 Gy, lung by 3.28 Gy, thyroid by 2.09 Gy, and mean body dose by about 40% [76]. Patients with lower mediastinal disease may benefit more from proton therapy, due to the potential gains in reducing the radiation dose to the heart as described in the ILROG guidelines [94]. The ILROG guidelines also discuss in detail both the advantages and disadvantages of proton therapy for lymphoma and identify parameters that can help clinicians better select the appropriate modality.

While proton therapy planning and deliver is more complex than photon-based treatments, multicenter clinical outcomes have demonstrated similar disease control rates with that of IMRT or 3DCRT [95]. Furthermore, risks of pneumonitis have been extremely low [96], and there can be improved cardiac sparing [97]. Proton therapy may also be helpful in other situations including relapsed and refractory patients that require higher doses of radiation, when the disease involves the axilla, due to the ability to spare the breasts with posterior fields, and in pediatric HL, where the risk of second cancers is highest. Fig. 9.6 shows representative colorwash dose distributions for the same patient across different radiation treatment approaches.

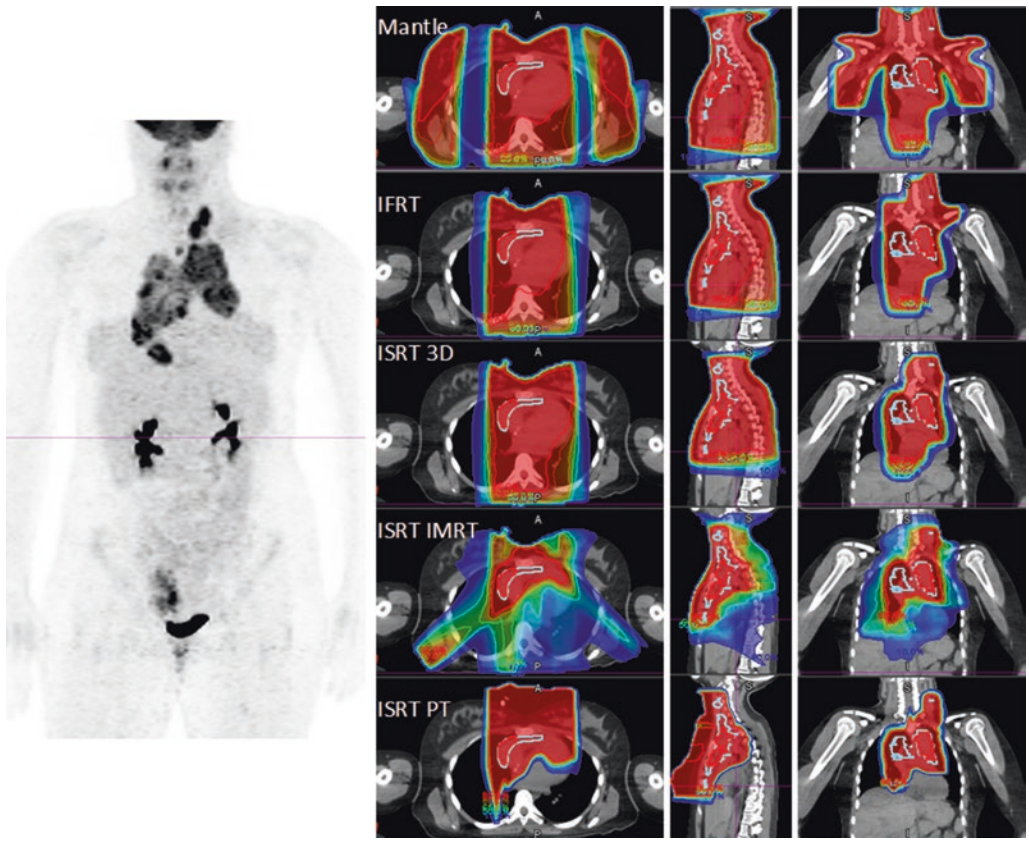


Fig. 9.6 A sample case of an 18-year-old woman with stage II HL at diagnosis with representative plans using various treatment modalities including mantle field, IFRT, ISRT using 3DCRT (ISRT 3D), ISRT using IMRT (ISRT IMRT), and ISRT using proton therapy (ISRT PT) (Courtesy of Brad Hoppe, MD MPH, University of Florida, United States of America)

9.8 Common Side Effects and Supportive Care During Radiation Therapy

The side effects of RT depend on the irradiated volume, dose administered, and technique employed. They are also influenced by the extent and type of prior chemotherapy, if any, and by the patient's age, habits, and presence of intercurrent disease. Most of the information that we use today to estimate risk of RT is derived from strategies that used radiation alone, with larger treatment volumes and higher doses. As noted previously, field sizes have been reduced and doses decreased, and other technological advances have all drastically reduced the radiation exposure to the OARs. It is thus misleading to inform patients of risks of RT using information from RT of the past as this is no longer practiced.

It is critical to remember that most of the data of long-term complications associated with RT and particularly second solid tumors and coronary heart disease were reported from databases of patients with HL treated more than 25 years ago. It is also important to note that we have very limited long-term follow-up data on patients with HL who were treated with chemotherapy alone.

9.8.1 Common Acute Side Effects

Radiation, in general, may cause fatigue, and areas of the irradiated skin may develop mild sun exposure-like dermatitis. The acute side effects of irradiating the full neck and portions of the mouth include dryness, change in taste, and pharyngitis. Patients who are treated to the neck and mediastinum may also develop mild dysphagia and esophagitis, which is self-limited. With the doses and techniques of irradiation currently employed in HL, all of these side effects are usually mild and transient. The main potential side effects of subdiaphragmatic irradiation are loss of appetite, nausea, and increased bowel frequency. Again, these reactions are usually mild and can be minimized with standard antiemetic medications.

9.8.2 Uncommon Early Side Effects

Lhermitte sign: Less than 3% of patients who have treatment that includes long lengths of the spinal cord may note an electric shock sensation radiating down the backs of both legs when the head is flexed (Lhermitte sign) 6 weeks to 3 months after mantle-field RT. Possibly secondary to transient demyelination of the spinal cord, Lhermitte sign resolves spontaneously after a few months and is not associated with late or permanent spinal cord damage. The risk is likely increased in the presence of prior neurotoxic chemotherapy such as vincristine or vinblastine.

Pneumonitis and pericarditis: During the same period, radiation pneumonitis and/or acute pericarditis may occur in <3% of patients; these side effects occur more often in those who have extensive mediastinal disease. Both inflammatory processes have become rare with modern radiation techniques.

The consideration and discussion of potential late side effects and complications of both RT and chemotherapy are of prime importance. A more complete discussion is detailed in Chap. 20.

9.8.3 Supportive Care During Treatment

It is important to prepare the patient for the potential side effects of RT, and in addition to physician-led discussion, many organizations and cancer centers also provide written patient information regarding RT for lymphomas. Since some level of xerostomia may be associated with RT that involves the upper neck and/or lower mandible and mouth, attention to dental care is advised. If dryness is a concern, it is advised to arrange for a consultation with a dental expert for overall dental evaluation and consideration of mouth guards (from scatter) and/or supplemental fluoride treatment during and after RT.

Soreness of the throat and mild-to-moderate difficulty of swallowing solid and dry food may also occur during neck irradiation, with onset at a

dose of approximately 20 Gy. These side effects are almost always mild, self-limited, and subside shortly after completion of RT. Skin care with hydrating lotion and sunscreen is advised for all patients undergoing RT. Temporary hair loss is expected in irradiated areas, and recovery is generally observed after several months.

9.8.4 Follow-Up After Treatment

We normally recommend a first post-RT follow-up visit 6 weeks after the end of treatment and obtain post-RT baseline blood count, standard biochemistry tests, as well as TSH levels (if there was neck irradiation) and lipid profile (if applicable) at that visit. Follow-up imaging studies normally commence 3 months after completion of treatment. Patients treated with radiation therapy alone for NLPHL should have a posttreatment PET scan to confirm a complete response. Other follow-up studies are included in the NCCN guidelines for HL [2].

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Principles of Chemotherapy in Hodgkin Lymphoma

10

David Straus and Mark Hertzberg

Contents

10.1 Historical Introduction

Hodgkin lymphoma (HL) was the malignant disease for which the possibility of cure with combination chemotherapy in the majority of patients was first realized. As such it has provided a model upon which studies in many other types of malignancy have been based, and it is interesting to follow the trajectory of knowledge from early single-agent work through combinations,

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_10

combined modalities, increasing complexity, and, most recently, selective de-escalation. Patients with advanced disease represent a minority of those affected by HL. However, these patients represent the group in which the development and effects of chemotherapy are most readily appreciated, because the role of radiation therapy is markedly less than in patients with localized disease.

As early as 1942, four patients with HL were treated with nitrogen mustard by Wilkinson and Fletcher at Manchester Royal Infirmary, although a military embargo prevented the dissemination of this information [1]. Similar considerations are applied to the bombing of the ship "USS Liberty" on December 3, 1943, in Bari, and the hematological consequences of a nitrogen mustard gas leak among the survivors. Cornelius Rhoads, an American cancer researcher, was involved in their care and understood from his observations of the effects on the bone marrow and lymphoid tissue that nitrogen mustard derivatives might be effective against lymphoid and hematological malignancies [2, 3]. In 1958, another alkylating agent, cyclophosphamide, proved effective in non-Hodgkin lymphoma (NHL) [4]. Shortly after this, vinblastine was first shown to be an effective drug in HL, as was vincristine. Although encouraging, the early results of chemotherapy were modest, with most responses short-lived after corticosteroids and alkylating and spindle cell agents [5–7]. There was a prevalent view that only extensive irradiation could yield complete cures [8, 9].

One of the first modern randomized studies was the EORTC H1 trial, which investigated whether "adjuvant" chemotherapy (weekly vinblastine for 2 years) could improve the results over radiotherapy alone [10]. A durable advantage was seen in the chemotherapy arm for relapse-free survival (RFS: at 15 years 60% vs. 38%; $P < 0.001$) although more than 50% of patients with mixed-cellularity histology developed recurrences [11]. To reduce the relapse rate, irradiation was extended to infradiaphragmatic nodal and spleen areas. Single-agent or doublet chemotherapy was added after radiotherapy, but no immediate attempt was made to use polychemotherapy, based upon the idea that the cure rate would depend upon the adequacy of irradiation [12, 13]. Two factors gradually undermined the dominance of strict pathological delineation and extensive irradiation as the basis of curative therapy in HL: the advent of accurate cross-sectional imaging by computed tomographic (CT) scanning and the recognition that relapses after irradiation alone had minimal impact on survival owing to the efficacy of salvage chemotherapy [14]. With the development of four-drug combination therapy, which for the first time resulted in cures for advanced HL without the need for irradiation, the transition to systemic therapy began in earnest.

10.2 Chemotherapy Applied to Advanced-Stage Hodgkin Lymphoma: Theories and Practice

10.2.1 Classes of Active Classical Agents in HL (Table 10.1)

Almost every class of chemotherapy drug has been shown to have some efficacy in HL, with the possible exception of the antimetabolite drugs such as 5-fluorouracil [15]. The original combination treatments were based upon evidence of single-agent activity among alkylating agents, vinca alkaloids, corticosteroids, and the hydralazine monoamine oxidase inhibitor procarbazine. All of these produced response rates of over 50% when used singly in patients not previously exposed to multiagent chemotherapy (Table 10.1). Later entrants to this field included the antibiotic drugs doxorubicin and bleomycin, the nitrosoureas and dacarbazine, and the podophyllotoxins, all of which showed appreciable single-agent activity after prior combination regimens. More recently, newer cytotoxics such as gemcitabine have been introduced, often in combination with platinum drugs, and found to produce significant response rates in recurrent disease. In 2011, brentuximab vedotin, an antibody-drug conjugate, was approved in the USA and conditionally in Europe

Table 10.1 Single-agent activity of cytotoxic drugs in Hodgkin lymphoma [15]

Drug	Overall response rate (%)	Complete response rate (%)
Single agents tested before combination chemotherapy		
Alkylating agents		
Chlorambucil	61	16
Mustine	63	13
Cyclophosphamide	54	12
Vinca alkaloids		
Vinblastine	68	30
Vincristine	60	36
Agents mainly tested after prior multiagent therapy		
Dacarbazine	56	6
Nitrosoureas		
Carmustine	44	5
Lomustine	48	12
Antibiotics		
Doxorubicin	30	5
Bleomycin	38	6
Podophyllotoxin		
Etoposide	27	6
Antimetabolite		
Gemcitabine	22	0
Antibody-drug conjugate		
Brentuximab vedotin	75	34

for treatment of relapsed or refractory HL after autologous stem cell transplantation (ASCT) or after at least two combination chemotherapy regimens in patients who are not transplant candidates. Approval was granted on the basis of an overall response (OR) rate of 75% and a complete response (CR) rate of 34% in a phase 2 trial in 102 HL patients relapsed after or refractory to ASCT, response rates approximately twice as high as those reported for other single agents [16]. This antibody-drug conjugate attaches an anti-CD30 antibody to a potent antimicrotubular agent, monomethyl auristatin (MMAE), by a protease cleavable linker. MMAE binds to tubulin and disrupts the microtubule network, inducing cell cycle arrest and apoptosis, a mechanism of action similar to those for vincristine and vinblastine [17].

It is clear that HL is broadly sensitive to phase-specific, cycle-specific, and non-cycle-specific agents, although it is less clear whether this is a feature of the malignant cells themselves or their associated inflammatory infiltrate, which may be critical to sustaining them. The development of combination therapies has been based mainly upon the use of agents with non-overlapping toxicity as far as possible, and as cure rates have risen, the emphasis has fallen increasingly upon avoiding long-term side effects. The most important among these are infertility and myelodysplasia, mainly caused by the alkylating agents; pulmonary fibrosis caused by bleomycin and nitrosoureas; and cardiomyopathy related to anthracyclines, a risk increased by the concomitant use of mediastinal radiotherapy.

10.2.2 Polychemotherapy: Models and Comparative Clinical Studies (Tables 10.2 and 10.3)

10.2.2.1 MOPP and Derivatives

Combination chemotherapy was first attempted clinically in childhood acute lymphoblastic leukemia by Jean Bernard [18], who designed two doublets of cortisone-methotrexate and prednisone-vincristine, at the same time as pursuing work on chemotherapy for HL. Lacher and Durant were the first to use doublet combination chemotherapy in HL with vinblastine and chlorambucil [19]. At the NCI, Freireich, Frei, and Katon added 6-mercaptopurine into the more effective VAMP (vincristine, amethopterin, mercaptopurine, and prednisone) regimen [7]. This led on to MOMP (cyclophosphamide, vincristine, methotrexate, and prednisone) and MOPP (mechlorethamine, vincristine, procarbazine, prednisone), developed by DeVita and Carbone, also at the NCI [20, 21]. Some of the critical features of success were prolonged treatment (6 months, more than any other regimen at the time); the use of each drug at "optimal" dose and schedule with a sliding scale for dose adjustment according to marrow suppression; an interval of 2 weeks for recovery of normal tissue (marrow, GI epithelium), ideally before HL recovery; and treatment with curative intent rather than palliation. MOPP provided an 80% response rate and long-term disease-free (DFS) and overall survival

Table 10.2 Chemotherapy regimens designed for advanced Hodgkin lymphoma

Drugs	Dose, mg/m^2	Route	Schedule
Four-drug regimens			
MOPP			q. 28 days
Mechlorethamine	6	Iv	d1 and 8
Vincristine	1.4 (cap 2 mg)	Iv	d1 and 8
Procarbazine	100	Po	d1–14
Prednisolone	40	Po	d1–14
MVPP			q. 42 days
Mechlorethamine	6	Iv	d1 and 8
Vinblastine	6 (cap 10 mg)	Iv	d1 and 8
Procarbazine	100	Po	d1–14
Prednisolone	40	Po	d1–14
ChlVPP			q. 28 days
Chlorambucil	6 (cap 10 mg)	Po	d1–14
Vinblastine	6 (cap 10 mg)	Iv	d1 and 8
Procarbazine	100	Po	d1–14
Prednisolone	40	Po	d1–14
COPP			q. 28 days
Cyclophosphamide	650	Iv	d1 and 8
Vinblastine	6	Iv	d1 and 8
Procarbazine	100	Po	d1–14
Prednisolone	40	Po	d1–14
ABVD			q. 28 days
Doxorubicin	25	Iv	d1 and 15
Bleomycin	10 iu/m^2	Iv	d1 and 15
Vinblastine	6	Iv	d1 and 15
Dacarbazine	375	Iv	d1 and 15
Hybrid regimens			
MOPP/ABV			q. 28 days
Mechlorethamine	6	Iv	d1
Vincristine	1.4	Iv	d1
Procarbazine	100	Po	d1–7
Prednisolone	40	Po	d1–14
Doxorubicin	35	Iv	d8
Bleomycin	10 iu/m^2	Iv	d8
Vinblastine	6	Iv	d8
ChlVPP/EVA			q. 28 days
Chlorambucil	6 (cap 10 mg)	Po	d1–7
Vincristine	1.4 (cap 2 mg)	Iv	d1
Procarbazine	90	Po	d1–7
Etoposide	75	Po	d1–5
Prednisolone	50	Po	d1–7
Doxorubicin	50	Iv	d8
Vinblastine	6 (cap 10 mg)	Iv	d8
BEACOPP baseline			q. 21 days
Bleomycin	10 iu/m^2	Iv	d8
Etoposide	100	Iv	d1–3
Doxorubicin	25	Iv	d1
Cyclophosphamide	650	Iv	d1
Vincristine	1.4 (cap 2 mg)	Iv	d8

Table 10.2 (continued)

Drugs	Dose, mg/m^2	Route	Schedule
Procarbazine	100	Po	d1–7
Prednisolone	40	Po	d1–14
Escalated regimens			
Escalated BEACOPP			q. 28 days
Bleomycin	10 iu/m^2	Iv	d8
Etoposide	200	Iv	d1–3
Doxorubicin	35	Iv	d1
Cyclophosphamide	1250	Iv	d1
Vincristine	1.4 (cap 2 mg)	Iv	d8
Procarbazine	100	Po	d1–7
Prednisolone	40	Po	d1–14
G-CSF		Sc	d8–14
BEACOPP-14			q. 14 days
Bleomycin	10 iu/m^2	Iv	d8
Etoposide	100	Iv	d1–3
Doxorubicin	25	Iv	d1
Cyclophosphamide	650	Iv	d1
Vincristine	1.4 (cap 2 mg)	Iv	d8
Procarbazine	100	Po	d1–7
Prednisolone	80	Po	d1–7
G-CSF		Sc	d8–13
Weekly regimens			
Stanford V			4-week cycle
Doxorubicin	25	Iv	d1 and 15
Vinblastine	6	Iv	d1 and 15
Mechlorethamine	6	Iv	d1
Vincristine	1.4 (cap 2 mg)	Iv	d8 and 22
Bleomycin	5 i.u./m^2	Iv	d8 and 22
Etoposide	60	Iv	d15 and 16
Prednisolone	40	Po	Daily to week 10 then taper
VAPEC-B			4-week cycle
Doxorubicin	35	Iv	d1 and 15
Cyclophosphamide	350	Iv	d1
Etoposide	75–100	Iv	d15–20
Vincristine	1.4 (cap 2 mg)	Iv	d8 and 22
Bleomycin	10	Iv	d8 and 22
Prednisolone	50	Po	Daily to week 6 then taper
BV/AVD			
Brentuximab vedotin	1.2 mg/kg	Iv	d1 and 15
Doxorubicin	25	Iv	d1 and 15
Vinblastine	6	Iv	d1 and 15
Dacarbazine	375	Iv	d1 and 15

(OS) of almost 50% and 40%, respectively [22]. The results have held up, and the 20-year analysis confirmed among 198 patients a CR rate of 81%, a 19% rate of induction failures, a 36% relapse rate, and a 54% mortality. Of the 106 deaths, 30 occurred in patients free of disease; among the 92 patients who survived (46%), only two had persistent HL [23]. These results have been reconfirmed in subsequent trials (Table 10.3) [24–27]. Although the rise in cures from HL can be

Table 10.3 Summary results of combination chemotherapy regimens used in first-line therapy of advanced Hodgkin lymphoma

Regimen	CR (%)	5 year EFS (%)	5 year OS (%)	≥7 year OS (%)
MOPP [22–25, 101]	67–81	40–60	65–73	51–70
MVPP [38, 102, 103]	72–76	60	65–75	
ChlVPP [39, 104]	57–74	55–60	66	65
ABVD [24, 47, 68, 69, 77, 78, 105]	68–92	61–80	73–90	77
MOPP/ABVD alternating [24, 106, 107]	83–92	65–70	75–84	74
COPP/ABVD alternating [62, 108]	85	69	83	75
MOPP/ABV hybrid [47, 107, 109, 110]	80–88	66–75	76–83	72
Stanford V [66–69]	72–91	54–94	82–96	
VAPEC-B [71]	47	62	79	
ChlVPP/EVA [71, 105]	67	82–84	89	
BEACOPP baseline [62]	88	76	88	80
Escalated BEACOPP [62]	81–96	87	91	86
BV/AVD [95]	73	82[a,b]	97[a]	

[a]2 Years
[b]Modified PFS (time to disease progression, death, or modified progression)

ascribed to multiple advances and not just the introduction of effective chemotherapy, the 1970 report convinced almost all groups treating HL to accept the inclusion of polychemotherapy (MOPP or MOPP derivatives) in the treatment strategy for localized as well as advanced disease. In almost all instances where a combined treatment was compared to irradiation alone, whether patients were staged or not with laparotomy, advantages in terms of response and disease- and relapse-free survival were observed when MOPP or a MOPP-derived chemotherapy was used [28].

Analysis of the results with MOPP has proven a fruitful source of information to design and interpret future studies. Thus, complete response was seen to be a prerequisite for sustained remission, and a high percentage of complete responses was correlated with higher survival rates. Capping the vincristine dose at 2 mg may have been detrimental to the results. Patient and initial disease characteristics were good predictors of outcome, with confirmation of the adverse prognostic significance of systemic "B" symptoms. Maintenance treatment with intermittent MOPP or carmustine did not appear beneficial [29]. In patients treated previously by irradiation and chemotherapy, MOPP was less well-tolerated and less effective [30]. Conversely, retreatment in relapsed patients whose initial remission lasted over a year proved efficient on the second occasion [31]. MOPP therapy carries consequences in terms of carcinogenicity, in particular with secondary acute myeloid leukemia (AML) [32, 33]. It is also responsible for impaired fertility in both men and women [34]. Immunosuppression related to the treatment, or to the underlying disease, brings risks of different types, in particular of opportunistic infection [35].

There were many attempts to improve upon these results. The three best-known MOPP-derived regimens have been MVPP, with vinblastine instead of vincristine; ChlVPP (chlorambucil, vinblastine, procarbazine, and prednisolone); and COPP, with an additional substitution of mechlorethamine, replaced by chlorambucil or cyclophosphamide (Tables 10.2 and 10.3). These alternatives have never undergone direct comparison, and historical controls are difficult to interpret. In addition, the proportion of patients who have also had radiotherapy varies considerably between series. For example, in the NCI series, 32/198 patients had been irradiated prior to MOPP, and 28/198 patients received total nodal irradiation (TNI) "to prevent recurrent disease in previously involved nodes" as consolidation after chemotherapy. MVPP, devised in the UK, proved easier to handle than MOPP (with less constipation and neurological toxicity), but was slightly more myelotoxic [36–38]. ChlVPP appeared more patient-friendly, inducing minimal nausea/vomiting, constipation or neurologic toxicity, and limited hematotoxicity, and the number of cycles could be adapted to the

response: a maximum of five beyond CR. The 66% OS rate in advanced HL was comparable to mustine-containing regimens, at lower toxic cost, for all of these acute toxicities, except myelosuppression [39, 40]. COPP is less myelotoxic than MOPP and is often used in children [41].

10.2.2.2 ABVD and Derivatives

The ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) was devised just 10 years after MOPP, in 1973, for intravenous-only administration at fixed 2-week intervals. Like MOPP, ABVD was a combination of hematotoxic and neurotoxic drugs. Both doxorubicin and vinblastine had been shown highly effective in HL. The results with dacarbazine were numerous but possibly less convincing, and bleomycin was also felt to have considerable potential [10, 42–45]. By comparison to MOPP, hematotoxicity after ABVD was predictable, noncumulative, and milder as a result of the intravenous dosing and short intervals. Further, ABVD was far less neurotoxic. Bonadonna developed ABVD at the Milan NCI with the intention: "to compare the efficacy of ABVD with MOPP, and to demonstrate absence of cross-resistance between the two regimens" [46]. The results of MOPP were well established and the potential of ABVD in terms of "alternative to MOPP to be used either in MOPP failures or in sequential combination with MOPP" was clearly in the mind of the authors, based on these very early results achieved in 45 patients. No significant cardiac toxicity was seen in this first series, probably because of the relatively small cumulative dose of doxorubicin (6 cycles = 300 mg/m^2), the short follow-up, and the small numbers of patients. Conversely, bleomycin pulmonary toxicity was apparent from the outset, while the effects upon fertility were initially overestimated through short observation which did not take into account the reversal of temporary amenorrhea in some women.

It took a surprisingly long time for ABVD to be accepted as a standard of care, and it was initially considered only as a salvage treatment in MOPP failures. However, the Milan group undertook a larger trial, comparing MOPP and ABVD directly in patients with stage IIB, IIIA, and IIIB HL. In 232 patients, a combined modality approach of three cycles before and after extensive irradiation yielded a CR rate of 80.7% after MOPP/radiotherapy and 92.4% after ABVD/radiotherapy ($P < 0.02$). At 7 years follow-up, ABVD surpassed MOPP for freedom from progression (FFP) (80.8% vs. 62.8%; $P < 0.002$), RFS (87.7% vs. 77.2%; $P = 0.06$), and OS (77.4% vs. 67.9%; $P = 0.03$). With longer follow-up, the disadvantages of MOPP in terms of fertility damage and second myelodysplasia (MDS) and leukemia were also more apparent. The final establishment of ABVD as the favored regimen, at least in North America, was based on two randomized trials for advanced HL. In the first, MOPP vs. ABVD vs. MOPP alternating with ABVD were associated with 5-year failure-free survival rates of 50%, 61%, and 65%, respectively. There was less toxicity with ABVD than with MOPP or MOPP alternating with ABVD and no significant difference in survival among the three regimens [24]. A second trial compared ABVD with a hybrid regimen, MOPP/ABV; 5-year failure-free survival rates were 63% and 66%, respectively. There was a greater incidence of acute toxicity, myelodysplastic syndrome, and leukemia for MOPP/ABV compared with ABVD. Again, there was no significant difference in survival [47].

Currently, ABVD is considered by most investigators as the standard chemotherapy for most patients with HL, with the possible exception of high-risk patients with advanced disease and poor prognostic features. Reasons to avoid ABVD relate to previous lung impairment and decreased left ventricular ejection fraction. Hematological toxicity is usually moderate, and ABVD may be delivered safely at full dose and on schedule to a non-selected average population of adult patients without the need to modify doses in the presence of neutropenia [48]. The most frequent serious toxicity with ABVD is pulmonary fibrosis, which may be fatal [49]. The discontinuation of bleomycin for toxicity during ABVD treatment does not appear to have an adverse effect on outcome, which calls into question the importance of bleomycin in the ABVD regimen [47, 49–51]. This possibility has recently been

tested prospectively in a randomized study of patients showing a good early response to ABVD, where patients either continued all drugs, or AVD only [17, 52]. The results confirmed the excess toxicity associated with bleomycin, particularly reduced lung function and more instances of venous thromboembolism. There was no decrease in efficacy by omission of bleomycin from the last four cycles of treatment.

10.2.2.3 The Dose/Response Relationship: Norton and Simon Model

Much of the thinking about how to maximize the cure rate in lymphoma has centered upon the relationship between dose and response to cytotoxic therapy. Theories of tumor cell ecology have suggested that as the mass of disease is reduced, the growth fraction may rise. This, together with the assumed selection of resistant subclones, underlies the idea that tumor eradication is dependent upon the delivery of treatment at adequate dose intensity early in a course of treatment. If doses are too small or too infrequent, the fractional cell kill might be expected to decline and allow the emergence of resistance [53].

Three prospective clinical trials have directly addressed the question of dose versus response using the same chemotherapy drugs in both arms. In the first-line treatment of advanced disease, a critical study, HD9, was performed by the German Hodgkin Study Group (GHSG), as detailed later, in which patients were randomized between the baseline BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen and an escalated regimen, with the doses of doxorubicin, cyclophosphamide, and etoposide increased to 140%, 185%, and 200%, respectively. This resulted in an increase in freedom from treatment failure (FFTF) at 5 years from 76% to 87% ($P < 0.01$), which was translated into a small but significant improvement in survival on longer follow-up (80% vs. 86% at 10 years; $P = 0.0053$). This was at the cost of an increased risk of MDS and AML in the escalated arm, but at a frequency too low to reverse the gain in survival from better control of the lymphoma [54].

There are two randomized studies for recurrent disease which have yielded similar data on the dose-response relationship. The UK group compared the myeloablative BEAM (carmustine, etoposide, cytarabine, and melphalan) regimen to mini-BEAM, which uses the same drugs at nonmyeloablative doses. The high-dose treatment yielded superior PFS ($P = 0.005$), although the trial was closed with only 44 patients recruited and had insufficient power to demonstrate a survival advantage [55]. A study of similar design was conducted by the GHSG, and this too demonstrated superior FFTF at 3 years (55% for BEAM, 34% for nonmyeloablative dexa-BEAM, $P = 0.019$), although once again no survival difference could be demonstrated [56].

While there is good evidence for an overall dose-response relationship, there are several areas of continuing uncertainty. For example, it is not clear whether the dose of treatment over a whole course is the critical determinant of outcome, or whether initial dose intensity during the first weeks of treatment is more important. From retrospective analyses comparing outcomes to doses administered, it appears that the most influential factor is the total dose of treatment given, with some scope for compensating suboptimal early treatment by later escalation, a finding that may distinguish HL from many other malignancies [57–59].

Dose/Response Relationships and Treatment Tolerance: An Individual Characteristic?

A dose response for both malignant and normal tissue toxicity is well-recognized, raising the question of whether the efficacy of tumor control can be related to toxic side effects, effectively using each subject as his or her own pharmacodynamic control. The GHSG explored hematotoxicity as a surrogate for pharmacological and metabolic heterogeneity, in relation to reduced systemic dose and disease control. Patients treated with various regimens in the HD6 trial (validated on two other cohorts) were retrospectively classified as showing WHO

grade leukocytopenia of 0–2 and >2, respectively. Patients with a high hematological toxicity had a 5-year FFTF rate of 68% versus 47% for those with low toxicity, independent of the actual drug doses received [60]. No pretreatment pharmacokinetic parameters could be found to explain these observations; however, recent work from the French Study Group of the Adult Lymphoma (GELA) has explored polymorphisms in a population of HL patients that might determine anticancer agent metabolism. The UGT1A1 polymorphism has been identified as a possible candidate for influencing the metabolism of several anticancer drugs and patient outcomes [61]. Unfortunately, similar dose-response relationships are also seen for long-term toxicities, for example, infertility and secondary leukemias [62–64].

10.2.2.4 Sustained/Weekly Regimens

Pursuing the idea of increased dose intensity, several groups developed novel, brief duration regimens for the treatment of advanced HL. The rationale for the development of these regimens was, firstly, increased dose intensity of chemotherapy by reduction in the total duration of treatment but an increase in the number of different agents and, secondly, reduced cumulative doses of drugs responsible for long-term toxic effects, including alkylating agents, doxorubicin, and bleomycin. The PACEBOM, VAPEC-B, and Stanford V regimens were all designed to deliver weekly treatments, alternating between myelosuppressive and nonmyelosuppressive agents. The preliminary results from single-arm studies appeared promising, with high response and survival rates [65]. Unfortunately, the results of randomized trials did not confirm the early promise of these regimens.

The Stanford V program developed from the close collaboration of radiotherapy and chemotherapy, endeavoring to minimize the use of each modality to achieve improved results with less toxicity. Initial chemotherapy was composed of the standard drugs from the MOPP/ABVD scheme (mechlorethamine, doxorubicin, bleomycin), plus etoposide, with dose intensity increased for better and earlier tumor response, while cumulative doses, thought to be responsible for late toxicity (marrow, heart, lung), were reduced. The use of alkylating agents was limited in order to avert gonadal damage. The final scheme was an abbreviated 12-week program with radiotherapy started 2–4 weeks after chemotherapy, restricted to sites at higher risk for relapse (bulky sites), and delivered at 36 Gy, in order to reduce the incidence of late cardiopulmonary effects, and "mini-mantle" instead of mantle fields, sparing the axillae to decrease the risk of secondary breast carcinoma. The results of the initial Stanford V phase 2 approach were confirmed in the Eastern Cooperative Oncology Group (ECOG) E1492 study in 45 patients, of whom 87% received radiotherapy; FFP was 85% at 5 years, and OS was 96% with one death from HL and one from an M5 AML [66]. Later analysis confirmed these excellent results and the relative preservation of fertility in both women and men; no case of secondary MDS/leukemia or NHL had been registered at a 65 months median follow-up [67].

A randomized trial (Italian Lymphoma Group: ILL) compared Stanford V to mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine (MOPPEBVCAD) and to ABVD as the standard in 355 patients with stage IIB–IV HL. In this trial, the Stanford V arm was inferior to the other two arms in terms of 5-year FFS (54% vs. 78% for ABVD and 81% for MOPPEBVCAD, respectively ($P < 0.01$) for comparison of Stanford V with the other two regimens) [68]. However, only 66% of patients in the Stanford V arm received irradiation, against 87% in the ECOG phase 2 study: this is important in a strategy that was originally designed to combine both modalities. The Stanford V program was also compared to ABVD in a large prospective trial run by the UK National Cancer Research Institute Lymphoma Group (NCRI) in 520 patients with stage IIB–IV HL. Results in the Stanford V and in the ABVD arm were similar for 5-year PFS and OS rates (76% and 90%, for ABVD; 74% and 92% for Stanford V, with radiotherapy administered in 53% and 73%, respectively) [69]. The North American Intergroup trial

led by ECOG (E2496) compared ABVD with IFRT only to bulky mediastinal sites with the combined modality Stanford V. There was no difference in response rates or in 5-year FFS or OS rates between the two arms of the trial. The relatively extensive use of radiotherapy required to achieve optimum results for weekly regimens makes them a less attractive choice for many patients: in the UK study, 73% of patients treated with Stanford V received consolidation radiotherapy, compared to 37% in the previous UK study using ABVD in a similar group of patients. In E2496, 75% of patients on the Stanford V regimen received radiation therapy, while 41% of those on ABVD had irradiation of bulky mediastinal sites [70]. The short 12-week duration of the Stanford V regimen has some appeal for patients and remains a reasonable approach for those with low-risk non-bulky disease, for whom limited or no irradiation is needed, but this is only a minority.

The only other weekly regimen to be compared with a hybrid regimen in a randomized trial featured myelosuppressive (doxorubicin, cyclophosphamide, and etoposide) and relatively non-myelosuppressive (vincristine and bleomycin) drugs given on an alternating weekly basis for 11 weeks: VAPEC-B. This regimen was compared to a hybrid ChlVPP-EVA schedule for advanced disease, was expected to still be significantly more myelosuppressive and to impair fertility, and showed inferior PFS for the weekly regimen in all but the best prognosis subgroup. Event-free survival at 5 years in newly diagnosed patients with advanced disease following the hybrid regimen was 78% versus 58% for VAPEC-B, which translated into better OS, at 89% versus 79% [71].

10.2.2.5 Escalated-Dose Regimens

In order to spare patients the acute gastrointestinal and hematologic toxicities, the original recommendation of the NCI to follow a "sliding scale" of dose adaptation for MOPP was gradually superseded by fixed doses at well-tolerated levels and intervals. Retrospective studies of MOPP and MVPP suggested that the cumulative dose, as much as frequency of administration or dose intensity, might determine the outcomes [25, 72]. These observations also appear to hold for ABVD [59], although all these studies are retrospective and need to be confirmed in a prospective study.

The GHSG has pioneered the exploration of two levels of dose increment, in the conventional dose range, by reducing the length of treatment and adding etoposide to the standard regimen, COPP/ABVD [73]. Further intensification was carried out by increasing the myelosuppressive drug doses, with growth factor support. Both intensified regimens provided higher CR and FFTF and, crucially, statistically higher OS rates as compared to standard COPP/ABVD [54]. The early effects of dose intensification were maintained in the long-term results at 10 years: FFTF was 64%, 70%, and 82% with OS rates of 75%, 80%, and 86% for patients treated with standard COPP/ABVD, BEACOPP baseline, and BEACOPP escalated, respectively ($P < 0.001$) [62]. The higher overall chemotherapy doses, as given in the escalated BEACOPP scheme, appear to provide greater disease control than any of the previous or contemporary regimens. This is supported by the very low number of deaths due to the progression of lymphoma (2.8%). The GHSG has conducted a series of studies, HD12, HD15, and HD18, all using escalated BEACOPP in advanced HL patients (under the age of 61) whose results replicate closely those of the escalated BEACOPP arm in the HD9 study [74–76].

The GHSG reported early on its concerns for the immediate toxicity, especially among patients older than 65, and, in younger patients, impaired fertility and risk of MDS or secondary AML. A review of the HD9 results concerning the cumulative incidence of all second tumors at 10 years confirmed that the rate for AML/MDS was lower after COPP/ABVD (0.4%) versus BEACOPP baseline (2.2%) and BEACOPP escalated (3.2%; log-rank test; $P = 0.03$). However, counting all secondary malignancies, there was no difference (5.3% after COPP/ABVD, 7.9% after BEACOPP baseline, and 6.5% after BEACOPP escalated) [62].

The immediate and long-term toxic effects of escalated BEACOPP and the reluctance of many specialists to consider COPP/ABVD as a standard

comparator have hindered acceptance of escalated BEACOPP as a new standard of care. Two Italian trials, HD2000 and GSM-HD, have demonstrated superior PFS with escalated BEACOPP in comparison to ABVD. In HD2000, BEACOPP resulted in an 81% (95% CI, 70–89%) 5-year PFS versus 68% (95% CI, 56–78%) for ABVD, but no significant OS difference was observed [77]. Similarly, the GSM-HD trial demonstrated a higher 3-year FFP for escalated plus baseline BEACOPP (4 + 4) versus ABVD (87 ± 3% and 71 ± 4%), respectively, but freedom from second progression (FF2P) and OS were alike [78]. ABVD was declared preferable, taking into account the lesser toxicity, including fewer toxic deaths (one vs. six).

The outstanding results of escalated BEACOPP, despite the toxicity, have made it most appealing for high-risk patients. This has been called into question by results in two recent randomized clinical trials. In a multi-institutional Italian trial comparing ABVD with BEACOPP (4 cycles escalated dose + 4 cycles standard dose) for patients with stages IIB, III, or IV HL, the superior freedom from first progression for BEACOPP was confirmed (at 7 years, 73% for ABVD vs. 85% for BEACOPP; $P = 0.004$), which was the primary endpoint of the trial. However, there was no significant difference in freedom from second relapse following ASCT or in OS between the two treatment arms. The treatment-related mortality was 4% for BEACOPP vs. 1% for ABVD [79]. This suggests that most patients can be treated initially with ABVD and only those who relapse be salvaged with ASCT and thus exposed to a treatment-related mortality similar to that with initial BEACOPP treatment. The EORTC randomized patients with high-risk stages III or IV HL (international prognostic score ≥ 3) to BEACOPP (4 cycles dose escalated + 4 cycles standard dose) or ABVD. There was no significant difference in 4-year event-free survival (EFS) or OS, which was the primary endpoint, although this trial also confirmed a superior PFS for BEACOPP [80]. Progression-free survival may not be the most clinically important treatment result, and these two trials suggest that ABVD is an acceptable initial treatment approach even for high-risk advanced-stage HL patients because of the effectiveness of salvage ASCT in the minority of patients who relapse.

As with ABVD, it was found that omission of bleomycin because of toxicity during treatment with BEACOPP did not have an adverse impact on PFS or OS. In addition, with this intensive regimen, omission of vincristine during treatment because of toxicity also had no adverse impact on these outcomes [81].

10.2.2.6 High-Dose Treatment and Autologous Stem Cell Transplantation as Part of Initial Therapy

Attempts have been made to improve results by using intensified consolidation and peripheral blood stem cell (PBSC) rescue for patients considered at high risk. Three randomized studies have explored this concept for HL. The Scotland and Newcastle Lymphoma Group HD3 study randomized 65 out of 126 high-risk patients, resulting in a nonsignificant advantage for the conventional arm (time to treatment failure 85% vs. 79%; $P = 0.35$) [82]. A European study of similar design randomized 163 high-risk patients achieving CR or partial response (PR) after four cycles of ABVD or an equivalent regimen to receive high-dose therapy plus ASCT (83 patients) or four more cycles of conventional chemotherapy (80 patients). There was no evidence of a benefit to the group receiving high-dose therapy (CR 92% vs. 89%, 5-year FFS 75% vs. 82%, and OS 88% vs. 88%, respectively) [83].

The Groupe Ouest-Est d'Etude des Leucémies et Autres Maladies du Sang (GOELAMS) undertook a randomized study in 158 high-risk patients, comparing conventional intensive chemotherapy with vindesine (5 mg/m^2), doxorubicin (99 mg/m^2), carmustine (140 mg/m^2), etoposide (600 mg/m^2), and methylprednisolone (600 mg/m^2) (VABEM) followed by low-dose lymph node irradiation in 82 patients versus four cycles of ABVD followed by myeloablative carmustine (300 mg/m^2), etoposide (800 mg/m^2), cytarabine (1600 mg/m^2), and melphalan (140 mg/m^2) and ASCT in 76 patients. The results were remarkably

similar for CR (89% vs. 88%), 5-year FFTF (79% vs. 75%), and OS (87% vs. 86%) [84].

In summary, there is no evidence to support the use of high-dose consolidation at first remission in HL at present.

10.2.2.7 Risk-Adapted Regimens Based on PET

Response to treatment for classical HL (cHL) is assessed by positron emission tomography–computed tomography (PET/CT) at end of treatment (EOT). Negative PET/CT is associated with a 10% or lower likelihood of relapse [85]. Interim PET/CT after one or two cycles of ABVD or similar regimens is also highly predictive of outcome [86, 87].

Three recent clinical trials have utilized PET/CT to determine if negative PET after or during treatment will identify a population of early-stage patients with non-bulky disease who can safely be treated with ABVD alone (Table 10.4). The Randomized Phase 3 Trial to Determine the Role of FDG-PET Imaging in Clinical Stages IA/IIA Hodgkin lymphoma (RAPID) found high rates of 3-year PFS among patients who were PET-negative after three cycles of ABVD, regardless of whether they received IFRT or no further treatment (90.8% vs. 94.6%; $P = 0.16$) [88]. Though the PFS rate for chemotherapy alone was excellent, non-inferiority criteria were not met when compared with addition of IFRT; OS did not differ between groups, as the 22 patients who relapsed without further IFRT were successfully treated with salvage therapy. Of note, 5 of the 22 received only radiation therapy as a salvage treatment, and only 7 of 22 received chemotherapy followed by ASCT. Negative PET was defined as a Deauville score of 1–2 (FDG uptake less than mediastinal blood pool).

Another phase 2 trial confirmed an excellent PFS for most patients treated with a short course of ABVD alone. CALGB 50604 treated patients with stages I/II non-bulky cHL with two cycles of ABVD. Interim PET/CT was performed and centrally reviewed. Patients whose interim PET/CT was negative, defined as Deauville scores of 1–3 (FDG uptake less than liver), received two more cycles of ABVD (total four cycles) and no irradiation (135/149; 91%). Patients whose interim PET/CT was positive received two cycles of more intensive chemotherapy with escalated BEACOPP and IFRT to a dose of 3060 cGy (13/149; 9%). Estimated PFS was 91% at 3 years for the interim PET-negative group. The estimated 3-year PFS for the interim PET-positive group was significantly lower, at 66%, than for the interim PET-negative group ($P = 0.011$), suggesting that the intensive treatment regimen did not provide benefit [89].

Table 10.4 Salvage regimens in common use for recurrent/refractory Hodgkin lymphoma drugs

	Dose, mg/m^2	Route	Schedule
Dexa-BEAM			q. 21d
Dexamethasone	24 mg daily	Po	d1–10
Carmustine	60	Iv	d2
Etoposide	250	Iv	d4–7
Cytarabine	100 bd	Iv	d4–7
Melphalan	20	Iv	d3
DHAP			q. 21d
Dexamethasone	40 mg daily	Iv	d1–4
Cytarabine	2000 bd	Iv	d2
Cisplatin	100	Ivi	d1
ESHAP			q. 21d
Etoposide	40	Iv	d1–4
Cytarabine	2000	Iv	d5
Cisplatin	25	Ivi	d1–4
Methylprednisolone	500 mg daily	Iv	d1–5

Table 10.4 (continued)

	Dose, mg/m^2	Route	Schedule
ICE			q. 21d
Ifosfamide	5000	Ivi	d2
Carboplatin	AUC 5	Iv	d2
Etoposide	100	Iv	d1–3
GDP			q. 21d
Gemcitabine	1000	Iv	d1 and 8
Dexamethasone	40 mg daily	Po	d1–4
Cisplatin	75	Iv	d1
GVD			
Gemcitabine	1000	Iv	d1 and 8
Vinorelbine	20	Iv	d1 and 8
Liposomal doxorubicin	15	Iv	d1 and 8
IGEV			
Ifosfamide	2000	Iv	d1–4
Gemcitabine	800	Iv	d1 and 4
Vinorelbine	20	Iv	d1 and 4
Prednisone	100	Po	d1–4
BeGEV			
Bendamustine	90	Iv	d2 and 3
Gemcitabine	800	Iv	d1 and 4
Vinorelbine	20	Iv	d1
Prednisone	100	Po	d1–4
BV-Benda			
Bendamustine	90	Iv	d1 and 2
Brentuximab vedotin	1.8 mg/kg	Iv	d1
BV-ESHAP			
Brentuximab vedotin	0.9–1.2–1.8 mg/kg	Iv	
Etoposide	40	Iv	d1–4
Cytarabine	2000	Iv	d5
Cisplatin	25	Iv	d1–4
Methylprednisolone	500 mg daily	Iv	d1–5
BV-DHAP			
Brentuximab vedotin	1.8 mg/kg	Iv	d1
Dexamethasone	40 mg daily	Iv	d1–4
Cytarabine	2000 bd	Iv	d2
Cisplatin	100	Iv	d1

The larger phase 3 H10 trial compared a similar interim PET-adapted approach to combined-modality therapy (CMT) for all patients [90]. Patients with early-stage cHL received two cycles of ABVD and underwent interim PET/CT. Interim PET-negative favorable patients in the PET-adapted arm received two more cycles of ABVD (total four) and no RT, while those in the CMT arm received one more cycle of ABVD (total three) and involved-node radiation therapy (INRT). Favorable patients who were interim PET-positive in the PET-adapted arm received two cycles of escalated BEACOPP and INRT, while those in the CMT arm received two more cycles of ABVD and INRT. Interim PET-negative unfavorable patients in the PET-adapted arm received four more cycles of ABVD (total six) and no RT, while those who were interim PET-negative in the CMT arm received two more cycles of ABVD (total four) and INRT. Interim PET-positive unfavorable patients in the PET-adapted arm received two cycles of escalated BEACOPP and INRT, while interim PET-positive patients in the CMT arm received two more

cycles of ABVD (total four) and INRT. Overall, in favorable and unfavorable groups together, this trial demonstrated a 5-year PFS benefit for a CMT regimen as compared with a PET-adapted regimen (91% vs. 77%; $P = 0.002$) [91]. The 5-year PFS for interim PET-negative patients in the favorable group was 87% for the PET-adapted arm versus 99% for the CMT arm. The 5-year PFS for interim PET-negative unfavorable patients was 90% for the PET-adapted arm versus 92% for the CMT arm. PFS favored CMT over PET-adapted treatment, and non-inferiority could not be demonstrated in the large number patients undergoing analysis.

In the recent HD16 randomized trial, early-stage favorable cHL patients received two cycles of ABVD + 20 Gy IFRT (control) or two cycles of ABVD plus PET, with PET-negative patients receiving no further treatment and PET-positive patients receiving 20 Gy IFRT (risk adapted). Following two cycles of ABVD only, PET-negative patients had a relapse rate of 10% at 5 year PFS, higher than those who received standard two cycle ABVD + 20 Gy IFRT [92].

These trials demonstrate a 5–10% higher relapse rate for 2–4 cycles of ABVD alone as compared with CMT for favorable early-stage cHL. Opinions differ as to whether it is more important to reduce the late risks of radiotherapy with chemotherapy only, given the excellent salvage options, or to provide a more optimal PFS with frontline treatment by adding radiotherapy to chemotherapy.

Four recent trials have employed interim PET after two cycles of chemotherapy to tailor treatment for patients with advanced-stage cHL. S0816, a phase 2 trial conducted by the US Intergroup, treated stage III and IV patients with two cycles of ABVD followed by interim PET/CT. Interim PET-negative patients received 4 more cycles of ABVD, while those who were interim PET-positive received two cycles of escalated BEACOPP. The estimated 2-year PFS was 82% for interim PET-negative patients and 64% for interim PET-positive patients. Of note, there were two treatment-related deaths (4%) among the 49 interim PET-positive patients who receive escalated BEACOPP [93].

The Response-Adapted Trial in Advanced Hodgkin Lymphoma (RATHL) treated patients with stages IIB, III, and IV and high-risk stage IIA with two cycles of ABVD followed by interim PET/CT. Patients who were interim PET-negative were randomized to treatment with four cycles of ABVD or four cycles of AVD without bleomycin. Patients who were interim PET-positive were treated with escalated BEACOPP or BEACOPP-14 depending on results of further interim PET/CT studies. For post-cycle 2 interim PET-negative patients, the 3-year PFS was 85.7% for the ABVD and 84.4% for the ABVD/AVD groups, respectively. For the interim PET-positive patients treated with BEACOPP, the 3-year PFS was 67.5%. These findings justify reducing exposure to bleomycin with its attendant pulmonary toxicity for patients with advanced-stage cHL who are interim PET-negative after two cycles of ABVD [52].

The HD18 trial administered two cycles of escalated BEACOPP to patients with advanced-stage cHL followed by interim PET. Patients who were interim PET-negative just received two more cycles of escalated BEACOPP and no additional radiotherapy. PET-positive patients after two cycles of escalated BEACOPP received a total of four or six additional cycles and radiotherapy to PET-positive residual disease. For PET-negative patients, 5-year PFS was 91.2% for 8/6 escalated BEACOPP and 91.8% for four escalated BEACOPP, and there was less toxicity in the latter group [94].

The LYSA AHL2011 trial randomized advanced-stage cHL patients to standard treatment with six cycles of escalated BEACOPP plus interim PET after two and four cycles or experimental treatment. In the experimental arm, treatment was initiated with two cycles of escalated BEACOPP. Following interim PET/CT, treatment was changed to four cycles of ABVD in interim PET-negative patients, while interim PET-positive patients continued four cycles of escalated BEACOPP. There was no significant difference in 4-year PFS between the standard (86.2%) and

experimental arms (85.7%). These results suggest that treatment can be safely de-escalated to ABVD for patients with advanced-stage disease who are PET-negative after two cycles of escalated BEACOPP (Casanovas O, Presentation USHL11, Cologne, October 29, 2018).

The goal of a PET-adapted approach, by starting with either BEACOPP escalated or ABVD, is to maintain efficacy and minimize long-term toxicities. Ideally, a more effective risk-allocation strategy would use novel biomarkers such as TARC or ctDNA, with or without baseline PET parameters such as total metabolic tumor volume (TMTV). Such a strategy would allow patients with highest-risk baseline features to receive the potential benefit of more-intensive initial therapy and would identify those for whom less-intensive or de-escalation strategies can be successfully applied.

10.2.2.8 Incorporation of Antibody-Drug Conjugate in Primary Treatment of Advanced-Stage cHL

Brentuximab vedotin (BV) is an anti-CD30-drug conjugate consisting a monoclonal antibody to CD30 linked to monomethyl auristatin E, a tubulin inhibitor. As a single agent in relapsed/refractory cHL, it achieves an overall response rate of 75% and a CR rate of 34%, which is at least twice as effective as any single conventional chemotherapy agent [16]. The ECHELON-1 trial was an open-label, multicenter randomized phase 3 trial of six cycles of standard ABVD versus six cycles of BV + AVD in newly diagnosed patients with stages III and IV cHL. The 2-year modified PFS was 77.2% for ABVD and 82.1% for BV + AVD ($P = 0.03$). This result led to approval of BV + AVD for this indication by the US Food and Drug Administration. Some subgroups seemed to particularly benefit from BV + AVD, and further analyses are being performed to better define these groups. Given cost and toxicity considerations, it is unclear, at least in the USA, whether BV + AVD will be adopted as a standard treatment for all patients with stages III and IV cHL or in particular subgroups [95].

10.3 Chemotherapy Treatment for Recurrent and Refractory Hodgkin Lymphoma

10.3.1 New Systemic Treatments

There have been relatively few new conventional cytotoxic agents developed recently for HL, but both monoclonal antibodies, immune therapies, and small molecule therapeutics targeting specific abnormal pathways in HL have shown some promising results.

Antibody therapies have been directed at relatively specific molecules, such as CD30 on the surface of Reed-Sternberg cells, but the results with an unconjugated anti-CD30 were discouraging, probably because it targets only a small proportion of the cells within a mass of lymphoma [96]. On the other hand, antibody-drug conjugates (ADC) have shown very promising results, with a response rate of 75% reported using brentuximab vedotin for patients with recurrent and refractory disease, as described in Sect. 10.2.1 [16].

Anti-CD20, given with the intention of targeting the infiltrating B cells and interrupting autocrine growth factor loops, has shown some promise in an early pilot study [97], but awaits confirmatory data from a prospective trial. This approach may find more application in the treatment of nodular lymphocyte predominant disease, in which CD20 is present on the surface of the malignant cells [98].

Among the small molecule therapies being tested, proteosome inhibitors have been disappointing in HL [99], whereas inhibitors of histone deacetylase (HDACi) have resulted in significant responses in early-phase studies, despite significant marrow toxicity [100]. It is not clear whether the principal target of HDACis is the malignant cell itself or the surrounding inflammatory infiltrate, but further studies using

a range of more- or less-specific agents targeting different members of the HDAC family may yield further information.

10.4 Conclusions

A variety of pharmacologic hypotheses have been tested in the course of the last 50 years, and none has been found entirely satisfactory for predicting the outcomes of treatment. The superiority of ABVD over MOPP is established. Similarly, the more effective multiagent BEACOPP regimen is being used in more and more countries and groups. There appears to be a potential trade-off between the intensity of chemotherapy and the value of consolidation radiotherapy in advanced disease: it is not clear whether any chemotherapy is intensive enough for radiation to be dropped altogether, but functional imaging holds promise for lowering the proportion of patients irradiated very significantly.

As treatment has evolved, the balance between toxicity and efficacy has been established, and new approaches using response-adapted therapy hold the promise of identifying the minority of patients for whom early intensification is a necessity, while allowing de-escalation of treatment in those destined to do well. The addition of brentuximab vedotin, the antibody-drug conjugate, has slightly improved efficacy in the treatment of stages III and IV HL. Finally, there are a small number of novel agents currently undergoing testing against recurrent and refractory disease which appear to hold some promise.

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Treatment of Early Favorable Hodgkin Lymphoma

11

Wouter Plattel and Pieternella Lugtenburg

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,

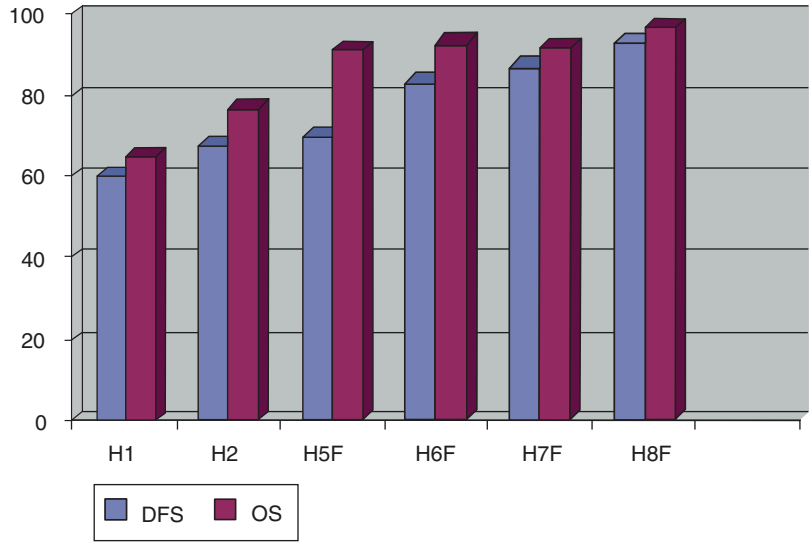

Fig. 11.1 Disease-free survival and overall survival in consecutive EORTC Lymphoma Group trials on early-stage favorable Hodgkin lymphoma (HL). *DFS* disease-free survival, *OS* overall survival

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

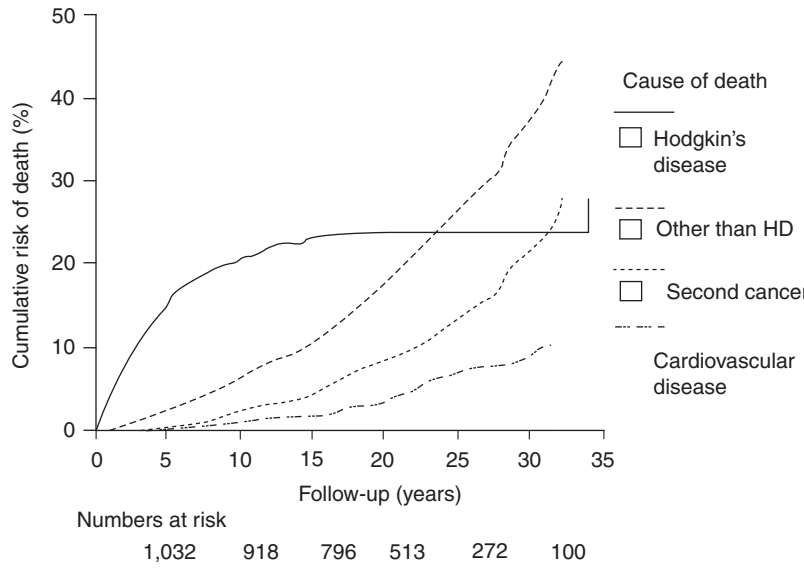

Fig. 11.2 The actuarial risks of death from major disease categories in 1261 Dutch HL patients. Data from Dutch database on Hodgkin lymphoma (Reprinted from Aleman et al. [25] with permission)

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.

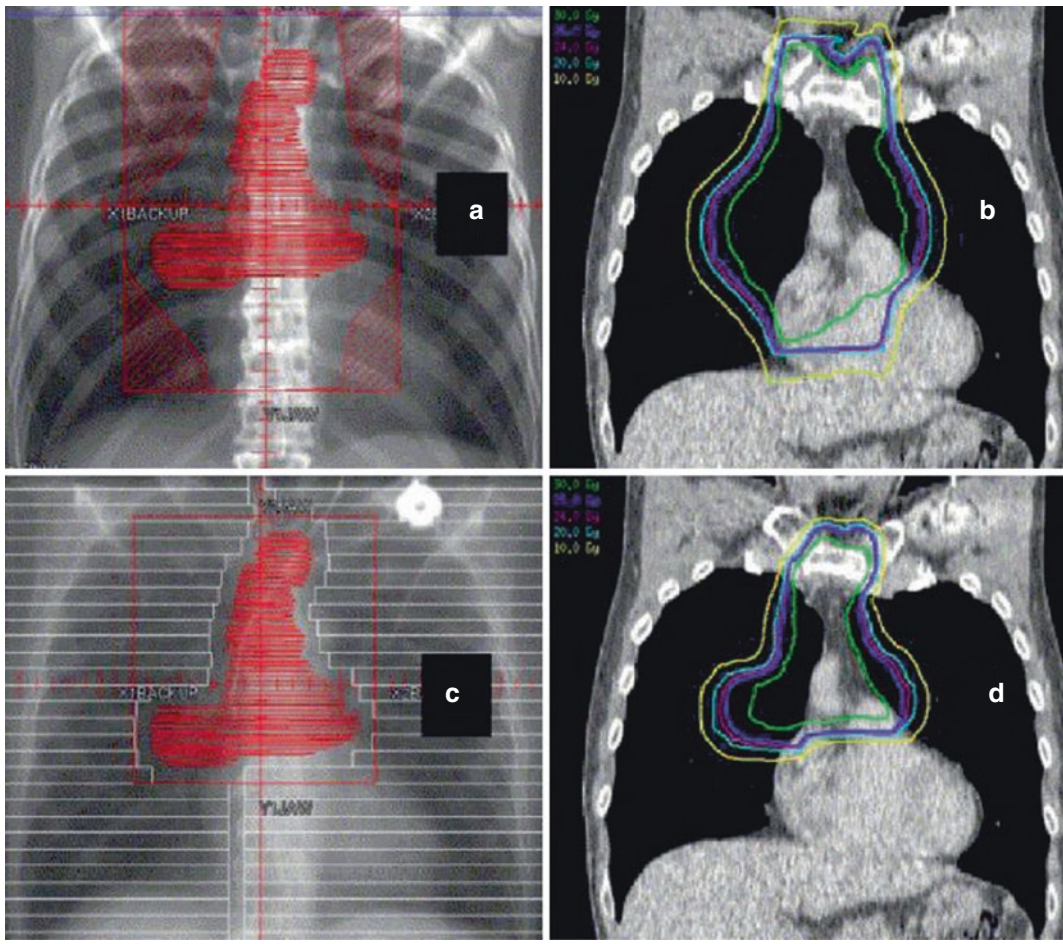

Fig. 11.3 Comparison between radiation field sizes and the volume of heart irradiation using either IFRT (**a**, **b**) or INRT (**c**, **d**) for a mediastinal tumor mass (PTV in red color) (Reprinted from Girinsky et al. [39] with permission)

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

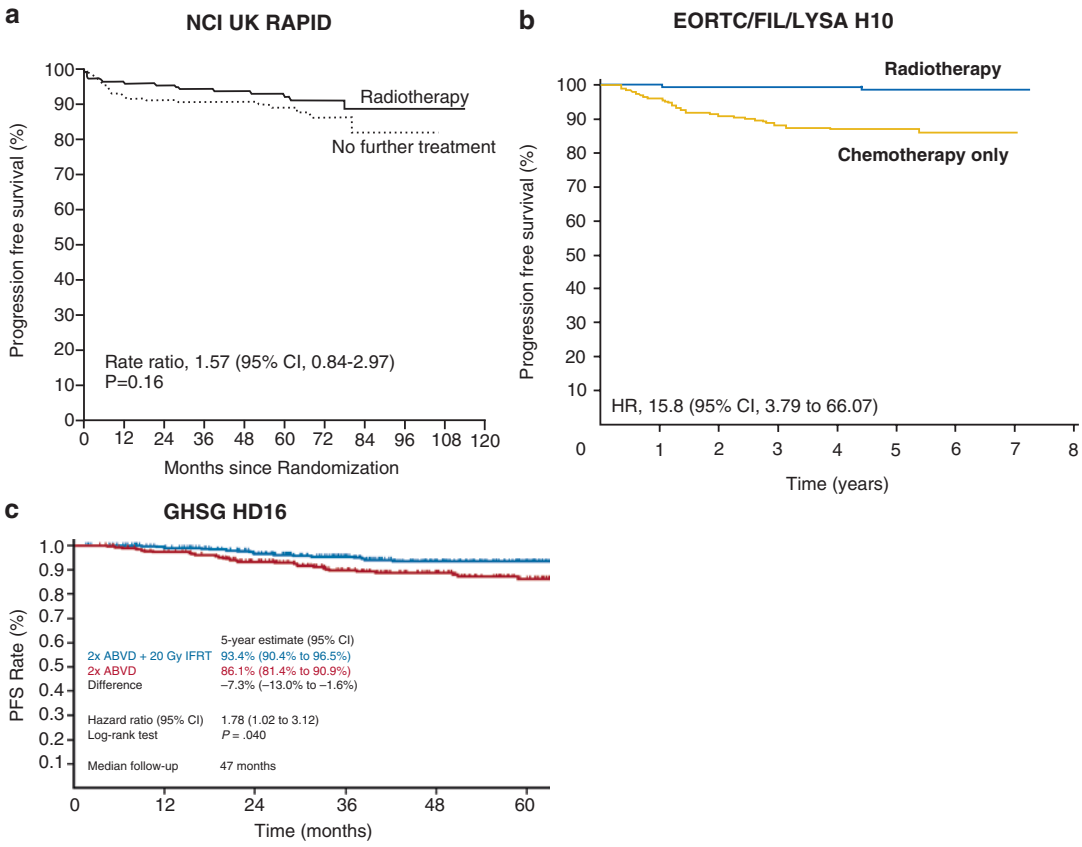

Fig. 11.4 Results of the recently published trials of PET adapted trials in early favorable Hodgkin lymphoma. Shown are progression-free survival curves for the UK RAPID trial (**a**), EORTC/LYSA/FIL H10 favorable (**b**) and GHSG HD16 (**c**)

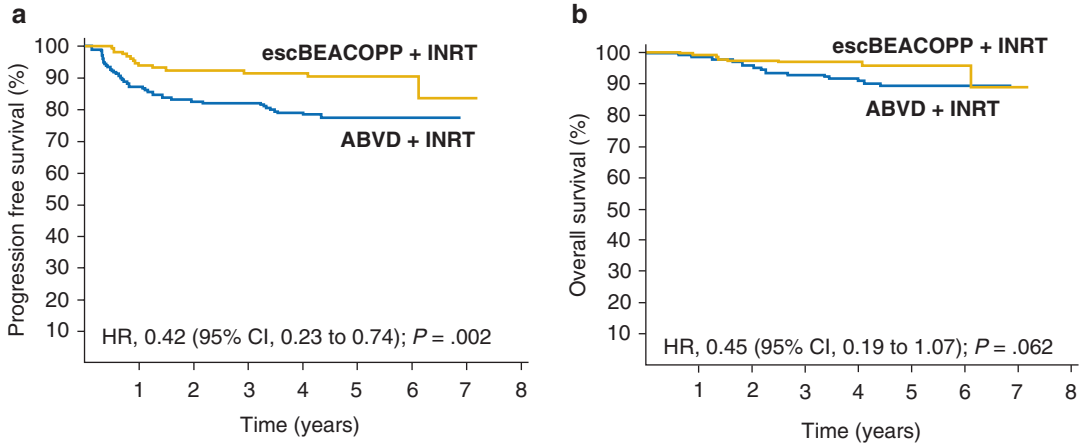

Fig. 11.5 Results of the EORTC/LYSA/FIL H10 trial in case of a positive FDG-PET scan after 2 ABVD among patients with both favorable and unfavorable early-stage HL. Shown are progression-free survival (**a**) and overall survival (**b**)

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.

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Treatment of Early Unfavorable Hodgkin Lymphoma

12

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Contents

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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

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_12

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

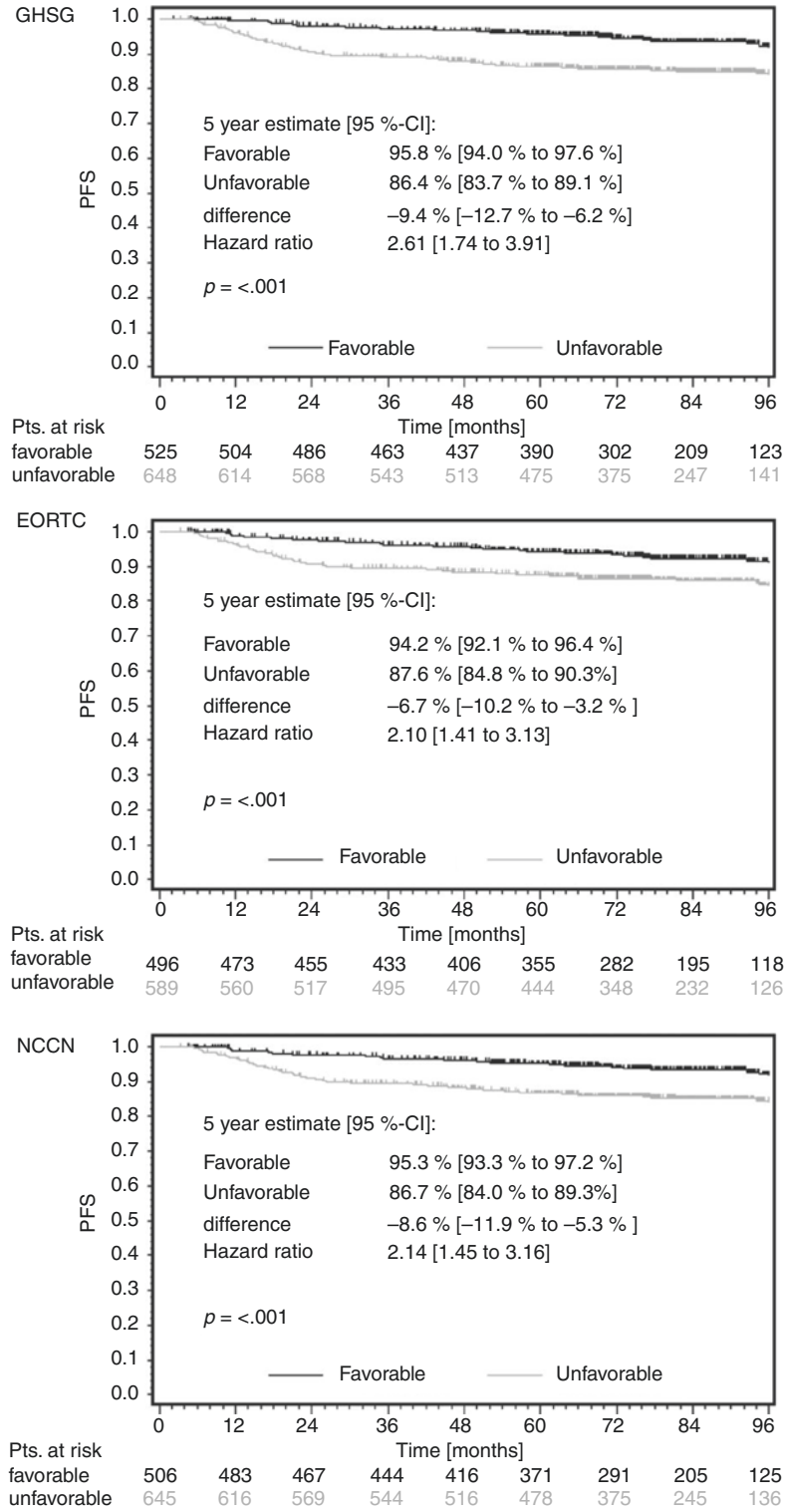

Fig. 12.1 Estimated progression-free survival using staging definitions of the German Hodgkin Study Group, the European Organization for Research and Treatment of Cancer (*EORTC*), or National Comprehensive Cancer Network (*NCCN*) [6]

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

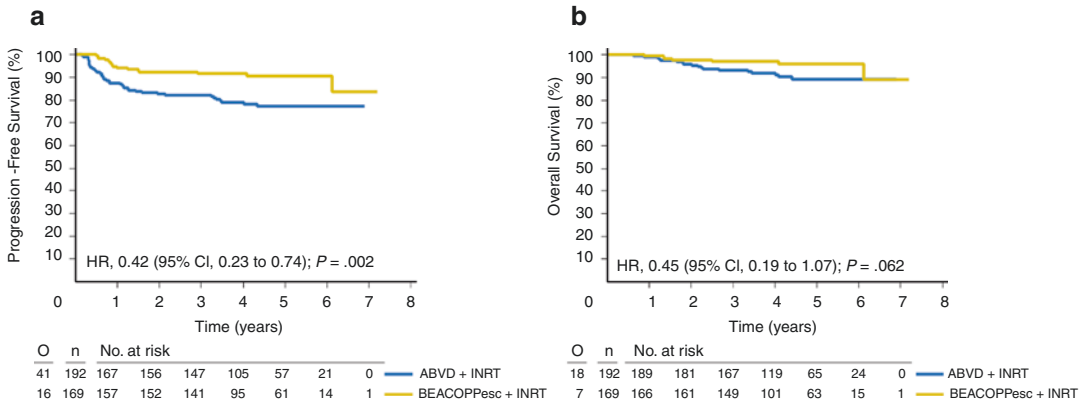

Fig. 12.2 PFS (**a**) and OS (**b**) of patients iPET positive patients included in the H10 trial. After 2xABVD patients were randomized between 2xABVD and 30 Gy INRT vs. 2xBEACOPPesc and 30 Gy INRT. Reprinted from André et al. with permission

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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Treatment of Advanced-Stage Hodgkin Lymphoma

13

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13.1 Introduction and Early History of Combination Chemotherapy

The definition of advanced stage in Hodgkin lymphoma (HL) has evolved over time. Megavoltage radiotherapy (RT) techniques proved efficacious in stage I and IIA disease in the 1950s and 1960s, whereas only few patients with stage III disease were cured by RT alone, despite extended fields of treatment [1]. At the

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_13

time, more than 95% of patients with stage IV HL succumbed to their disease within 5 years. The first encouraging trials on combination chemotherapy included patients with stages III and IV. Thus, from a historical perspective, advanced disease may be defined by risk groups where curative combination chemotherapy is planned as the primary treatment, while RT is either not used or not the major component. The definition of advanced disease has therefore varied between academic study groups and between trials. This should be borne in mind when evaluating treatment recommendations and results from trials. For most studies, stages IIB, III, and IV are considered advanced disease, while stage IIA is sometimes included, but only in the presence of other risk factors such as bulky disease or multiple sites of involvement.

With the advent of more exact diagnostic tools and targeted treatment, the distinction between classical HL (cHL) and nodular lymphocyte-predominant HL has become more robust and more important for treatment. The current chapter covers the development of treatment for cHL only, recognizing that in the past this distinction was not as clear as it is today.

The introduction by DeVita and coworkers of the MOPP regimen to treat patients with advanced HL was a milestone in oncology [2, 3]. MOPP resulted in long-term remission in nearly 50% of patients with stage III and IV disease and has been used for than 40 years. Bonadonna and coworkers were the first to report on the importance of anthracyclines in developing ABVD [4]. ABVD replaced MOPP as the preferred first-line treatment worldwide as the result of a series of randomized trials comparing ABVD, MOPP, and/or MOPP/ABVD alternating, sequential, or hybrid regimens [5–10]. The results were better for ABVD or ABVD-containing regimens than for MOPP alone, with failure-free (FFS) or event-free survival (EFS) rates at 5–10 years of 50–80% for ABVD-containing regimens, compared to 35.9% for MOPP in Bonadonna's original trial and 50% in the Cancer and Leukemia Group B (CALGB) trial reported by Canellos in 1992 (Table 13.1).

The acceptance of ABVD over MOPP and MOPP-like regimens during the 1980s and 1990s was not only motivated by its greater efficacy but also by concerns about toxicity. Follow-up of the early trials showed that irreversible gonadal dysfunction as well as acute leukemia occurred far

Table 13.1 MOPP and ABVD in randomized trials

Trial	Year	Combination regimen	Number of patients	Outcome	Follow-up and comments
Bonadonna et al. [5]	1986	MOPP/ABVD alternating	43	64.6% (FFP) 83.9% (OS)	8 years
		MOPP	45	35.9% (FFP) 63.9% (OS)	
Santoro et al. [6]	1987	3×MOPP-RT-3×MOPP	114	62.8% (FFP) 77.4% (OS)	7 years; (sub)total nodal irradiation in all patients
		3×ABVD-RT-3×ABVD	118	80.8% (FFP) 67.9% (OS)	
US Intergroup [7]	2003	ABVD (6 cycles)	433	63% (FFS) 82% (OS)	5 years; MDS and AML only in MOPP-treated patients
		MOPP/ABV hybrid (6 cycles)	419	66% (FFS) 81% (OS)	
Viviani et al. [8]	1996	MOPP/ABVD alternating (6 cycles)	211	67% (FFP) 74% (OS)	10 years; stage IB and IIA included
		MOPP/ABVD hybrid (6 cycles)	204	69% (FFP) 72% (OS)	
Connors et al. [9]	1997	MOPP/ABVD hybrid (8 cycles)	153	71% (FFS) 81% (OS)	5 years; radiotherapy or prolonged chemotherapy after cycle 6 for PR
		MOPP/ABVD alternating. (8 cycles)	148	67% (FFS) 83% (OS)	

(continued)

Table 13.1 (continued)

Trial	Year	Combination regimen	Number of patients	Outcome	Follow-up and comments
CALGB [10]	1992	ABVD	115	61% (FFS) 73% (OS)	5 years
		MOPP	123	50% (FFS) 66% (OS)	
		MOPP/ABVD alternating	123	65% (FFS) 75% (OS)	

Abbreviations: *CALGB* Cancer and Leukemia Group B, *GHSG* German Hodgkin Study Group, *FFS* failure-free survival, *FFP* freedom from progression, *FFTF* freedom from treatment failure, *OS* overall survival, *MDS* myelodysplastic syndrome, *AML* acute myelogenous leukemia

more often in patients treated with MOPP and MOPP-like regimens. With improved control of the lymphoma, there was an increasing need to balance the likelihood of cure and the risk of serious or fatal complications from treatment. This balance has since been a key concept in the development of better treatment options for advanced-stage cHL.

ABVD is a safe outpatient regimen without the need for close white blood cell monitoring, is feasible in most adult patients up to the age of 60, and can be administered in less-developed healthcare systems [11]. However, bleomycin may cause fatal lung toxicity, especially in older patients, and a long-term higher risk of cardiac morbidity has been reported for patients treated with 6–8 cycles of ABVD [12, 13]. Furthermore, Canellos and coworkers reported the long-term outcome for 123 patients treated with ABVD for advanced cHL in the CALGB trial with a FFS of only 47% and overall survival (OS) 59% after 14 years [14]. Therefore, alternative approaches were developed to improve these results.

13.2 Fourth-Generation Regimens

13.2.1 Hybrid and Alternating Regimens

Several academic groups developed combination regimens containing different drugs with known efficacy in HL, and many of these fourth-generation regimens were tested in randomized trials against ABVD [15–22]. According to standards of the time, most of these trials used consolidation RT as part of first-line treatment in a varying proportion of patients (Table 13.2). None of these studies has established any regimen as superior to ABVD, with the notable exception of the BEACOPP escalated regimen developed by the German Hodgkin Study Group (GHSG).

13.2.2 BEACOPP Escalated

The development of BEACOPP was motivated by the recognition that dose intensity plays a role in chemotherapy of advanced HL. Hasenclever and coworkers developed a statistical model of dose-response characteristics for drugs used in 706 patients treated with COPP (cyclophosphamide, vincristine, procarbazine, prednisone)/ABVD-like regimens [23]. The model was then used to simulate the effect of dose escalation and changes of schedule and architecture of COPP-ABVD and to design the BEACOPP regimen. G-CSF was mandatory to compensate for the myelotoxic effects. In a phase II study, the optimal doses of the BEACOPP baseline and BEACOPP escalated regimens were determined [24]. The subsequent HD9 trial of the GHSG found the predicted dose-response curve to be correct when comparing the original COPP/ABVD to BEACOPP baseline and BEACOPP escalated [20]. Results from 1195 randomized patients showed a clear superiority of 8 cycles of BEACOPP escalated over BEACOPP baseline and COPP/ABVD at 5 years. Importantly, follow-up data at 10 years confirmed these results: with a median follow-up of 112 months, freedom from treatment failure (FFTF) and OS rates were 64 and 75% in the COPP/ABVD group, 70 and

Table 13.2 Fourth generation trials

Trial	Year	Combination regimen	Number of patients	Outcome	Follow-up and comments
GHSG HD6 [15]	2004	COPP/ABV/IMEP hybrid (4 cycles)	223	54% (FFTF) 73% (OS)	7 years
		COPP/ABVD alternating (4 cycles)	245	56% (FFTF) 73% (OS)	
Intergroup Italy [16]	2005	ABVD (6 cycles)	122	78% (FFS) 90% (OS)	5 years; radiotherapy to initial bulk and residual mass
		Stanford V (12 weeks)	107	54% (FFS) 82% (OS)	
		MOPPEBVCAD (6 cycles)	106	81% (FFS) 89% (OS)	
UK Lymphoma Group LY09 [17]	2005	ABVD (6–8 cycles)	394	75% (EFS) 79% (FFP) 90% (OS)	3 years; stages I and II included
		ChlVPP/EVA (6–8 cycles)	112	77% (EFS) 84% (FFP) 89% (OS)	
		ChlVPP/PABlOE (3–4 cycles alternating)	282	74% (EFS) 78% (FFP) 87% (OS)	
UK and Italy [18]	2002	ChlVPP/EVA hybrid (6 cycles)	144	82% (FFP) 78% (EFS) 89% (OS)	5 years; radiotherapy to initial bulk and residual mass
		VAPEC-B (11 weeks)	138	62% (FFP) 58% (EFS) 79% (OS)	
UKNCRI [19]	2009	ABVD (6–8 cycles)	261	76% (PFS) 90% (OS)	5 years; radiotherapy to initial bulk and splenic deposits; stage I and II disease included
		Stanford V	259	74% (PFS) 92% (OS)	
GHSG HD9 [20]	2003	COPP/ABVD alternating (8 cycles)	260	69% (FFTF) 83% (OS)	5 years; radiotherapy to initial bulk and residual mass
		BEACOPP baseline (8 cycles)	469	76% (FFTF) 88% (OS)	
		BEACOPP escalated (8 cycles)	466	87% (FFTF) 91% (OS)	
GHSG HD12 [21]	2011	BEACOPP escalated (8 cycles)	836	86.4%(FFTF) 92% (OS)	5 years; second randomization to radiotherapy (initial bulk or residual disease) versus observation
		BEACOPP escalated and baseline (4 + 4)	834	84.8% (FFTF) 90.3% (OS)	
GHSG HD15 [22]	2012	BEACOPP escalated (8 cycles)	705	84.4% (FFTF); 91.9% (OS)	5 years; radiotherapy to PET positive residuals only
		BEACOPP escalated (6 cycles)	711	89% (FFTF) 95.3% (OS)	
		BEACOPP-14 (8 cycles)	710	85.4% (FFTF) 94.5%/(OS)	

Abbreviations: *UKNCRI* United Kingdom National Cancer Research Institute Lymphoma Group, *GHSG* German Hodgkin Study Group, *FFS* failure-free survival, *FFP* freedom from progression, *FFTF* freedom from treatment failure, *EFS* event-free survival, *PFS* progression-free survival, *OS* overall survival

80% in the BEACOPP baseline group, and 82 and 86% in the BEACOPP escalated group, respectively [25].

However, BEACOPP escalated is associated with higher rates of acute and long-term toxicity. The high rate of secondary malignancies, including myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) and solid cancers, and high rates of infertility could be attributed to the higher doses of alkylating agents and the frequent use of RT in the HD9 trial [20, 25]. The subsequent GHSG HD12 trial aimed at de-escalating treatment by comparing four courses of BEACOPP escalated with four courses of escalated and four courses of baseline BEACOPP ("4+4") [21]. The role of RT was tested by a second randomization of consolidating radiation to initial bulky and residual disease versus no RT. At 5 years, OS was 91%, FFTF 85.5%, and progression-free survival (PFS) 86.2% with no statistical difference between 8 cycles of BEACOPP escalated and the 4+4 arm but no apparent benefit in terms of toxicity with the reduced regimen. Because a number of patients randomized to the arm without RT were in fact irradiated based on recommendations by a blinded expert panel, the conclusions to be drawn from this part of the trial are limited. Since there was no relevant benefit in terms of toxicity in the 4+4 treated patients, 8 cycles of BEACOPP escalated remained standard for advanced-stage HL patients in the GHSG. Recent long-term updates of both the HD9 and 12 trials confirm the superior initial results for BEACOPP escalated [26].

The subsequent HD15 study also tested de-escalation of chemotherapy with a reduction in the number of cycles from 8 to 6 and the introduction of a dose-dense BEACOPP baseline regimen (BEACOPP-14) [22]. In addition, PET-guided omission of RT to residual disease was investigated. A total of 2182 patients were randomized among the 3 study arms. Surprisingly, when comparing 6 cycles of BEACOPP escalated with 8 cycles, both PFS (90.3% versus 85.6%) and OS (95.3% versus 91.9%) were significantly better with the reduced number of cycles. With omission of RT in cases of PET-negative residual masses, only 11% of all patients received additional RT without compromising tumor control, and the negative predictive value for the end of treatment PET at 12 months was 94.1% [27]. In summary, HD15 established six cycles of BEACOPP escalated as a new standard of care to be tested further in PET response-adapted trials (see below).

With extensive evidence from clinical trials, BEACOPP escalated is a highly effective regimen for patients with advanced HL. Acute toxicity requires monitoring of patients between cycles, hospitalization in around one third of patients, and vigilance for potentially lethal neutropenic infections. Special attention should be paid to patients above the age of 50 years and patients of poor performance status at start of treatment. With the reduction of cycle numbers and less use of consolidation RT, rates of secondary malignancies seem to be decreasing, but determining the true rate of such complications will need longer observation [26]. Infertility in both women and men treated with BEACOPP is still a concern [28].

13.3 ABVD or BEACOPP Escalated as Standard First-Line Treatment?

These developments led to the emergence of two alternative strategies for the treatment of advanced HL: balancing cure rates and toxicity, the first strategy proposed ABVD as the standard front line regimen, with salvage treatment, high-dose chemotherapy (HDCT), and autologous stem cell transplantation (ASCT) for those patients failing initial therapy. With this strategy, the majority of patients could be cured with ABVD without exposing them to the toxicity of BEACOPP. The second strategy used BEACOPP escalated as first-line treatment, aiming to cure as many patients as possible with first-line therapy, but accepting more toxicity for those patients who might have been cured with a less intensive approach. Data are now available from direct comparative trails and from meta-analyses to address this question.

Table 13.3 ABVD versus BEACOPP in direct comparisons

Study	Year	Combination regimen	Number of patients	Disease control	*p*	Overall survival	*p*	Follow-up and comments
HD 2000 [29]	2009	ABVD	99	68% (PFS)	0.038*	84%	ns	5 years
		BEACOPP (4 esc +2 bas)	98	81%		92%		
		CEC	98	78%		91%		
Michelangelo-GITIL-IIL [30]	2011	ABVD	168	73% (FFFP)	0.004	84%	ns	7 years; salvage treatment specified
		BEACOPP (4 esc + 4 bas)	163	85%		89%		
EORTC 20012 IPS 3–7 [31]	2016	ABVD (8 cycles)	275	72.8% (PFS)	0.005	86.7%	ns	4 years; EFS primary endpoint
		BEACOPP (4 esc + 4 bas)	274	83.4%		90.3%		
LYSA H34 IPS 0–2 [32]	2014	ABVD	77	75% (PFS)	0.007	92%	0.06	5 years
		BEACOPP (4 esc + 4 bas)	68	93%		99%		

Abbreviations: *GITIL* Gruppo Italiano di Terapie Innovative nei Linfomi, *IIL* Intergruppo Italiano Linfomi, *LYSA* Lymphoma Study Association *EORTC* European Organization for Research and Treatment of Cancer, *IPS* International Prognostic Score, *CEC* cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, bleomycin, *FFFP* freedom from first progression, *EFS* event-free survival, *PFS* progression-free survival, *p* p-value for comparison, *esc* escalated, *bas* baseline
**BEACOPP* versus ABVD

Four studies have been conducted comparing these two approaches, all smaller and so far with shorter follow-up than the HD9 trial. All studies compare four escalated BEACOPP followed by two or four baseline BEACOPP with six to eight cycles of ABVD (Table 13.3).

The Italian HD2000 trial enrolled 307 patients in 3 different treatment arms showing a significant superiority of BEACOPP (4+2 fashion) over 6 cycles of ABVD in terms of PFS but not for OS [29]. At 5 years, the PFS rate was 68% for ABVD and 81% for BEACOPP: OS was 84% for ABVD and 92% for BEACOPP, respectively. The data of this trial were updated at 10 years follow-up, and the authors were not able to confirm the superiority of BEACOPP over ABVD in terms of PFS, mainly because of higher mortality from second malignancies observed after BEACOPP [33].

The Michelangelo Foundation, the Gruppo Italiano di Terapie Innovative nei Linfomi (GITIL), and the Intergruppo Italiano Linfomi (IIL) study compared 6–8 courses of ABVD and BEACOPP given in 4+4 fashion plus preplanned salvage with HDCT [30]. Patients with a higher risk profile based on international prognostic score (IPS) of 3 and more were included. Two thirds of the patients also received RT. The final analysis showed a 7-year rate of freedom from first progression (FFFP) of 85% in patients who received initial treatment with BEACOPP and 73% for those who received ABVD ($p = 0.004$). A total of 65 patients (20 in the BEACOPP group and 45 in the ABVD group) needed HDCT. After completion of the planned treatment including salvage therapy, the 7-year OS rates were 89 and 84%, respectively ($p = 0.39$). This trial was not powered to detect differences in OS, and the conclusion on overall treatment outcome should be cautioned.

The slightly larger intergroup trial organized by the EORTC had a similar design as the Michelangelo-GITIL-IIL study [31]; 8 courses of ABVD were compared to BEACOPP 4+4 with no RT allowed. With a median follow-up of 3.6 years at the time of the final report, the 4-year rates for EFS and OS were similar in ABVD-treated (63.7% and 86.7%, respectively) and BEACOPP-treated patients (69.3% and 91.5%). However, the secondary endpoint, PFS, was significantly lower in the ABVD than in the BEACOPP arm (72.8% versus 83.4%, $p = 0.0052$). There were no clear differences in toxicity between the two arms.

Patients with low-risk advanced-stage disease (IPS 0–2) were enrolled in the H34 trial conducted by the Lymphoma Study Association (LYSA) [32]. With 150 patients randomized in

this trial, the complete remission rate was 85% for ABVD and 90% for BEACOPP. With a median follow-up of 5.5 years, 7 patients died: 6 treated with ABVD and 1 with BEACOPP. The PFS at 5 years was 75% and 93% ($p = 0.007$) and the OS 92% and 99% ($p = 0.06$) for ABVD- and BEACOPP-treated patients. Although the number of patients recruited in this trial was rather small, these results suggest that BEACOPP is also more effective than ABVD in advanced-stage patients with lower risk.

All trials comparing ABVD and BEACOPP directly are smaller than the GHSG trials and evaluated different numbers of BEACOPP escalated (4+4 or 4+2, escalated, and baseline, respectively). 6 cycles of escalated BEACOPP have been shown by the GHSG to represent the most effective strategy. Since there was uncertainty regarding the difference in OS between ABVD and BEACOPP, a network meta-analysis was performed to indirectly compare these and other regimens [34]. The final analysis included nearly 10,000 patients from 14 different trials. Reconstructed survival data suggested that 6 cycles of BEACOPP escalated have a 10% advantage over ABVD in terms of OS at 5 years (95% confidence interval 3–15%), offering advanced-stage HL patients the highest chance of cure. Another more recent meta-analysis with data from four of the trials mentioned above (and including one trial comparing ABVD and BEACOPP in early unfavorable disease) confirmed the superiority of BEACOPP escalated over ABVD in term of PFS and OS [35]. There was a significantly increased occurrence of MDS or AML in BEACOPP-based strategies (relative risk 3.90, $p = 0.02$), but not for second malignancies in total. The risk of infertility could not be assessed by these meta-analyses due to lack of data.

13.4 Outcome Prediction

13.4.1 The International Prognostic Score

With the choice between ABVD and BEACOPP, it would be preferable to treat each advanced cHL patient according to their individual risk in order to balance efficacy and toxicity. The development of the IPS paralleled the quest for more effective regimens than ABVD and was aimed to further assess each patient's risk of treatment failure under ABVD- and ABVD-like regimens [36].

The score was derived from 5141 patients who had been treated with ABVD-like regimens with or without RT. Seven factors had similar independent prognostic effects: serum albumin of less than 4 g/dL, hemoglobin level of less than 10.5 g/dL, male sex, age of 45 years or older, stage IV disease (according to the Ann Arbor classification), leukocytosis (white cell count of at least 15×10^{-9} L), and lymphocytopenia (lymphocyte count of less than 0.6×10^{-9} or less than 8% of white-cell count). As outlined, several studies evaluating BEACOPP escalated have selected patients not only based on stage and B symptoms, but also on a higher IPS. It is assumed that the more intensive treatment will have the greatest effect in high-risk patients. This is in part supported by the results of the HD9 trial, where the absolute benefit in terms of improved OS in those treated with BEACOPP escalated seems greater in intermediate risk than in low-risk patients, although not in the high-risk group [25]. The LYSA H34 results in low-risk patients suggest a significant 18% benefit in PFS rates and a borderline significant improvement in OS of 9%, both at 5 years, but this requires confirmation [32].

13.4.2 Positron Emission Tomography

Assessment of the risk of treatment failure by IPS has been partly displaced by early response evaluation. To determine the optimal amount of treatment needed, functional imaging in the form of FDG-PET has been developed to provide an early indication of chemosensitivity in HL. PET is discussed in detail elsewhere in this book (see Chap. 7). In patients with mostly advanced disease, retrospective studies showed that the early PET response (after two cycles of ABVD) overshadowed the prognostic value of the IPS and thus could be an important tool for response-

adapted treatment planning in advanced HL [37]. The utility of FDG-PET has been facilitated by development of a highly reproducible 5-point scale, the Deauville scale, for reporting results [38].

Several recent studies have tested early response evaluation by FDG-PET as a means of adjusting subsequent therapy according to the response to initial treatment. Strategies based on initial ABVD or BEACOPP have helped to define new standards of care in which each patient receives as much therapy as deemed necessary.

13.5 Response-Adapted Therapy

13.5.1 De-escalation of Therapy in Early Responders

Groups using either ABVD or BEACOPP as initial therapy have aimed to reduce treatment intensity in patients with a negative interim PET, by omitting potentially toxic components of the regimens, by reducing the number of cycles, or by omitting RT (Table 13.4).

In the international RATHL trial, all patients initially received two cycles of ABVD [39].

Table 13.4 Response adapted therapy in randomized trials

Study	Year	Upfront regimen	Number of patients	%PET-2 negative/ positive	PFS	OS	Follow-up and comments
RATHL [39]	2016	ABVD	1203	86 DS 1-3	85% (ABVD) 84.4% (AVD)	97.2% 97.6%	3 years; ABVD vs AVD in PET-2 negative disease
				16 DS 4-5	67.5% (BEACOPP)	87.8%	BEACOPP escalated/-14 in PET-2 positive disease
GITIL/ FIL0607 [40]	2018	ABVD	782	81 DS 1-3	87% (ABVD)	99%	3 years; with or without RT in bulky PET-2 negative disease
				19 DS 4-5	63% (R-BEACOPP) 57% (BEACOPP)	89%	BEACOPP with or without R in PET-2 positive disease
GHSG HD18 [41]	2016	BEACOPP esc	275	52 DS 1-2	92.2% (4×BEACOPPesc)	97.7%	5 years; 6–8 vs 4 cycles BEACOPP escalated in PET-2 negative disease
					90.8% (6–8×BEACOPPesc)	95.4%	
				48 DS 3-5	88.4% (R-BEACOPPesc)	93.6%	BEACOPP escalated with or without R in PET-2 positive disease
					89.7% (BEACOPPesc)	96.4%	
LYSA AHL2011	2018	BEACOPP esc	823	87 DS 1-3	89.4% (ABVD)	96.4%	5 years; modified Deauville criteria for PET-2, OS similar in PET-driven and standard arm
				13 DS 4-5	88.4% (BEACOPPesc)	99%	

Abbreviations: *RATHL* Response adapted therapy in Hodgkin lymphoma, *GITIL/FIL* Gruppo Italiano Terapie Innovative Linfomi/Fondazione Italiana Linfomi, *LYSA* Lymphoma Study Association, *GHSG* German Hodgkin Study Group, *PFS* progression-free survival, *OS* overall survival, *DS* Deauville score, *PET-2* PET scan performed after 2 cycles of therapy, *BEACOPPesc* BEACOPP escalated, *R* Rituximab

Using a Deauville score cut-off between 3 and 4, 83.7% of the patients were interim PET negative and were randomized. In the experimental arm, bleomycin was not given in the remaining four cycles. The results showed 3-year PFS rates of 85.7% and 84.4%, respectively, in the standard ABVD and AVD groups. Pulmonary toxicity was reduced in patients treated with AVD in cycles 3 through 6. Thus, bleomycin is redundant in advanced-stage patients who have achieved a complete metabolic response after two cycles of chemotherapy.

In patients with advanced HL who have a negative PET, defined as Deauville scores 1–3, after two and six cycles of ABVD, the GITIL/Fondazione Italiana Linfomi (FIL) HD0607 trial demonstrated that consolidation RT to initially bulky lesions can be omitted without a decrease in tumor control at 3 years [40]. The 3-year PFS was 87% in the interim PET-negative group.

The proportions of interim PET-negative patients in the RATHL and GITL/FIL HD0607 studies and 3-year PFS rates are remarkably similar. They are comparable to other prospective phase II trials using the same approach [42, 43]. However, the negative predictive value of interim PET-CT in these prospective trials appears lower than anticipated from previous retrospective studies using non-standardized criteria for reporting PET results. This means that the largest number of treatment failures in advanced-stage HL treated initially with ABVD will occur in the interim PET-negative group.

Interim PET-CT has also been used to de-escalate therapy in early responders to BEACOPP escalated. Using the FDG uptake in the mediastinal blood pool as reference, corresponding to Deauville scores of 1 and 2, the randomized GHSG HD18 trial demonstrated that the number of cycles of BEACOPP could be reduced from six to four in patients with a negative interim PET after two cycles [41]. With 1005 out of 1945 randomized patients (52%) having a negative interim PET by these criteria, the HD18 trial indicated an excellent 5-year OS rate of 95% and a significant reduction of severe acute hematological and non-hematological toxicities. The GHSG later provided post hoc evidence that the excellent outcome of PET-negative patients also holds for those with an interim Deauville score of 3, and despite the fact that these had all received six cycles of BEACOPP escalated in the trail, a total of four escalated BEACOPPs to patients with an interim score of 1–3 are currently recommended [44].

The randomized LYSA AHL2011 trial evaluated whether a PET-driven strategy allows for a tailored shift from BEACOPP escalated to ABVD in advanced HL [45]. In the experimental arm, patients with a negative PET after two cycles of BEACOPP escalated completed treatment with four cycles of ABVD, while the interim PET-positive patients continued with four cycles of BEACOPP escalated. Patients assigned to the standard arm received a total of six cycles of BEACOPP escalated. After a median observation time of 50 months, 5-year PFS rates did not differ, 86.5% and 85.7% in the standard and experimental arms, respectively. Using a Deauville score cut-off between 3 and 4 in the experimental arm, 84% of patients received 2 escalated BEACOPP and 4 ABVD with a significant reduction in toxicity. Thus, it appears possible to switch to ABVD on the basis of a negative interim PET after two cycles of escalated BEACOPP without loss of tumor control. By extrapolation from the RATHL study, it may be possible to switch to AVD and thereby avoid the risk of continued bleomycin exposure. The LYSA AHL2011 used a modified Deauville score for assessment of interim PET-CT defining score 4 and 5 as a residual lesion uptake equal or higher than 140% and 200% of the liver uptake, respectively. These more stringent criteria may explain the lower rate of interim PET-positive patients in the AHL2011 (12.6%) than in the HD18 trial (24%) and the higher treatment failure rate in the PET-positive group in AHL2011 compared to HD18 study.

13.5.2 Escalation of Therapy in Early Nonresponders

Several groups tested prospectively the approach of escalating treatment in patients not responding to two cycles of ABVD as defined by PET posi-

tivity (Table 13.4). With the limitations mentioned above, based on the historical data, these patients have a very poor outcome with ABVD or ABVD-like therapy. The 2- or 3-year PFS is reported between 6% and 38% [46]. Most investigators have therefore considered it unethical in these patients to compare any experimental therapy to ABVD in a randomized fashion.

The RATHL trial tested the escalation to either BEACOPP escalated four cycles or BEACOPP-14 six cycles in interim PET-positive patients [39]. Of the 182 patients with positive findings on interim PET-CT scans according to protocol, 94 received BEACOPP-14 and 78 received escalated BEACOPP. The results of a third PET-CT scan were available for 160 patients, of whom 119 (74.4%) had negative findings. The 3-year PFS rate for the group as a whole was 67.5%, and the OS rate was 87.8%.

Similar results were reported in the GITIL/FIL HD0607 trial [40]. 149 of 150 patients with interim PET-positive results continued on BEACOPP (4 escalated and 4 baseline) with or without the addition of rituximab. After four BEACOPP escalated, a PET evaluation was performed in 136 patients. At the time of the report, disease progression was registered in 27 of 108 PET-negative scans compared with 25 of 28 PET-positive scans. The 3-year PFS rate was 60%, and the 3-year OS rate was 89% in the interim PET-positive group.

The American South West Oncology Group (SWOG) followed the same principles of escalating to six cycles of BEACOPP escalated after ABVD with similar results for the interim PET-positive group compared to RATHL and GITIL/FIL HD0607 trials [42]. Escalation to an alternative regimen consisting of ifosfamide, gemcitabine and vinorelbine (IGEV) followed by HDCT was pursued in the Italian HD0801 study [43]. In an intention-to-treat analysis, the authors reported for the PET-positive patients (excluding those with Deauville score 3) a 2-year PFS of 75%.

Taking together the shift from ABVD to BEACOPP escalated or variants thereof seems justified in interim PET-positive patients. Whether other salvage regimens including HDCT might improve the outcomes further is unknown at present. Nonetheless, the results remain suboptimal, and further improvements, possibly by incorporation of novel drugs, are needed.

Following the success with initial BEACOPP escalated in the HD9, HD12, and HD15 trials, the GHSG tested whether it might be possible to improve the results by adding rituximab, a monoclonal antibody binding to CD-20 on the surface of B cells, in patients with interim PET-positive disease [47]. The rationale is derived from the recognition of a minority of cHL cases with CD-20-positive Hodgkin or Reed-Sternberg cells and the possible benefit of targeting normal B cell in the tumor microenvironment. In the HD18 trial, patients with interim PET-positive disease (Deauville score 3–5) after two cycles of escalated BEACOPP were randomized to six further cycles with or without rituximab. The PFS rates at 3 years for PET-positive patients were 93.0% and 91.4% with or without rituximab, respectively, better than expected from the previous HD15 trial and without any benefit of adding rituximab.

Patients with an interim Deauville score 4 (post hoc analysis of HD18) or 4–5 (LYSA AHL2011) after 2 BEACOPP escalated have reduced PFS rates compared to interim PET-negative patients with a score of 1–3. As mentioned, a later post hoc analysis of the HD18 study showed that in patients receiving 6 cycles of BEACOPP escalated, 3-year PFS rates were 92.2%, 95.9%, and 87.6% with interim PET scores of 1–2, 3, and 4, respectively [44]. The univariate hazard ratio (HR) for PFS in patients with score 4 versus score 1–3 was 2.3 ($p = 0.002$). Deauville score of 4 was the only factor remaining significant for PFS in a multivariate analysis including the associated baseline risk factors. In the LYSA AHL 2011 trial, using more stringent definitions of Deauville score 4 and 5, interim PET positivity was associated to a higher risk of relapse or progression with 5-year PFS of 70.7% versus 88.9% and a HR = 3.59 ($p < 0.0001$). Whether these results for interim PET-positive patients after initial BEACOPP therapy can be improved, i.e., by the incorporation of novel drugs, has not been tested yet.

The concept of response-adapted therapy in advanced-stage HL has considerably changed the way in which patients are treated. Unfortunately, there is no direct comparison of strategies starting with ABVD and escalating in poor responders versus starting with BEACOPP escalated and reducing treatment in the early responders.

13.6 Introduction of Brentuximab Vedotin into First-Line Treatment

With the approval of brentuximab vedotin (BV) for relapsed and refractory disease (see Chap. 21), a novel targeted drug has been introduced into the treatment of cHL. This has shown an excellent balance of efficacy and tolerability in persistent or recurrent disease [48]. Therefore, BV is an ideal candidate to improve both the ABVD and the BEACOPP regimens.

BV was initially combined with ABVD in a phase I study; however, life-threatening pulmonary toxicity in this bleomycin-containing combination was observed [49]. BV at a fixed dose (1.2 mg/kg body weight) was given safely with bleomycin-deleted AVD (given the name A+AVD, as Adcetris, the proprietory name for BV) to 26 patients. 25 of the 26 (96%) had complete response after treatment. Neuropathy, probably as a result of coadministration of two microtubule-disrupting agents (monomethyl auristatin E and vinblastine), neutropenia and complications thereof, including the need to add growth factors in a number of patients, were noted as relevant toxicities. In a recent update on long-term outcome, the 5-year FFS and OS were 79% and 92% after ABVD plus BV and 92% and 100% after A+AVD, respectively [50].

After the initial encouraging results with A+AVD, this regimen has been tested in a large company-sponsored trial, comparing the new regimen to ABVD [51]. Patients with stage III and IV disease were entered and interim PET-CT after two cycles guided an optional switch to alternative frontline therapy at the treating physician's discretion, but only for patients with a Deauville score of 5. The primary endpoint was modified PFS, defined as time to disease progression, death, or modified progression (with the latter defined as evidence of non-complete response after completion of frontline therapy according to review by an independent committee, followed by subsequent anticancer therapy). With 1334 randomized patients and a median follow-up of 24.6 months, the 2-year modified PFS rates in the A+AVD and ABVD groups were 82.1% and 77.2%, respectively, a difference of 4.9 percentage points ($p = 0.04$). There was higher rate of febrile neutropenia in the A+AVD group, and growth factor support was introduced as mandatory during the course of the trial. There was also more severe neuropathy in the experimental arm, but as reported for other BV trials, this appeared to be reversible in most patients. As expected from the omission of bleomycin, lung toxicity was reduced. These results produced a debate as to whether A+AVD should be accepted as a new standard of care. Follow-up is short, and the new endpoint, incorporating into the definition of progression any treatment given to patients with residual PET-positive disease (Deauville scores 3–5), hampers comparison with other trials. With a modest difference between treatment arms, increased toxicity, and the absence of a documented survival benefit, the same principles as in the debate over ABVD and BEACOPP will apply. Another consideration is the considerable drug cost of BV and expense of the necessary growth factors.

An interesting aspect of the Echelon-1 trial is the prospective less stringent approach to PET-guided adaptation, where patients with an interim PET-CT of 4 or 5 were either planned to continue treatment with A+AVD or ABVD (Deauville score 4) or allowed to do so as an alternative to intensive chemotherapy (Deauville score 5). The data thus reflect the outcome of ABVD-treated interim PET-positive patients in the modern era, using PET-CT in a prospective way and with uniform criteria comparable to other studies [52]. PET positivity rates were strikingly lower than in other similar studies, with Deauville ≥4 found in 7% (47/644) in the A+AVD arm and 9% (58/670) with ABVD; 5 patients with a Deauville score of 5 switched to alternative frontline therapy. Subgroup analyses of the ABVD arm showed a

2-year modified PFS rate of 80.9% versus 42.0% for interim PET-negative and PET-positive patients, respectively.

Following the aim to improve tolerability while maintaining efficacy, the GHSG has modified the BEACOPP regimen and introduced BV. A randomized phase II trial testing six cycles of two variants of BEACOPP was published recently: in one arm, vincristine was replaced by BV and bleomycin omitted (BrECAPP) [53]. A more experimental regimen additionally replaced dacarbazine for procarbazine and short-term dexamethasone instead of long-term prednisone (BrECADD). 104 patients were enrolled to the study (52 were assigned to each study arm). Complete responses were seen at completion of BrECAPP and BrECADD in 86% and 88% of patients, respectively. Particularly, the BrECADD regimen was associated with a more favorable toxicity profile and therefore selected for comparison to standard BEACOPP escalated in advanced cHL in the ongoing HD21 trial (NCT02661503). This trial is testing 4/6 cycles of escalated BEACOPP (in a PET response-adapted design) against 4/6 cycles of BrECADD.

13.7 Introducing Programmed-Death-1 Inhibitors into First-Line Treatment

The second class of drugs recently introduced for relapsed and refractory cHL is the checkpoint inhibitors targeting programmed-death receptor (PD) 1, on the surface of cells in the microenvironment of cHL. It appears that Hodgkin and Reed-Sternberg cells by expression of the PD-ligand (PD-L)-1 and PD-L2 orchestrate the tissue microenvironment for tumor survival and growth (reviewed in Chap. 22). These mechanisms seem to be operable also in previously untreated cases [54]. Studies are underway to explore the effect of PD-1 inhibition also in the context of first-line treatment of advanced disease. So far, no results are reported. An initial study using nivolumab as sole initial therapy prior to the addition of AVD showed a response rate of 69% for monotherapy and promising short term outcomes, with PFS of 92% at 9 months [55].

13.8 The Role of Radiotherapy

The use of RT in advanced-stage HL has evolved over time, from subtotal or total nodal RT (i.e., treating also areas of initial possible microscopic disease) to involved-field RT (i.e., treating only areas of initial macroscopic disease) or as RT in situations associated with a higher risk of local relapse (most often site of initial bulky lesions or residual macroscopic disease possibly representing active tumor). The role of consolidation RT for advanced HL also depends on the efficacy of the prior chemotherapy (see Chap. 9 for further details).

After MOPP or MOPP-like regimens, there appeared to be a potential advantage of IFRT in a meta-analysis of 16 randomized studies, whereas this advantage is not evident after ABVD or ABVD-like regimens [56, 57]. A randomized EORTC study demonstrated that consolidation IFRT did not improve outcomes in patients in complete remission after six to eight courses of MOPP-ABV, but potentially improved the outcome of patients with a partial response [58]. A randomized Groupe d'Etude des Lymphomes de l'Adulte (GELA) trial showed that consolidation with subtotal or total nodal RT for patients in remission after doxorubicin-containing systemic treatment was not superior to two additional cycles of chemotherapy [59]. Thus, patients achieving a complete radiological response with ABVD or ABVD-like regimens do not need consolidation RT.

In current treatment algorithms, the chemosensitivity and quality of remission in each individual patient are assessed by FDG-PET, either as an interim PET during or a PET done at the end of treatment. PET results may be especially helpful in assessing the need for consolidation in situations with residual fibrotic masses after chemotherapy. The GITIL/FIL HD0607 trial randomized patients with advanced HL with a large nodal mass at diagnosis (≥5 cm) and a negative PET after two and six cycles of ABVD to RT of the site of the initial large mass or observation alone [40]. In 296 randomized patients, there was no significant PFS improvement at 3 years, 97% versus 93%, respectively ($p = 0.29$). Together, patients treated with ABVD that are in

complete remission by radiological criteria or PET negative after two cycles can safely omit RT, even in presence of residual masses. Whether certain patients with residual masses that are PET negative at the end of treatment (in the absence of any interim PET) or patients with interim or end of treatment positive PET in the context of ABVD benefit from the addition of RT has not been analyzed systematically.

The HD15 trial prospectively analyzed the omission of RT in cases of PET-negative residual masses after six or eight cycles of BEACOPP [27]. All patients with residual disease of ≥2.5 cm after chemotherapy were evaluated using additional PET and based on the criteria at the time; those with a PET-positive result were irradiated to the site of residual disease. Only 11% of all patients received additional RT without compromising tumor control, and the negative predictive value for the end of treatment PET at 12 months was 94.1%. PFS at 4 years was similar for patients without residual disease and patients with PET-negative residuals, 92.1% and 92.6%, respectively, showing that RT can be safely omitted in both situations. PFS for PET-negative or PET-positive patients was 92.6% and 86.2% at 48 months (p = 0.022). Thus, a positive PET after chemotherapy was associated with higher risk of subsequent treatment failure, even though PET-positive patients were treated with additional RT. The frequency and pattern of relapses still suggest that local RT to PET-positive residual disease is sufficient for these patients [60].

13.9 Summary

Advanced-stage HL has become a curable disease for the majority of patients, and treatment decisions need to take into account the risk of serious long-term consequences of therapy. After a decade of debate whether first-line treatment with six to eight cycles of ABVD or BEACOPP escalated best balances the likelihood of cure and risk of complications, individualized treatment based on early response to chemotherapy has now become a standard in many developed countries. Starting with ABVD, de-escalation by omission of bleomycin and/or RT is possible in interim PET-negative patients. In case of an inadequate response, a shift to BEACOPP escalated may still cure a reasonable number of patients, subjecting only a minority of patients to the increased toxicity associated with BEACOPP. Similarly, the total number of cycles can be reduced from six to four or therapy switched to four ABVD in patients with interim negative PET results after two cycles of BEACOPP escalated. RT can be safely omitted in BEACOPP-treated patients with an end of treatment negative PET. With still short follow-up, the OS in either approach is excellent, with the interim PET-positive group after ABVD representing a candidate group for implementation of novel approaches. Apart from these more personalized treatment strategies, early results from a combination of BV with AVD show modest improvements in disease control but increased toxicity and costs. BV is also tested in the context of a modified BEACOPP regimen to enhance tolerability. After decades of substantial but slow advances in the treatment of advanced-stage HL, personalized treatment strategies have resulted in better treatment options for our patients. Targeted and immunological approaches may improve results further in the near future.

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Optimizing Decision Making in Hodgkin Lymphoma

14

Susan K. Parsons, Joshua T. Cohen, and Andrew M. Evens

Contents

14.1 Treatment Choices and Individualized Care

Hodgkin lymphoma (HL) is one of the best curable cancers, particularly when presenting as early-stage disease [1–3]. Although outcomes differ by age, cure rates exceed 80–85% across most stages and ages. Despite these overall excellent outcomes, there is no clear consensus regarding treatment recommendations across age groups, and individual patients, with regard to several treatment options, including which chemotherapy regimen to use, the optimal number of chemotherapy cycles, and the role of sequential adjunctive radiation therapy (RT) [1, 2, 4–13]. Furthermore, choices and debate over therapeutic

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_14

options have further expanded to include if and how to integrate and use early/interim positron emission tomography (PET) therapy to guide treatment (i.e., response-adapted therapy), as well as the optimum integration of novel therapeutics into frontline therapy [6, 14–17].

14.2 Treatment-Related Late Effects and Associated Human Cost

Critically, because the majority of newly diagnosed HL patients are young (median age 35 years) [18], curing disease can come at considerable "human cost," including treatment-related toxicities and late effects (LE) (e.g., secondary malignant neoplasms [SMN], cardiovascular disease [CVD]) and potential loss of young lives. The incidence of CVD and SMN rises exponentially >20–30 years after treatment. Results from analyses led by Dutch investigators and others have shown that the risk of SMNs do not appear to differ or be significantly lower over consecutive time periods [19–21]. Both Ng et al. [15] and Castellino et al. [18] have highlighted increased mortality among long-term HL survivors, although both of these studies reflect the impact of historical treatment approaches, including extended field radiotherapy.

Additionally, cost-per-death analyses also have shown that HL has the *second highest cost per death or lost productivity cost*, behind only malignant melanoma [22]. Further, productivity analyses of cancer mortality have shown HL to be the second most costly cancer in terms of lost lifetime earnings [23]. In addition to economic consequences, HL survivors also experience significantly compromised health-related quality of life (HRQL) due to LEs [24].

14.3 Risk, Impact, and Variability of Treatment-Related Late Effects

The risk of SMN depends on many clinical factors (e.g., age at exposure, sex, stage) as well as several treatment-related factors (e.g., chemotherapy [type and number of cycles] and RT [dose and field]). A recent Dutch analysis highlighted the impact of radiation dose and field, sex, and smoking on the risk of breast, lung, and other cancers [19]. Studies have investigated the impact of age and sex on the development of solid cancers after treatment for HL [25] and the impact of sex and type of treatment (i.e., anthracycline chemotherapy ± radiation) on the incidence of major cardiac disease [26, 27]. However, it is not possible to use current population-level findings to reliably predict outcomes of alternative therapies for specific, individual patients and hence contribute to fully informed decision-making.

14.4 Paucity of Harmonized Data to Guide Providers and Patients Towards Individualized Treatment Choices

Helping clinicians assess and navigate alternative HL treatment options for individual patients poses substantial challenges. First, ideal information is not available. Often, empirical data for contemporary therapies is limited to relatively short-term follow-up with differences in initial risk and response criteria driving therapy and limited information about the risk and severity of treatment-related LEs. While follow-up data from previous treatment eras offer insights [28], treatment changes and improvements over time limit the relevance of existing information. Second, the benefits and risks of different therapies depend in part on individual characteristics, such as patient age and sex, among other factors. A recent HL position paper by Travis and Ng et al. recommended development of comprehensive risk prediction models for LEs to customize treatment strategies [29].

There is a need to harmonize individual patient data across age groups from recent trials and existing datasets while establishing a data repository that facilitates incorporation of future data. The past 15 years have seen publications of several clinical trials involving many pediatric and adult HL patients with early-stage and advanced-stage disease [3, 30]. However, each study exam-

ined a slightly different HL question and most used different treatments. The result was a range of distinct findings and hence a wide range of therapeutic choices (Table 14.1).

Over the past 10 years, most HL studies worldwide have integrated PET-response-adapted designs, an approach that directs the type and/or amount of therapy based on PET scan results (positive vs. negative) early during the patient's treatment course, usually after two chemotherapy cycles [16, 33]. These PET-response-adapted data have significantly expanded the range of treatments that providers and patients must consider in assessing treatment options for individual HL patients.

Taken together, there remains a multitude of unanswered questions, especially for individual HL patients, as exemplified by the index case example above, including: (1) What is the efficacy of alternative treatments, and how do individual patient and disease characteristics influence efficacy? (2) What is the HRQL impact of each treatment option? (3) What are the incidence and severity of LEs (absolute risk for different SMNs and/or CVD), and how do these outcomes depend on treatment, individual patient characteristics, and disease characteristics? (4) How does "real-world" HL data inform treatment decisions in light of patient preferences?

Table 14.1 HL case example

A 29-year-old female presents with increasing size and number of lymph nodes and fatigue. Biopsy shows nodular sclerosis HL. PET staging shows non-bulky disease in right neck/supraclavicular, right hilum, and bilateral axillary (i.e., stage IIA unfavorable). Past family history includes father with myocardial infarction at age 50.
Based on HL clinical study results, multiple valid alternative treatment options exist for this common case presentation, including:
– ABVD × 4–6 cycles (dependent on CT response) without RT (NCI-C) [4, 5]
– ABVD × 3 with PET-based decision on RT (i.e., none for CR) (RAPID) [6]
– ABVD × 4 cycles + RT based on PET (with escalation to escalated BEACOPP for PET-2 positivity) (EORTC H10) [14, 15]
– 2 ABVD + 2 escalated BEACOPP + RT (GHSG HD14) [15]
– ABVD × 2 with PET-2 and then ABVD × 2 (PET negative) and BEACOPP × 2 (PET positive) CALGB 50604 [31]
– 2 ABVD with PET-2 and then AVD × 6 (PET negative) or BEACOPP × 6 (PET positive) RATHL [32]

14.5 Disease Classification and Prognostication

In adults, "early-stage" HL is often subdivided into two categories designated "favorable" and "unfavorable," with the distinction made on the basis of clinical factors and blood test results [3]. However, there are several different classifications that have been developed and studied over the past 20 years in prospective HL clinical studies. The criteria used by the German Hodgkin Study Group (GHSG) and the European Organization for Research and Treatment of Cancer (EORTC) differ with regard to several factors, such as number of nodal groups. Furthermore, the "nodal maps" differ, reflecting differences between GHSG and EORTC clinical studies [14, 15, 34, 35]. In addition, clinical studies conducted in North America have utilized different criteria to delineate early-stage disease, and some HL clinical trials have not separated early-stage patients into different groups [4, 5]. These staging definition differences can influence the treatment patients receive and their outcomes. Advanced disease has generally been classified as Ann Arbor stage III and IV, but clinical trials have often included patients with high-risk stage II disease, such as those with B-symptoms, involvement at multiple sites, and/or bulky disease. The inclusion criteria have often varied on a study-by-study basis, leading to substantial patient heterogeneity across HL studies.

Pediatric oncology research groups in the United States and across the world have used different criteria than adult groups use to categorize HL patients [10, 36]. While both pediatric and adult groups rely on the Ann Arbor classification system for staging, risk stratification has varied within these risk groups. For example, some adult studies classify patients with stage IIB disease with bulk as having early-stage disease, while pediatric trials currently designate patients as having advanced-stage disease based on inferior outcomes. Similarly, application of adult criteria would classify pediatric patients with stage IIIA disease as having advanced disease even though

these patients have had superior outcomes compared to other pediatric subgroups (e.g., stage IIIB, IVA, IVB). Some pediatric trials do not include these patients in advanced-stage studies, but, rather, designate them to be at "intermediate" risk.

Prognosis in adult advanced-stage HL as defined by the International Prognostic Index (IPS) in 1998 includes measurements of albumin, hemoglobin, sex, ages >45 years, stage IV, and the presence of leukocytosis or lymphocytosis [37]. HL patients with higher IPS scores had inferior treatment outcomes and were thus identified as potentially requiring more intensive therapy. The British Columbia Cancer Agency (BCCA) conducted an updated analysis of the IPS that showed that the utility of the IPS was altered [38]. In this analysis, the 5-year freedom from progression (FFP) ranged from 62% to 88% and 5-year OS ranged from 67% to 98% with a much narrower range of outcomes for patients ages <65 years (FFP ranging from 70% to 88% and 5-year OS ranging from 73% to 98%). Furthermore, in a multivariate regression analysis, which controlled for all IPS factors, only age and hemoglobin level retained independent significance.

Notably, no new and more comprehensive prognostic models have been developed for HL (early stage or advanced stage) in more than 20 years. Because age is an integral component of the original IPS, attempts have been made to develop and validate a child-specific prognostic score, known as CHIPS (Childhood Hodgkin International Prognostic Score) [39]. The original testing found that several factors were independent predictors of event-free survival (EFS), including stage IV, large mediastinal mass, low albumin, and fever. Further validation in other cohorts of children and adolescents with advanced disease is underway.

14.6 Simulation Modeling

Statistical and simulation modeling offers a rigorous approach to systematically and explicitly incorporate assumptions and information based on multiple data sources to explore how alternative treatments affect outcomes of interest, including LEs, survival, and quality-adjusted survival. Collectively, harmonization of independent patient data from large, international prospective studies and prominent cancer registries, along with development of common data standards, will establish robust "patient-specific" disease progression and LE probabilities that may be harnessed for dynamic decision-making tools with the expectation of ultimately improving outcomes across pediatric and adult HL.

Decision models have proved useful in connection with other diseases when treatment options involve trade-offs, and the risks and benefits can vary substantially, depending on patient characteristics. Here, we review the models developed to evaluate measures to either help prevent or treat two conditions: (1) lung cancer and (2) diffuse large B-cell lymphoma (DLBCL).

14.6.1 Low-Dose CT Scan for Lung Cancer

The National Lung Screening Trial (NLST) demonstrated that for patients at high risk for lung cancer mortality, low-dose computed tomography (LDCT) reduces lung cancer mortality by 20 percent compared to screening by conventional chest X-ray [40]. Cost-effectiveness analysis revealed that compared to no screening, LDCT accrues 0.02 quality adjusted life years (QALYs) per person screened at an incremental cost of $1631 [41]. The corresponding cost-effectiveness ratio suggesting an outlay of $81,000 per QALY gained represents "good value" relative to contemporary benchmarks for the United States [42].

Nonetheless, there remains the possibility that more narrowly targeted selection of the population to be screened would accrue even greater benefits and, hence, achieve a more favorable cost-effectiveness ratio. Kovalchik et al. [43] reported that after ranking the NLST population by estimated lung cancer mortality risk, screening prevented one lung cancer death for every 5276 individuals in the lowest-risk quintile, but that it achieved the same benefit for every 161 screened among the highest-risk quintile. The risk function developed by Kovalchik et al. therefore offers an approach for reducing the amount of screening needed to achieve the same mortality reduction.

Kumar et al. [44] investigated the efficiency of targeting individuals at even higher risk for lung cancer mortality than the NLST population as a

whole. Using a different risk model than Kovalchik et al., Kumar et al. reported similar efficiency gains for reducing lung cancer mortality. Screening top decile individuals yielded a nearly eightfold gain in averted deaths per person screened, compared to screening of individuals in the bottom decile. Assessment using other outcome measures yielded less impressive efficiency gains. For life years gained, the benefit per person screened was 3.6 times greater for top mortality risk decile individuals, compared to the bottom decile. For quality-adjusted life year gains (QALYs), the corresponding ratio was 2.4. Finally, the cost-effectiveness of screening improved across the risk deciles by an even smaller relative margin, from $75,000 per QALY gained in the lowest-risk decile to $53,000 per QALY gained in the highest-risk decile, a ratio of approximately 1.4.

The broad range of efficiency gains for different outcome measures illustrates both the strengths and limitations of risk targeting. When the targeting criterion—lung cancer mortality risk, in this case—matches the outcome measure, targeting vastly improves efficiency. On the other hand, when the outcome measure is less tightly related to the targeting measure, potential efficiency gains can decrease. Kumar et al. note, for example, that in the NLST cohort, higher-risk individuals were older, had greater smoking exposure, and were more likely to have a preexisting diagnosis of chronic obstructive pulmonary disease [44]. Because the characteristics making these individuals "high risk" also reduce life expectancy, targeting is less effective at maximizing life year gains. Likewise, mortality risk is inversely associated with future quality of life and positively associated with higher future care costs. Those factors further mitigate the efficiency gains from mortality risk targeting measured in terms of QALY gains and cost-effectiveness.

14.6.2 Diffuse Large B-Cell Lymphoma (DLBCL)

Because there are multiple treatments for patients with DLBCL, and because treatments vary in terms of their intensity and side effects, an accurate prognosis is crucial to identifying a course of care that appropriately accounts for a patient's risks and benefits.

In recent decades, clinicians have relied on the International Prognostic Index (IPI) to characterize risk [45]. The IPI produces a risk score ranging from 0 to 5 based on a series of dichotomized risk factors, including age (less than 60 vs. 60 or older), number of extranodal sites (0–1 vs. 2 or more), Ann Arbor stage (I or II vs. III or IV), lactate dehydrogenase levels (not elevated vs. elevated), and Eastern Cooperative Oncology Group performance status (2 or less vs. greater than 2). Incorporation of additional prognostic characteristics has improved the prognostic accuracy of the IPI, but limitations remain, including the dichotomous characterization of inputs and the tool's semi-qualitative characterization of risk that does not specify probabilities for key outcomes such as mortality.

To address these limitations, Biccler et al. [45] developed a model to predict overall survival and event-free survival as a function of both categorical characteristics (e.g., sex, Ann Arbor stage, presence or absence of B symptoms, among others) and continuous values (e.g., log leukocyte count, hemoglobin level, among others). The prediction reflects a weighted average of statistical models, with weights selected to maximize prediction accuracy.

The authors have made the model available on the Internet (https://lymphomapredictor.org/). The results show overall survival (compared to background survival) and event-free survival, both of which are projected over a period of five years. Because this model incorporates fine-grained individual characteristics and reports outcome probabilities over time, it represents a substantial improvement over earlier prognostic tools. Nonetheless, it has two key limitations. First, its projections are limited to a period of five years. That limitation reflects the extent of the follow-up in the population data used to build the model. Second, the model does not describe how alternative treatments influence outcomes. While clinicians and patients may infer that higher risks warrant more intensive treatment, the model does not quantify the resulting trade-offs.

Altogether, trade-offs, in the form of adverse events and resource costs, are common. Typically, these downside impacts do not depend on the size

of the potential benefit. The size of the potential benefit, and hence the magnitude of the net benefit, often depends on how big the baseline risk is. As a result, targeting individuals at highest risk for disease or severe outcomes often increases efficiency. The effectiveness of this strategy depends on the strength of the association between the risk stratification measure and the benefit measure. Prognostic risk models can help clinicians and patients weigh treatment alternatives, but these models can be limited by their time horizon and the extent to which they incorporate the impact of alternative therapies.

14.7 Decision Models in Hodgkin Lymphoma (HL)

Given the varying treatment approaches and their trade-offs relative to disease control and LE risks and the impact of individual patient characteristics, such as gender and age at the time of exposure, there has been considerable interest in the development of decision models for newly diagnosed HL. Our initial model of early-stage HL utilized published, group-level data from recent clinical trials to estimate simulated short-term and long-term outcomes [46]. We began with the development of a detailed disease map (Fig. 14.1), which highlights the *health states* through which a patient can move once diagnosed with HL. Based on best available information, we estimated the probability of transitioning from one health state to the next and the HRQL of each health state in the form of utility weights.

To test the model, we created two hypothetical cases that differed with regard to gender, disease location, and extent of disease. We then compared the projected outcomes (life expectancy and QALYs) for each patient for each of two treatment modalities—chemotherapy alone and combined modality therapy [46]. Sensitivity analyses explored the impact on projected clinical outcomes of age at diagnosis and the assumed incidence and severity of late effects. The purpose of this initial model was not to identify which modality might be definitively superior to the other, but, rather, to illustrate that treatment recommendations should reflect patient factors,

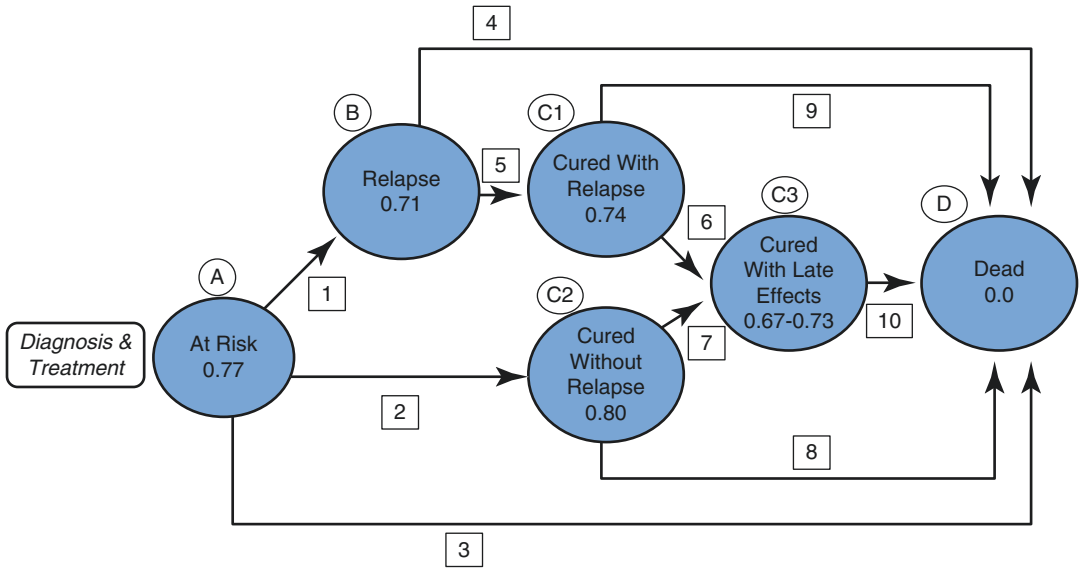

Fig. 14.1 Utility Weight Simulation Model: The State Transition Diagram. The bubbles represent individual health states. The value within each bubble is the utility weight (or health-related quality of life impact) of that health state. The arrows represent transition pathways between states. Scaling each year of survival by that year's utility weight (specified for each health state in the figure) and then summing the quality-adjusted years yields quality-adjusted survival

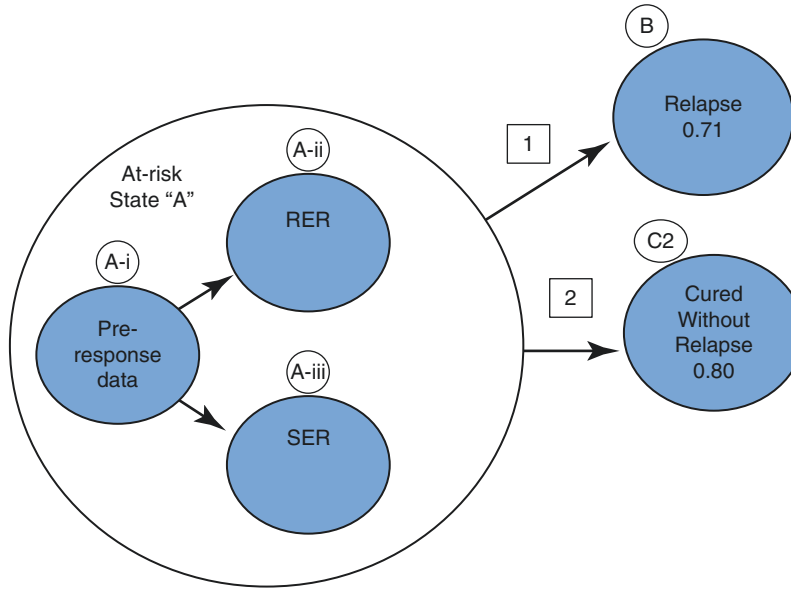

Fig. 14.2 The State Transition Diagram—therapeutic-response enhanced model. Individuals in State A can proceed to States B or C2. The transition rates depend on whether the patient experiences a rapid or slow response to initial therapy—i.e., whether the individual progresses from substate A-i to A-ii, or to A-iii

disease characteristics, and the outcome preferences of the patient and his/her provider.

Decision models such as these can also be adapted as new information becomes available. For example, consider the use of early PET-based response. In the figure below, we have added the PET-adapted response as a new health state (that is, rapid early response or slow early response) (Fig. 14.2). Because addition of this new health state requires revision of the probabilities downstream, such as risk of relapse, the revised decision model can be run to estimate updated clinical outcomes.

To extend this one step further, one could utilize this type of model as patients transition from one phase of care to another, namely, from active treatment to active surveillance or active surveillance to survivorship. By incorporating emerging information, patients and their providers can refine ongoing care needs and clarify areas of likely risk and uncertainty.

The development of these types of dynamic decision models requires individual patient data from large numbers of patients to account for differences across patients in terms of their demographic characteristics and disease factors. Moreover, model development depends on identifying data projecting the impact of contemporary treatment on short- and long-term outcomes, including toxicity, death, relapse, and LEs. Data must also be updated, as additional information becomes available (e.g., from new trials, or from further follow-up of existing trials) and as new therapies are introduced.

Critical to the implementation and dissemination of these tools is an understanding of how patients, caregivers, and providers would use such models in the real world, what concerns they have, what kind of decision support they need, and what outcomes they are interested in. As noted, our first version of the model estimated life expectancy and QALYs, but these outcomes can be modified to reflect what is salient and/or accessible to different stakeholders.

14.8 Conclusion

Given the success of frontline treatments and the ability to salvage the majority of HL patients after disease progression or recurrence, the overall survival of HL is high. However, this survival comes at a cost to patients in the form of LEs, which can alter both the length and quality of survivorship. To reduce downstream LE risk, modifications have been made in frontline therapy, including: changes in indications for radiation, reduction in radiation dose and field among those

receiving treatment, risk stratification to determine need for either dose reduction or dose escalation to optimize outcomes, and incorporation of novel agents, initially in the salvage setting and more recently in frontline therapy.

Through data sharing and international collaboration, including across pediatric and adult specialties, we can create robust and nimble decision models to guide our patients and their families, alongside their providers, to enhance and optimize the difficult decisions that affect acute and long-term outcomes.

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Part III

Special Clinical Situations

Pediatric Hodgkin Lymphoma

15

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_15

15.1 Introduction

15.1.1 Comparison of Pediatric/Adolescent Vs. Adult HL

Pediatric/young adult Hodgkin lymphoma (HL) is one of the few childhood malignancies that shares aspects of its biology and natural history with an adult cancer. Historically, children were thought to have a worse prognosis than adults due to antiquated treatment approaches that were initially designed to mitigate toxicities in children. It is now clear that effective therapy provides similar or even superior outcomes in children/young adults. A comparison of the demographics of clinical presentations of pediatric/adolescent HL compared with adult HL is presented in Table 15.1. The first of the bimodal incidence peaks in HL occurs in teenagers and young adults (15–25-year age group). HL represents less than 5% of malignancies in children under the age of 15 years. In contrast, it represents 16–20% of malignancies in adolescents, making it the most common malignancy of this age group.

Childhood HL is biologically indistinguishable from HL of young and middle-aged adults other than the relative incidence of specific disease histologies (Table 15.1). Mixed cellularity (MC) and nodular lymphocyte predominant (nLP) HL are the common types of HL in the preadolescent child; adolescents and young adults are most frequently (85%) afflicted with nodular sclerosing (NS) HL [3]. Only a third of children will have advanced disease; approximately 25% will have B symptoms. The incidence of HL with adverse features increases with age. Although there were no discernable differences in clinical presentation, response to therapy, or long-term outcome for adolescents (16–21 years) vs. young adults (22–45 years) treated similarly for HL [4], the treatment of children/adolescents and adults has diverged over the years primarily due to concerns about the late adverse effects of therapy.

15.1.2 Classical Pediatric Hodgkin Lymphoma (PHL)

15.1.2.1 Overall Strategies

The adverse consequences of therapy have driven the pediatric treatment paradigm of care. Clinical trials for pediatric and adolescent HL have been designed to both reduce long-term organ injury and increase efficacy. Pediatric oncologists responded first to developmental issues in the young child and later to the long-

Table 15.1 Demographic and clinical characteristics at presentation of pediatric HL (modified from Refs. [1, 2])

	Childhood HL	AYA HL	Adult HL
Age range (years)	≤14	15–35	≥35
Prevalence of HL cases (%)	10–12	50	
Gender Male/female	2–3:1	1:1–1.3:1	
Histology Nodular sclerosis (%) Mixed cellularity (%) Lymphocyte depleted (%) NLPHL (%)	40–45 30–45 0–3 8–20	65–80 10–25 1–5 2–8	
EBV associated	27–54% Risk factors: male, younger age, mixed cellularity histology, economically disadvantaged countries	20–25%	34–40%
Other risk factors	Lower SES increasing family size	Higher SES, smaller family size, early birth order	
Stage at presentation	30–35% with stage III or IV disease, 25% with B symptoms	40% with stage III or IV disease, 30–40% with B symptoms	
Relative survival rates at 5 years	94% (<20 years)	90% (<50 years)	

AYA adolescents and young adults, *IPS* International Prognostic Score, *SES* socioeconomic status

term treatment consequences in all young survivors in the design of treatment approaches. Recognition of musculoskeletal hypoplasia in young children with HL treated with high-dose radiation such as shortened sitting height, thin necks, and narrow shoulders and chest [5–8] precipitated the development of pediatric-specific regimens for HL. Combined-modality treatments, even for low-stage disease, allowed for the reduction of radiation dose [9] and field size, thus sparing normal structures (Fig. 15.1). This strategy for care was extended to older children and adolescents when hypothyroidism [11, 12], secondary cancers, and valvular and atherosclerotic heart disease [13, 14] were also found to be attributable to high-dose radiation.

Low-dose radiation of 15–25 Gy has been the standard in childhood and adolescent HL for decades. This reduced the potential for long-term risk without adversely impacting event-free survival. A convergence of treatment approaches for adults and children/adolescents may be emerging as recent adult trials have begun to address these issues and reduce radiation doses. With overall survival over 90%, the quality of survival becomes paramount.

Early response to therapy was recognized [15, 16] as highly predictive of outcome. In Europe and the United States, response-based, risk-adapted approach to treating HL [17] allows therapy to be tailored to each individual, within the context of clinical trials. Dose-dense regimens [17] used are similar to those used by adult groups [18, 19], but the pediatric algorithms use the enhanced efficacy to support reduction of therapy.

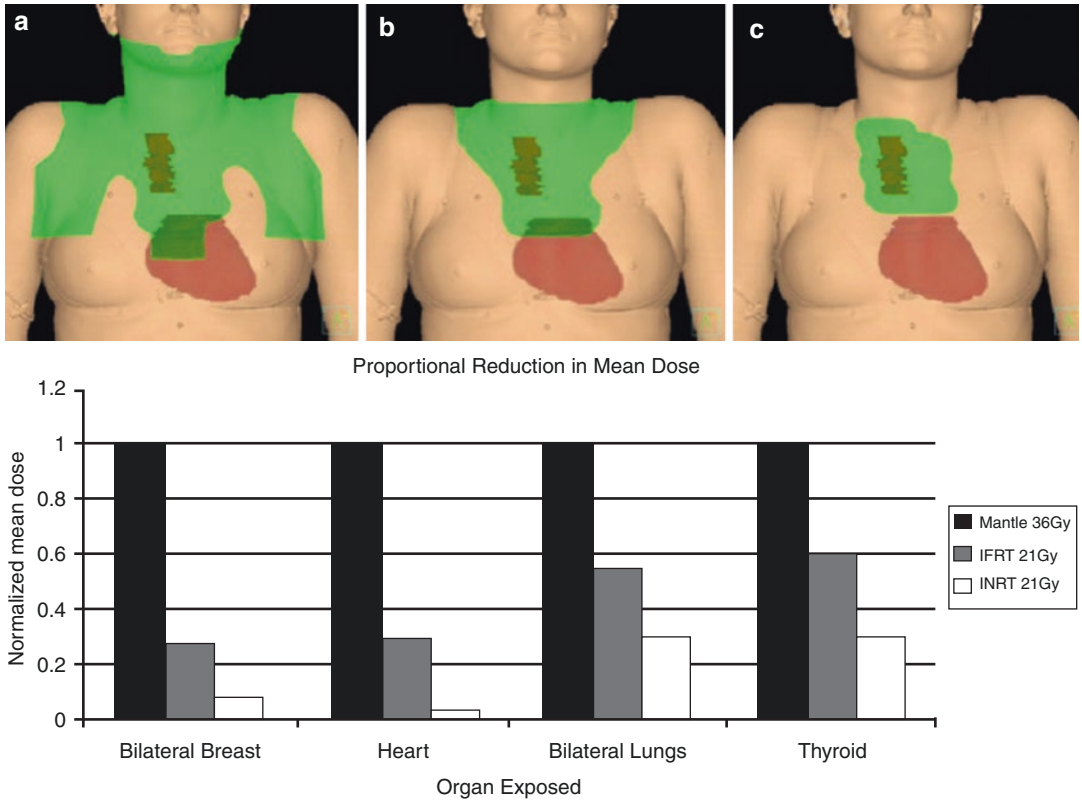

Fig. 15.1 CT-based planning images depicting a historic mantle RT, compared to standard involved field radiation treatment (IFRT) and involved-node RT (INRT) for a patient with stage I disease involving the mediastinum. The postchemotherapy volume of initially involved paratracheal nodes is depicted in dark red and the cardiac silhouette is also evident. (**a**–**c**) Demonstration of the reduction in dose to breast, lung, heart, and thyroid for the female patient shown in (**a**) from Mantle 36Gy to IFRT 21Gy to INRT 21Gy. From Hodgson et al. [10]

Table 15.2 Risk groups employed by selected pediatric study groups [20]

Study group	Risk features (RF)	Low risk	Intermediate/early unfavorable risk	High risk
Children's Oncology Group [21, 22]		IA/IIA no bulk/no LMA	All others IIB, IIIA IVA	IIIB, IVB
EuroNet-PHL-C1, C2 [23]		IA/B[a] IIA[a]	IIA, IIB (no E), IIIA (no E)	IIEB IIIEA/ IIIB IV
St. Jude/Stanford/ Dana-Farber	Categorized as favorable or unfavorable risk by IPS	IA/IIA no bulk	IA/IIA (RF), I IB IIIA IIII	IIB, IIIB, IV.

[a]No bulk, ESR < 30 mm/h

15.1.2.2 Low-Risk (Early Favorable) Disease

Although there have been differing definitions of low-risk disease (Table 15.2), risk-adapted approaches aim to define a cohort of patients that is curable with minimal therapy. Treatment group allocation, risk stratification, and response assessment vary according to each study group (Table 15.2), but all treatment groups define low risk based on stage and bulky disease. Children and adolescents with NLPHL are increasingly being treated with surgery alone or using low-dose regimens separate from those used for the treatment of classical HL.

In the decade following the introduction of MOPP, secondary leukemia and sterility emerged as significant concerns [24–27]. During the 1980s, alkylator exposure and leukemia risk were reduced by alternating MOPP and ABVD [28, 29]. The goal was to avoid reaching thresholds of toxicity for any specific agent. The Pediatric Oncology Group (POG) compared four cycles of MOPP/ABVD plus 25.5 Gy to six cycles of chemotherapy alone without detecting differences in efficacy [15]. However, the profound sensitivity of the testes to procarbazine continued to cause sterility in boys, even with only two cycles of procarbazine-containing chemotherapy [30]. Although early attempts to avoid procarbazine were unsuccessful [31], more recent regimens have achieved this goal [17].

ABVD is used routinely in adults [32], but also has not been standard of care in children. Successful regimens have been devised by the German Paediatric Oncology Hodgkin's Group (GPOH) [33] using OEPA (vincristine, etoposide, prednisone, and doxorubicin) in males (Table 15.3), by the French Society of Pediatric Oncology [36] using EBVP (etoposide, bleomycin, vincristine, prednisone), by Donaldson et al. [42] using VAMP (vincristine, doxorubicin, methotrexate, and prednisone), and by the Children's Oncology Group (COG) using ABVE (doxorubicin, bleomycin, vincristine, etoposide) [43] and ABV-PC [41] all avoiding the use of procarbazine. With these approaches, EFS of 88–92% can be achieved without significant radiation or alkylator toxicity. Patients treated on these newer regimens receive less than 200 mg/m^2 of doxorubicin plus or minus 20–25 Gy of involved-field radiation.

The traditional approach of most pediatric HL treatment groups has been to use combined-modality therapy. Currently, these study groups are involved in evaluating methods to define low-risk patients who may be cured without radiotherapy, i.e., with chemotherapy alone. However, patients with early-stage HL treated with chemotherapy alone most frequently relapse in the initially involved lymph node(s) [44]. Therefore, an effort has also been made to reduce the radiation field size by including only the initially involved lymph node(s)—so-called involved node-radiation (INRT) [45]. The complexity of defining the field for INRT has led to the development of an alternative approach termed "involved-site radiation therapy" (ISRT) [46–48]. This is a modification of IFRT, recommended for patients who when optimal pre-chemotherapy imaging (PET-CT in a position similar to what will be used at the time of radiation therapy) is not available that would be necessary for INRT treatment planning. Because the delineation of the area of

Table 15.3 Treatment results for early, favorable pediatric HL

Group or institution	Patients (*n*)	Stage	Chemotherapy	Radiation (Gy). field	Survival (%)		Follow-up interval (years)	References
					Overall	DFS, EFS, or RFS		
Combined-modality trials								
US CCG 5942	294	IA/B, IIA	4 COPP/ABV	21, IF	100	97	3 10	[34, 35]
SFOP MDH-90	171	I – II	4 VBVP, good responders	20, IF	97.5	91	5	[36]
	27	I – II	4 VBVP 1–2 OPPA, poor responders	20, IF		78	5	
GPOH-HD95	326,224	I, IIA IIB, IIIA	2 OEPA or 2 OPPA above + COPP	CR: No RT PR: 20 IF (10–15 Gy boost)	99 97	94 88	5	[37, 38]
GPOH-HD2002	195,139	IA, 1B, IIA, IE, IIB,IIAE, IIIA	2 OEPA or 2 OPPA Above +2 COPP or 2 COPDAC	20 ± 10–15 IF	99.5 98.5	92 88	5	[39, 40]
Chemotherapy alone								
US CCG 5942	106	CS IA/B, IIA	4 COPP/ABV	CR: None	100	91	3	[34]
Response based RT *AHOD0431 [D,E]* *St. Jude consortium[C]*	278 88	IA, IIA IA, IIA	4 AV-PC 4 VAMP	21 IF if PR 25.5 IF/ none if Early CR	99 100	80 89	4 5	[41]

ABVD Adriamycin, bleomycin, vinblastine, and dacarbazine, *AEIOP* Italian Association of Hematology and Pediatric Oncology, *CCG* Children's Cancer Group, *ChlVPP* chlorambucil, vinblastine, procarbazine, and prednisolone, *COPP* cyclophosphamide, vincristine (Oncovin), prednisone, and procarbazine, *COPP/ABV* cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone, Adriamycin, bleomycin, and vinblastine, *CR* complete response, *CS* clinical stage, *EF* extended field, *EFS* event-free survival, *HD* Hodgkin's disease, *IF* involved field, *MDH* multicenter trial, *MH* multicenter Hodgkin's trial, *MOPP* nitrogen mustard, vincristine (Oncovin), procarbazine, and prednisone, *M/T* mediastinal/thoracic ratio, *OEPA* vincristine (Oncovin), etoposide, prednisone, and Adriamycin, *OPA* vincristine (Oncovin), prednisone, and Adriamycin, *OPPA* vincristine (Oncovin), procarbazine, prednisolone, and Adriamycin, *PR* partial response, *PS* pathologic stage, *R* regional, *RFS* relapse-free survival, *RT* radiotherapy, *SFOP* French Society of Pediatric Oncology, *VAMP* vinblastine, Adriamycin, methotrexate, and prednisone, *VBVP* vinblastine, bleomycin, etoposide (VP-16), and prednisone, *AVPC* doxorubicin, vincristine, prednisone, etoposide
Mediastinal thoracic ratio < 0.33, lymph node <6 cm

involvement is less precise, a somewhat larger treatment volume is treated than with INRT, but less than traditionally used with IFRT. Other radiation techniques that are contemporary and reduce the treatment volume include intensity-modulated radiation therapy, deep inspiration breath holding (to reduce the volumes of the lung and heart that might be exposed), and protons [49].

Nachman et al. showed an increased relapse rate in patients who did not receive radiation despite achieving CR at the end of chemotherapy [34, 35]. Late-response evaluation may not have identified the optimal cohort for reduction of radiation. Early response may better define the profoundly chemotherapy-sensitive patient who does not need radiation. Based on the

excellent outcomes of low-risk HL patients achieving CR after two cycles of chemotherapy [15], recent trials in the COG, the St. Jude/DFCI/Stanford Consortium, and the EuroNet PHL group [50, 51], have examined early response to determine who does or does not require radiation post-chemotherapy.

The prognostic importance of early chemotherapy response rather than end of chemotherapy response has led to the use of early response assessment (after 6–9 weeks) to titrate individual therapy and dose-dense regimens to maximize the early response rates. The St. Jude/DFCI/Stanford Consortium has reported 2-year EFS of 90.8% in early-responding, low-risk patients with either classical or nodular lymphocyte-predominant HL treated with 4 cycles of VAMP without radiation [51]. The most recent COG study (AHOD0431) found that early assessment by PET after one cycle is a predictor of recurrence [41, 52]. The current EuroNet PHL-C1 classical HL trial is evaluating PET activity after two intensive cycles of OEPA (cumulative dose of anthracycline is 160 mg/m^2) to predict who does not require radiotherapy [53]. All such reductions in treatment may increase the risk of relapse; hence, adverse outcomes such as the need for high-dose salvage therapy (e.g., stem cell transplant or high-dose radiation) must be closely monitored.

15.1.2.3 Intermediate- and High-Risk (Advanced, Unfavorable) Disease

For children with advanced-stage disease, improving efficacy while limiting long-term toxicity is even more challenging. The approach in pediatric HL has been to increase the number of agents so as to limit cumulative doses of individual agents. Regimens used in the 1980–1990s alternated MOPP/ABVD [29, 54] or used the hybrid COPP/ABV [34] to avoid the cumulative doses of doxorubicin (300–400 mg/m^2) and bleomycin (120–160 mg/m^2) associated with six to eight cycles of the four-drug ABVD regimen [28, 32].

Minimalistic dose regimens in combined-modality protocols, such as VEPA (Table 15.4), that eliminated traditional alkylating agents were not successful and resulted in a 70 and 49% 5-year EFS for stage III and IV HD, respectively [61].

It has been known for decades that outcome in HL is optimized by chemotherapeutic dose intensity. Only recently has this knowledge been considered a clue to improving outcome [62–64]. ABVE-PC was developed by the COG (by adding prednisolone and cyclophosphamide to ABVE) for the treatment of advanced HL and dose density was increased by the use of 3-week cycles [17]. This regimen is similar to dose-dense regimens such as Stanford V and BEACOPP, developed simultaneously in the adult groups [18, 19]. BEACOPP and escalated BEACOPP are dose-intensive regimens with improved efficacy compared to COPP/ABVD. Instead of further cumulative dose escalation, the COG and EuroNet PHL take advantage of dose-dense delivery to limit cumulative cytotoxic therapy. Such dose-intensive regimens also limit the cumulative dose of agents delivered to the early responders. The GPOH-HD/EuroNet PHL group has substituted dacarbazine for procarbazine, resulting in excellent long-term results [40].

ABVE-PC is the backbone for all COG trials. This dose-dense approach allows for the elimination of procarbazine and the limitation of the doxorubicin and etoposide dose. The first such study (POG 9425) resulted in 5-year EFS of 84% and 5-year overall survival (OS) of 95% for advanced HL. Early responders (after three cycles of ABVE-PC) on this study proceeded directly to receive 21 Gy regional RT. Others received two more cycles (total five ABVE-PC in 15 weeks) prior to 21 Gy RT This backbone was used in AHOD0031 to evaluate a response-based vs. standard approach to therapy for intermediate-risk disease and to study augmentation of therapy for high-risk patients with a slow early response to therapy [65].

Low-dose, involved-site radiation remains a relevant modality of therapy in high-risk disease. The multicenter trial GPOH-HD95 used OPPA/COPP for girls and OEPA/COPP for boys with radiation dose determined by end of chemotherapy response. For the intermediate- and higher-risk groups (TG2 and TG4), outcome was

Table 15.4 Treatment results for advanced, unfavorable pediatric Hodgkin lymphoma

Group of institution	Patients (*n*)	Stage	Chemotherapy	Radiation (Gy), field	Survival, %		Follow-up interval (year)	Reference
					Overall	DFS. EFS. or RFS		
Combined-modality trials								
Germany, Austria HD-95 (2001) (2013)	280	II_EB, III_EA/B, IIIB, IVA/B	2 OEPA/OPPA + 4 COPP	PR:20–35, IF CR: No RT	97	84	3 10	[37] [38]
HD-2002	239	IIBE, IIIAE, IIIB, IV	2 OEPA, 4 COPDAC	20 ± 10–15 Gy IF RT	95	87	5	[40]
AHOD 0031	380	Not I/IIA no bulk, III, IVB	RER:ABVE-PC × 4	21GY IF RT	97.8	87.9		[55]
	382 151		RER: ABVE-PC × 4 SER: ABVE-PC × 4	No RT 21GY IF RT	95.3	84.3 75.2		
	153		SER: ABVE-PC × 4 add DECA × 2	21GY IF RT		79.3		[56]
AHOD 0831	145				95.9	80.2		
	77	III, IVB	RER: 5 ABVE-PC	21 GY to residual or bulky disease				
	68		SER: Add Iifos/vinor × 2	21GY IF RT				[57]
CCG 59704	99				97	94		
		IIB, IIIB, IV	BEACOPP × 4 RER (F): BEACOPP × 4	No				[16]
			RER (M): ABVD × 4 SER: BEACOPP × 4	21 GY 21 GY				[34] [35]
St. Jude's, Stanford, DFCI (2004)	159	CS IB/IIB or Bulky>6 cm	6 VAMP/COP	15 IF if CR	93	76	5	[58]
		CS III/IV		25.5 IF if PR				
COG—P9425 (2009)	216	CS IB, IIB, $IIIA_2$, IIIB, IV	RER: 3 ABVE-PC SER: 5 ABVE-PC	21 IF	95	86	5	[17]
		IIA/IIIA1 "bulk"		21 IF		84		
Chemotherapy alone UKCCSG (2002)	67	CS IV	6–8 ChlVPP	None[a]	80.8	55.2	5	[59]

(continued)

Table 15.4 (continued)

Group of institution	Patients (*n*)	Stage	Chemotherapy	Radiation (Gy), field	Survival, %		Follow-up interval (year)	Reference
					Overall	DFS. EFS. or RFS		
US CCG (2002)	394	CS I/II[b], CS IIB, CS III	6 COPP/ABV	None	100	83	3	[34]
	141	CS IV	COPP/ABV, CHOP, AraC/VP-16	None	94	81	3	
US POG (1997) *Response-based RT* AHOD0031 (2010)	81 1712	CS IIB, III2A, IIIB, IV All except: IA, IIA non-bulk IIIB, IVB	4 MOPP/4 ABVD Standard arm; 21 IF/4 ABVE-PC	None Randomized: RER: ± RT SER: ± 2 DECA	96 98	79 85	5 4 [60]	[16]

ABVD Adriamycin, bleomycin, vinblastine, and dacarbazine, *ABVE-PC* Adriamycin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide, *AEIOP* Italian Association of Hematology and Pediatric Oncology, *AraC* cytosine arabinoside, *CAPTe* cyclophosphamide, Adriamycin, prednisone, and teniposide, *CCG* Children's Cancer Group, *CCOPP* vincristine (Oncovin), procarbazine, and prednisone, *ChlVPP* chlorambucil, vinblastine, procarbazine, and prednisolone, *CHOP* cyclophosphamide, hydroxydaunomycin, vincristine (Oncovin), and prednisone, *COMP* cyclophosphamide, vincristine (Oncovin), methotrexate, and prednisolone, *COPP* cyclophosphamide, vincristine (Oncovin), prednisone, and procarbazine, *COPP/ABV* cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone, Adriamycin, bleomycin, and vinblastine, *CR* complete response, *CS* clinical stage, *CVPP* cyclophosphamide, vinblastine, procarbazine, and prednisone, *DFS* disease-free survival, *EF* extended field, *EFS* event-free survival, *HD* Hodgkin's disease, *IF* involved field, *MDH* multicenter trial, *MH* multicenter Hodgkin's trial, *MOPP* nitrogen mustard, vincristine (Oncovin), procarbazine, and prednisone, *NR* no response, *OEPA* vincristine (Oncovin), etoposide, prednisone, and Adriamycin, *OPA* vincristine (Oncovin), prednisone, and Adriamycin, *OPPA* vincristine (Oncovin), procarbazine, prednisolone, and Adriamycin, *POG* Pediatric Oncology Group, *PR* partial response, *PS* pathologic stage, *R* regional, *RFS* relapse-free survival, *RT* radiotherapy, *SFOP* French Society of Pediatric Oncology, *TLI* total lymphoid irradiation, *UKCCSG* United Kingdom Children's Cancer Study Group, *VAMP* vinblastine, doxorubicin, methotrexate, and prednisone, *VEEP* vincristine, etoposide, epirubicin, and prednisolone, *VEPA* vinblastine, etoposide, prednisone, and Adriamycin, *DECA* dexamethasone, etoposide, cisplatin, cytarabine

[a]Presence of adverse features = (t)hila, >4 nodal sites, bulk

[b]12 patients received 20–35 Gy, IF; 2 received whole lung irradiation

significantly better for those receiving radiation therapy (TG2, 0.78 vs. 0.92; TG 2 + 3, 0.79 vs. 0.91) [33, 38]. The Children's Cancer Group also noted improved outcome for patients treated with radiation, despite CR at the end of chemotherapy [34, 35]. Kelly et al. [66] reported excellent results using a modified approach to BEACOPP that reduced doses of chemotherapy for girls and for boys with a rapid response. Nonetheless, this regimen is not being used currently because cumulative doses of chemotherapy remain high.

Recent trials in both the COG and in Europe addressed early-response-directed approaches to limit the need for radiation. AHOD0031 for intermediate-risk HL used the dose-dense ABVE-PC regimen to support and evaluate the concept of an early-response-based algorithm [60]. This study showed that rapid early response (RER) could identify a cohort comprising 45% of patients who did not benefit from radiation. However, in a subset analysis from this study of patients with anemia and bulky limited-stage disease, the EFS was 89.3% for rapid early responder or complete remission patients who received IFRT, compared with 77.9% for patients who did not receive IFRT ($P = 0.019$) [67]. For patients who had a slow early response (SER), a marginal benefit from augmented chemotherapy was observed. The high-risk study (AHOD-0831) limited radiation fields for rapid early responders while augmenting therapy for slow early responders; outcomes were similar to POG9425 but used less radiation for RER and less doxorubicin for SER [E].

Adult patients with high risk randomized to ABVD vs. brentuximab with AVD have been reported to have a reduced risk of progression, death, or non-complete response [68], resulting in approval in the United States for this indication. However, it is not clear that this approach has an advantage in the setting of pediatric regimens that have had greater efficacy than ABVC. COG has a randomized, ongoing study comparing standard ABVE-PC to ABrVE-PC (Harker-Murray et al.), and the St. Jude Consortium is similarly evaluating the use of brentuximab with their backbone therapy.

15.1.2.4 Future Considerations in Classical Pediatric and Adolescent HL

Progress has been made in the treatment of children with HL with all stages of disease and risk factors, but several issues remain to be resolved. Response to chemotherapy may define both the total amount of chemotherapy required and the need for radiotherapy (RT). For early-stage patients, the balance between chemotherapy dose and radiation exposure continues to be explored. Restriction of RT to initially involved lymph nodes (involved-node irradiation or involved-site irradiation) rather than chains (or regions) of nodes may affect the balance of risk. For high-risk disease, dose-dense chemotherapy improves efficacy and supports tailoring of therapy to the patient's response. RT is clearly effective in enhancing the local control of PHL, but has a dose-dependent toxicity profile favoring a limited volume/dose approach. Ongoing studies are needed to assess the role of RT for initial bulky disease, to residual postchemotherapy disease (particularly if it is PET negative), and to involved organs. Carefully designed and sequential evidence-based studies are needed to continue to improve efficacy while limiting toxicity.

15.1.3 Nodular Lymphocyte-Predominant HL (NLPHL)

An indolent, peripheral, NHL-like disease, NLPHL was recognized in the early 1990s as a clinicopathologically distinct form of HL [69]. Unlike classical HL, NLPHL is a CD20-positive, CD30- and CD15-negative, B cell lymphoma that is not associated with EBV genomic integration. There is a distinct male predominance (ratio 2–3:1) with nearly 90% of pediatric patients having early-stage disease (IA/IIA). A higher percentage (10–20%) of children have NLPHL [3] compared to adults (3–8%) [70], and although >50% of pediatric and adolescent cases are under the age of 14 years [71], the incidence peaks between 14 and 18 years. Peripheral lymphadenopathy is the most common presentation involving the axilla, cervical, and

inguinal regions, often present for months or years. Rarely is advanced or central disease seen.

Adults with early-stage NLPHL are treated with involved-field radiotherapy, standard cHL therapy, or combined-modality therapy. Children have, until 2005 and the start of NLPHL-specific clinical trials, received standard pediatric cHL therapy with combined-modality chemoradiotherapy [72], which is excessively toxic.

Morbidity, even mortality, secondary to repeated courses of intensive therapy to eradicate this indolent, usually nonfatal disease has resulted in a drive to reduce the intensity of therapy to avoid late effects [71].

Children with fully resected early-stage nLPHD have been cured without the need for any chemoradiotherapy [73–76], but the specific situations in which this strategy is appropriate are currently under investigation. Two nonrandomized clinical trials, EuroNetPHL-LP1 and COG's AHOD03P1, have looked at reducing the toxicity of upfront therapy for early-stage disease (stage I and II) [73, 74]. As salvage therapy is effective for late or even multiple relapses which generally recur at the original site of disease with no stage upgrade, OS is expected to remain near to 100% [77]. The EuroNetPHL-LP1 used surgical resection alone or low-dose anthracycline-free CVP chemotherapy for non-resectable disease, and COG's AHOD03P1 used AVPC (equivalent to CHOP) with selective radiotherapy. Excellent EFS rates of 60–75% with no or low-dose chemotherapy have been obtained and only 10% of COG patients received RT, maintaining 100% OS [78].

Because of transformation rates of approximately 5% to aggressive B-NHL [79] in adults, usually diffuse large B cell lymphoma [80], concerns regarding reduced therapy that could potentially allow persistence of the CD20 clone and increased transformation rates remain. In theory, the addition of rituximab would help to specifically eradicate the CD20 clone and reduce transformation rates. However, transformation rates in children are not known but appear extremely low.

Rituximab has been studied in adults for use in this and all other CD20-positive lymphomas [81]. The pediatric community have traditionally been wary about using rituximab in young children because of impact on immune status/memory. As early-stage NLPHL is viewed as a highly curable disease with minimal chemotherapy or surgery alone, the use of rituximab has been reserved for treating more aggressive, advanced, or relapsed disease. Assessing the impact of adjuvant rituximab therapy on EFS and transformation rates in children within a randomized clinical trial has been the unattainable aim of clinicians for well over a decade. The reluctance of the pediatric community to use rituximab in this and other CD20+ lymphomas is abating.

Current proposed clinical trials using low-dose NHL-like therapy including anti-CD20 therapy are focused on the natural history, establishing risk categories, variant histologies, and transformation rates, with biological substudies looking at specific molecular characteristics.

15.1.4 Recurrence, Relapse, and Salvage in PHL

15.1.4.1 Introduction

Relapsed and refractory classical Hodgkin lymphoma (HL) remains a clinical and therapeutic challenge. Approximately 10% of patients with early-stage and up to 30% with advanced-stage disease relapse after first-line chemotherapy.

Cure can still be achieved in a substantial proportion of patients with recurrent disease, but there is no uniform approach to salvage therapy. The optimal salvage treatment has not been defined in children and adolescents as there are no randomized trials defining the "best" salvage chemotherapy regimen or comparing standard-dose chemotherapy (SDCT) vs. high-dose chemotherapy and autologous stem cell transplant (HDCT/ASCT), which is often considered the standard of care in adult practice. Pediatric practice adopts a more individualized risk-stratified and response-adapted approach to salvage treatment with both non-transplant (SDCT plus radiotherapy) and transplant (SDCT plus HDCT/ASCT) salvage.

At the point of relapse, a full disease reassessment including histologic confirmation is mandatory and then an analysis of pre-salvage risk factors is undertaken. All patients have a common starting point with re-induction SDCT and this is followed by consolidation treatment. The choice of consolidation treatment is guided by

risk stratification based on prognostic factors as well as an assessment of chemosensitivity which is commonly done after two cycles of SDCT and includes FDG-PET response. Achieving a complete metabolic remission on FDG-PET prior to consolidation has been shown to be highly prognostic in the relapse setting and is considered to be a major goal of re-induction SDCT [82]. Consolidation after SDCT will be radiotherapy only in "low-risk" relapse or HDCT/ASCT in "standard-risk" relapse, and these two strategies will be appropriate for the vast majority of relapse/progressive HL. A small number of patients are refractory to SDCT and do not achieve a CR with two or more lines of SDCT and these are "high-risk" patients [82]. Consolidation in these high-risk patients may be either conventional HDCT/ASCT possibly with post-HDCT consolidation RT or maintenance-targeted therapy such as brentuximab vedotin, or alternative experimental approaches may be applied including novel agents such as checkpoint inhibitors or allogeneic transplantation.

15.1.4.2 Standard-Dose Salvage Chemotherapy Regimens

After recurrence is noted, the first step is reinduction with a SDCT salvage regimen. There is no "best" chemotherapy regimen at salvage, and there are no randomized studies comparing standard-dose chemotherapy regimens. The choice of regimen should take account of primary therapy, use of non-cross-resistant drugs, and cumulative drug toxicities. The aim of salvage therapy is to obtain cytoreduction and to demonstrate chemosensitivity which is done most accurately now with FDG-PET as first-line treatment. It also facilitates collection of peripheral stem cells for ASCT. Salvage regimes can be divided into intensive conventional regimens[1] (mini-BEAM), cisplatin-based regimens[2] (ESHAP, DHAP [ESHAP, DHAP, APPE, DECAL]), ifosfamide-based regimens[3](EPIC, IEP, ICE, IV), or others[4] (GV, IGEV). The COG uses IV as its standard regimen because of efficacy and with the intent of avoiding etoposide-induced secondary malignancy after stem cell transplantation [83]. In Europe, alternating IEP/ABVD was used in the EuroNet-PHL-R1 trial but more recently the IGEV regimen has been widely adopted. The decision to continue salvage therapy with RT consolidation vs. HDCT/ASCT is based on assessment of predictive factors.

15.1.4.3 Prognostic Factors at Relapse in Pediatric HL: Standard-Dose Chemoradiotherapy Vs. High-Dose Chemotherapy/ Stem Cell Transplantation

Prognostic factors at relapse may be used to allocate patients to a risk-stratified salvage approach. This is in contrast to adult practice where consolidation with HDCT/ASCT is considered standard of care. There are currently no universally accepted prognostic criteria in children (or adults) defining individualized salvage treatment plans. Factors which are prognostically important include time to relapse, prior treatment in first line, stage/disease burden at relapse, and response to salvage chemotherapy. In children, low-risk patients may be salvaged with RT consolidation only, while standard-risk patients are salvaged with HDCT. The cut point between low- and standard-risk patients is not universally defined. In Europe, low-risk patients salvaged with SDCT plus RT only include those with early relapse after up to 4 cycles of chemotherapy and late relapse after up to 6 cycles with *all* of the following: nodal relapse, no prior RT (or relapse only outside prior RT fields), consolidation RT that has acceptable toxicity (i.e., no excessive RT fields), and chemotherapy-responsive disease. All other patients have intensification with HDCT/ASCT.

[1] Mini-BEAM; BCNU, etoposide, cytarabine, melphalan

[2] *ESHAP,* etoposide, methylprednisolone, cytarabine, cisplatin; *DHAP,* dexamethasone, cytarabine, cisplatin; *APPE,* cytarabine, cisplatin, prednisone, etoposide; *DECAL,* cytarabine, cisplatin, prednisone, etoposide, asparaginase

[3] *EPIC,* etoposide, vincristine epirubicin, prednisolone; *IEP,* ifosfamide, etoposide, prednisolone; *ICE,* ifosfamide, carboplatin, etoposide; *IV,* ifosfamide, vinorelbine

[4] *GV* gemcitabine, vinorelbine; *IGEV,* ifosfamide, gemcitabine, vinorelbine, prednisolone

Time to relapse from end of first-line treatment is the most important pretreatment risk factor and highly significant for OS and EFS in pediatric studies [84–86] and dominated all other prognostic factors in multivariate analysis of the ST-HD-86 trial, the largest prospective pediatric relapse trial published to date [87], with DFS of 41, 55, and 86% for those with refractory disease, early relapse, and late relapse, respectively. This study showed that salvage can be risk adapted because subgroups with markedly better or worse prognosis can be defined. Stage IV and extranodal disease were also associated with lower OS.

A recent French experience [88] found the only relevant prognostic factors to be time to relapse and chemoresistance with primary progressive HL having an EFS <40% compared with approximately 80% in late relapse and chemosensitivity (CR or PR >70%) to salvage associated with a DFS of 77% vs. 10% with poor response ($p < 0.0001$). Chemosensitivity to SDCT and disease status at transplantation are also predictive of outcome. In one study, 5-year FFS was 35% for patients with chemosensitive disease vs. 9% with chemoresistant disease [84]. Another group found 68% OS and 59% FFS at 5 years in chemosensitive patients vs. 18% and 0% in chemoresistant patients [85]. Several particularly adverse factors have been noted. Chemoresistant patients had 5-year FFS of 0% with HDCT/ASCT [85]. Adolescents with B symptoms at recurrence had poor OS even after HDCT/ASCT (11-year OS 27% with B symptoms vs. 60% without) [89]. No difference in OS or FFS between age subgroups or in comparison with adult cohorts has been reported by several studies [84, 85, 90]. Of note, many of these studies did not incorporate FDG-PET response assessment which is now well recognized as the most important prognostic factor, which may overcome the significance of some factors as is the case in first-line treatment [91].

15.1.4.4 Role of Radiotherapy in Relapsed Hodgkin Lymphoma

Radiotherapy has an important role in salvage, but must be individualized based on previous radiation exposure, in or out of field recurrence, stage at recurrence, and the toxicities of total treatment burden [92]. Increasing numbers of patients are RT naïve at relapse as the use of RT is increasingly restricted in first-line treatment and RT fields are also becoming highly restricted in some first-line trials to FDG-PET-positive residua. Therefore, at relapse many patients have never received RT, and some other patients may relapse in prior disease sites that have never received RT because they received focal targeted RT only. Salvage with RT alone is generally not recommended, but integration of RT in salvage is relevant in two contexts:

1. As consolidation treatment in low-risk group patients after SDCT.
2. In selected patients as consolidation after HDCT/ASCT

15.1.4.5 High-Dose Chemotherapy and Autologous Stem Cell Transplant

COG protocols have studied HDCT/ASCT and immunomodulatory therapy in all patients except the lowest-risk group (late relapse without bulky disease or B symptom in those initially treated for IA/IIA disease with minimal systemic therapy) [93]. In Europe, HDCT/ASCT has a recognized role in salvage for those with higher-risk features, namely, all primary progressive HL and early relapse after 6 cycles of first-line chemotherapy, all relapse with poor response to reinduction, and finally those patients in whom RT consolidation is either not feasible (advanced-stage relapse) or too toxic (extensive RT fields required or re-irradiation of prior irradiated sites). Patients without high-risk features and who achieve a complete FDG-PET-defined response after two cycles of SDCT may receive only consolidation SDCT plus RT.

There are no studies that define the most effective HDCT. BEAM and CVB (cyclophosphamide, etoposide, carmustine) are commonly used. TBI-containing regimens confer no benefit and are associated with increased toxicity and late effects. Transplant-related mortality is down to 0–2% in some series. A higher TRM rate has been associated with history of atopy, thoracic irradiation, multiple chemotherapy regimens, and multiple relapses.

Series with HDCT/ASCT in pediatric and adolescent patients are small and report EFS rates of 31–67% [84, 85, 90, 94]; outcome for children is similar to adults with HDCT/ASCT [84, 90]. Studies that evaluate survival benefit rather than event-free survival after disease recurrence often rely on transplant after second or later recurrence to achieve good OS [85, 95]. Patients with primary progressive disease and those resistant to salvage regimens remain a huge challenge. SDCT with radiotherapy will not afford a chance of cure, but even HDCT/ASCT is inadequate therapy for most such patients. New approaches to such patients, such as use of post-HDCT consolidation maintenance-targeted treatment, were tested in the Aethera trial with up to 16 cycles of brentuximab vedotin or post-HDCT radiotherapy which is also an option to minimize further relapse. Allogeneic SCT or immunomodulatory therapy may prove beneficial [93].

Long-term follow-up is required post-HDCT for detection of late relapse and development of second cancers, which have been reported at a rate of 5–10% at 5 years and substantially higher at 20 years or more in some series. Thirty-eight percent of deaths occurred 4–12 years after ASCT; 85% of relapses occur within 2 years of ASCT [86].

15.1.4.6 High-Dose Chemotherapy and Allogeneic Stem Cell Transplantation

The role of allogeneic transplant in relapsed HL remains unknown. The poor outcome with HDCT/ASCT in chemotherapy poor responders to salvage and those who remain FDG-PET positive after salvage has resulted in exploration of alloSCT. Allogeneic transplantation is not recommended as the initial transplant approach outside of a clinical trial setting [96] due to the high non-relapse mortality (NRM) rate, mainly caused by graft vs. host disease and infection. Reduced intensity conditioning (RIC) ameliorates the NRM while maintaining theoretical graft vs. lymphoma effect. Allogeneic-SCT may be an option for relapse post-HDCT/ASCT and for patients with refractory advanced-stage HL and chemoresistant disease at salvage.

Children and adolescents allografted for HL had an OS of 45% and PFS of 30% at 5 years [97]. All were heavily pretreated, almost half with HDCT/ASCT. Those with chemosensitive disease and good performance status achieved 3-year OS of 83% and PFS of 60%. NRM was 21 ± 4% in both the RIC and myeloablative conditioning groups. RIC was associated with a significantly higher relapse risk compared to myeloablative conditioning. Graft vs. host disease did not affect relapse rate.

Although studies based on registry data are useful, prospective trials are required to gain a better understanding of the role of allogeneic transplantation. The indications, optimal time point, conditioning regimen, and GVHD prophylaxis still need to be better defined. With the advent of newer immunotherapy agents, including checkpoint inhibitors, the role of alloSCT globally in HL is under review and the numbers of such transplants are declining globally.

15.1.4.7 Brentuximab Vedotin and Checkpoint Inhibitors

In recent years there have been two early-phase pediatric trials investigating novel agents in children. The first is the phase I/II pediatric trial (ClinicalTrials.gov number NCT01492088) investigating single-agent brentuximab vedotin in R/R HL and anaplastic large cell lymphoma [98]. The recommended phase II dose was 1.8 mg/kg as in adults and the ORR was 47% (CR rate 33%, PR rate 12%) in HL patients and toxicity was manageable. This compares with the pivotal phase II study in adults where the ORR was 75% (CR rate 34%) [99]. The second is the ongoing risk-stratified and response-adapted phase II salvage trial in first R/R HL of nivolumab plus brentuximab vedotin followed by bendamustine plus brentuximab vedotin in poor initial responders in first R/R HL in children and young adults (Checkmate 744 trial, AHOD1721; NCT02927769) [100]. The preliminary results of this study are recently presented showing 64% of patients achieved a CMR after brentuximab vedotin plus nivolumab. Of those inadequate responders that switched to second-line brentuximab vedotin plus bendamustine, all achieved a CMR after 2 cycles of this intensification.

The overall CMR rate with either first or second salvage in this trial was 86%, demonstrating that only a small number of patients cannot achieve a CMR pre-HDCT with these combinations.

Treatments that block the interaction between programmed death-1 (PD-1) and its ligands have shown high levels of activity in adults with HL. The anti-PD-1 antibody nivolumab induced objective responses in 20 of 23 adult patients (87%) with relapsed HL [101]. Another anti-PD-1 antibody, pembrolizumab, produced an objective response rate of 65% in 31 heavily pretreated adult patients with Hodgkin lymphoma who relapsed after receiving brentuximab vedotin [102]. These agents may be used as a bridge to transplant, as post-HDCT maintenance brentuximab vedotin, or as alternatives to conventional SDCT. These novel agents when used as a single agent achieve CR rates of 19–33%, but in combination achieve higher CR rates as in the Checkmate trial [100]. An interesting combination is brentuximab vedotin plus bendamustine [103] which achieves CR rates in excess of 75% which means that most patients can achieve a CR prior to HDCT making the use of alloSCT which is often used in patients that cannot achieve a CR less appealing.

15.1.5 Late Effects

Long-term adverse sequelae of greatest concern in children treated for HL (particularly with regimens including high-dose radiation) include impairment of muscle and bone development [5] and injury to the lungs [104], heart [105], thyroid gland [11, 12], and reproductive organs [106]. Cardiovascular dysfunction, pulmonary fibrosis, and secondary malignancies significantly compromise the quality and length of life in survivors [107].

15.1.5.1 Cardiac Toxicities

High-dose (>30 Gy) radiation to the mediastinum has been associated with significant long-term effects in patients with HL. Stanford investigators reported that the actuarial risk of developing cardiac disease necessitating pericardiectomy was 4% at 17 years in a series of long-term survivors of childhood HL who had received high-dose radiation [14]. Screening echocardiogram, exercise stress test, and resting and 24-h ECG identified numerous clinically significant cardiac abnormalities in HL patients who had mediastinal irradiation at a median age of 16.5 years (range, 6.4–25 years). Significant valvular defects were detected in 42%, autonomic dysfunction in 57%, persistent tachycardia in 31%, and reduced hemodynamic response to exercise in 27% of patients [108]. With the introduction of techniques that reduce the radiation dosage to the heart, rates of radiation-associated cardiac injury have declined dramatically.

Mediastinal irradiation given for HL may further predispose patients with PHL to anthracycline-related myocardiopathy [14, 109]. Cardiac dysfunction after anthracycline therapy itself is notable, with the highest risk in those receiving high cumulative doses or in young children who may be affected by an adverse effect on cardiac myocyte growth [14, 109]. Fortunately, most pHL patients are adolescents and current pHL regimens doses are significantly lower than those used in adult ABVD regimens.

15.1.5.2 Pulmonary Toxicities

Chronic pneumonitis and pulmonary fibrosis should be rare in the current era of treatment for primary HL (Fig. 15.1). Predisposing therapies include thoracic radiation and bleomycin chemotherapy [104, 105]. The bleomycin in ABVD can cause both acute pulmonary compromise and late pulmonary fibrosis and can be augmented by the fibrosis that can be associated with pulmonary radiation. Asymptomatic pulmonary dysfunction that improves over time has been observed after contemporary combined-modality treatment.

15.1.5.3 Thyroid Toxicities

Thyroid sequelae are common after RT for PHL. Hypothyroidism, hyperthyroidism, thyroid nodules, and thyroid cancer have been observed in long-term survivors [11, 12]. Of these, hypothyroidism, particularly compensated hypothyroidism, defined as thyroid-stimulating hormone (TSH) elevation in the presence of a normal thyroxine

(T4) level, is the most common thyroid abnormality. The primary risk factor for hypothyroidism is higher cumulative radiation dosage; the influence of age remains controversial [11, 12]. As many as 78% of patients treated with radiation dosages greater than 26 Gy demonstrate thyroid dysfunction, as indicated by elevated TSH levels [11].

15.1.5.4 Secondary Malignancies

The overall cumulative risk of developing a subsequent malignancy after treatment for PHL has been reported to range from 7% to 10% at 15 years from diagnosis and rises to 16–28% by 20 years (Table 15.5) [116]; these data are based on patients treated in earlier decades. The most common secondary malignancies historically included both secondary acute myeloid leukemia (MDS/secondary AML) and solid tumors. However, leukemias are now infrequent due to changes in chemotherapy. Female breast cancer is a particular concern but is likely to be less common with current radiation doses and techniques, since it is associated with RT fields that include breast tissue (especially mantle fields) and higher radiation doses (Fig. 15.1).

15.1.6 Summary/Future Directions

Tremendous strides have been made in treating children with HL, both in terms of cure and reduction of toxicity. Devising new strategies to treat children with HL is problematic because of the overall success of current treatment regimens. However, grouping patients into different risk categories, using response-based therapy and newer imaging techniques, allows investigators to construct protocols intended to diminish therapy-induced toxicity for patients with favorable prognoses. These protocols also aim to improve efficacy of treatment for patients with intermediate and unfavorable prognoses. Unfortunately, the ability to conduct clinical trials, where the difference in survival between treatment arms is likely to be small, is compromised by the large patient numbers required to detect such differences. If a reduction in treatment toxicity is the intended goal of a new regimen, then many years of follow-up are necessary to prove efficacy. For patients with refractory, or multiple relapsed disease, phase II studies investigating the use of monoclonal anti-CD30 and anti-PD-1 antibodies alone and in combination, and with other checkpoint inhibitors, in children and adolescents are ongoing internationally. The importance of investigators working together throughout the world to share data and new treatment approaches in order to cure children with HL safely is clear.

Acknowledgments Thanks to Laura Finger, Rochester, for her help with the final draft and references of the third edition 2019.

Table 15.5 Secondary cancers after childhood HL

Reference	Cohort size	Time period studied	Number of secondary cancers	Cumulative incidence (%) (years)	Standardized incidence ratio
Stanford [110]	694	1960–1995	59	Males, 9.7% (20 years); females, 16.8% (20 years)	Males, 10.6; females, 15.4
LESG [111]	1641	1940s to 1991	62	18% (30 years)	7.7
[112]	1136	1955–1986	162	26.4% (40 years)	
Roswell [113]	182	1960–1989	28	26.7% (30 years)	9.4
LESG [114]	1380	1955–1986	135	31.2% (30 years)	17.9
US/European [115]	5925	1935–1994	195	Solid tumors: 11.7% (25 years)	7.7
University of Rochester/Johns Hopkins/University of Florida/ St. Jude/Dana-Farber [116]	930	1960–1990	102	19% (25 years)	Males, 8.41; females, 19.93

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The Management of Older Patients with Hodgkin Lymphoma

16

Boris Böll and Andrew M. Evens

Contents

16.1 Introduction

Survival rates for Hodgkin lymphoma (HL) have substantially improved over the past few decades. Using stage-adapted chemotherapy and innovative radiation techniques, 5-year progression-free survival (PFS) has reached almost 90% in younger patients [1–3]. Since the median age at diagnosis is approximately 32 years, these excellent results account for the majority of patients. However, this progress has not translated into similar benefits for older patients, especially for advanced-stage disease [4–8]. Survival rates for HL patients ages ≥60 years have been disproportionately inferior compared with younger patients.

"Older age" is often defined as age over 60 years, in part due to the poor tolerability of aggressive chemotherapy with advancing age. Accordingly, these patients are often excluded

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_16

from randomized controlled trials (RCTs). Thus, the percentage of older patients is often underestimated using data from RCTs [9]. On the other hand, population-based studies estimate that patients over 60 years account for a substantial proportion of patients in clinical practice, i.e., about 20–25% of the total HL population [10]. In part because older patients had historically not been included in clinical trials, a "standard of care" for this patient cohort has been difficult to define [9, 11]. The lack of improvement in outcome for these patients will become magnified as the most rapidly growing segment in the population are patients age > 65 years, especially the age group ≥80 years; the latter has increased >250% between 1960 and 2000 and it is expected that the population age > 75 will triple by the year 2030 [12].

More recent approaches integrating novel therapeutic agents into frontline therapy which appear to be associated with improved outcomes compared with historical controls [13]. In this chapter, we summarize the currently available data on the management of older patients with HL and address the question of including elderly patients into prospective studies in order to improve the outcome of this particular group of patients [14].

16.2 Epidemiology

Many prospective studies and RCTs have excluded older patients on the basis of age or performance status. Historically, only 5–10% of patients included in RCTs have been older than 60 years [5, 15, 16]. The most accurate assessments have come from population-based studies. Two Swedish studies covering from 1979 to 1988 and 1973 to 1994 showed a proportion of 31% and 26% of HL patients older than 60 years, respectively, in the population [4, 17, 18]. The Scotland and Newcastle Lymphoma Group (SNLG) data demonstrated that from 1979 to 2003, 624 (20%) of 3373 patients registered on the population registry were over 60 years [19]. For the registry period 1994–2003, 399 of 1701 patients were > 60 years (23%). This is a percentage confirmed in the Northern UK regional survey of elderly HL, where the age-specific incidence was 1.97/100,000 for patients aged 60–69 and 2.18/100,000 for patients aged 70 or older [10, 11]. The incidence is somewhat higher than that reported by trial study groups since the SNLG data is population-based and, therefore, likely to have fewer exclusions. An analysis of the British National Lymphoma Investigation Group (BNLI) found about 15% of all HL patients older than 65 years, but only 5% had been included in BNLI studies [16], while another population-based study confirmed the proportion of about 20% of older HL patients [10].

Additionally, there are apparent race differences in HL based in part on age. In an analysis of US Surveillance, Epidemiology, and End Results (SEER) data, there were distinct age-related incidence patterns based on race [20]. Incidence rates for older HL patients (i.e., ages >64 years) were highest among Hispanics, followed by Whites and Blacks (see Fig. 16.1).

16.3 Pathology

With regard to histology, there are notable differences between older and younger HL patient populations. The German Hodgkin Study Group (GHSG) published a prior comprehensive retrospective review of elderly patients [5]. Mixed cellularity was more common in older patients (35%) as compared with younger patients (19%) ($p < 0.001$). By contrast, nodular sclerosis was less frequent among older patients with 41 vs. 66% in younger patients ($p < 0.001$). However, this subtype still remains the most common in both groups. The remaining rare subtypes, lymphocyte predominant and lymphocyte depleted, were represented with the same frequency in elderly and younger patients.

Comparable results have been obtained in other studies. A higher frequency of the mixed cellularity subtype was reported by the Nebraska Study Group, CALGB (the Cancer and Leukemia Group B), ECOG (Eastern Cooperative Oncology Group), and a Chicago series [6, 7, 15, 21].

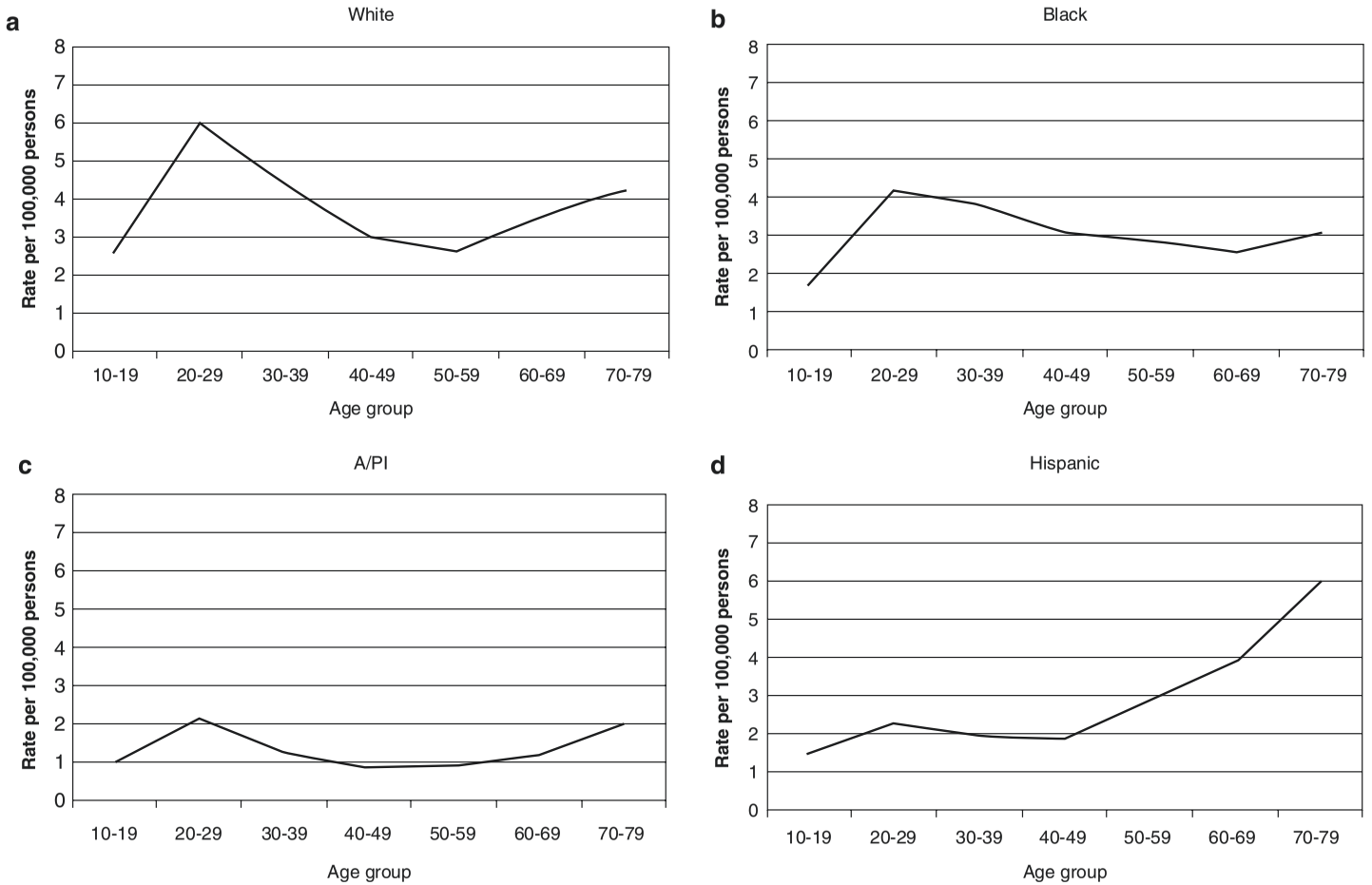

Fig. 16.1 Age-specific incidence of Hodgkin lymphoma by race. Data shown are age-specific incidence rates for 10-year age groups ranging from ages 10 to 79 years for each race (non-Hispanics Whites [referred to as Whites], Hispanic Whites [referred to as Hispanics], Blacks, and A/PIs). Rates are presented in terms of cases per 100,000 population. (**a**) Whites showed a continued bimodal age–incidence pattern, while (**b**) Blacks had a much less clear bimodal distribution. (**c**) A/PIs exhibited a bimodal pattern and have the lowest incidence rates of any race/ethnic group. (**d**) Age-specific incidence in Hispanics was distinctly not bimodal with a small increase at ages 20–29 followed by an exponential-like rise in incidence. Abbreviation: *A/PI* Asian/Pacific Islander. Reprinted with permission [20]

Jarrett et al. have drawn attention to the issue of Epstein–Barr virus (EBV) positivity in the Hodgkin and Reed–Sternberg (H-RS) cells at diagnosis [22]. EBV-associated disease was more often present in patients aged 50 years and older as compared to patients aged 15–34 years and 35–49 years. Importantly, EBV positivity was recognized as a poor prognostic factor for clinical outcome in patients over 50 years, but not in the other groups [22]. Stark et al. also recognized EBV-associated disease as a negative prognostic factor [10]. The EBV-positive status was also associated with advanced-stage disease. It is speculated that such patients have failure of immune response to EBV and present with an enhanced state of immunodeficiency and hence more advanced-stage disease.

16.4 Clinical Presentation

There have been several population-based publications on the clinical presentation of older HL patients [4, 6, 23]. In a study by Erdkamp et al., there were significantly more patients in stage II among younger patients ($p < 0.001$) [6]. Enblad et al. reported in their study more patients with advanced stages among elderly patients ($p = 0.02$) [4]. The comprehensive analysis of elderly HL patients treated within clinical trials of the GHSG among 372 patients aged ≥60 years also found a significant difference in clinical stage with more pronounced incidence of advanced stage in the elderly population [5]. Interestingly, in a recent Swedish registry analysis, the proportion of patients with advanced-stage disease increased in recent decades although these changes could partly be due to the increasing use of PET/CT.

With regard to clinical symptoms, Erdkamp et al. report a trend for a higher number of patients over 50 years presenting with B-symptoms [6]. The GHSG analysis showed statistically significant more female patients and more patients presenting with B-symptoms, elevated erythrocyte sedimentation rate, and worse ECOG performance status. Furthermore, there were less patients with large mediastinal mass and bulky disease as compared with 3879 patients aged <60 years. Additionally, the Nebraska Study Group and a subgroup analysis from the E2496 phase III study that randomized advanced-stage HL patients to ABVD vs. Stanford V showed statistically significant more older patients with poor performance status, B-symptoms at diagnosis, and less with bulky mediastinal disease [7, 21].

To summarize, compared with younger patients, older HL patients present more often with B-symptoms, in a poorer performance status, but with less bulky disease. Furthermore, the stage distribution is also different with older patients presenting more commonly with advanced-stage disease.

16.5 Age Issues Affecting Treatment and Outcome

16.5.1 Comorbidity

Several analyses have documented the prognostic impact of comorbidities in older HL patients. Van Spronsen et al. analyzed 194 HL patients and 904 NHL patients registered between 1993 and 1996 with regard to their age-specific comorbidities and the potential impact on the outcome [24]. The most frequent comorbidity in the HL patient cohort was cardiovascular disease (18%), followed by chronic obstructive lung disease (13%), diabetes mellitus (10%), and hypertension (3%). Taken together, 56% of HL patients aged over 60 years had severe comorbidity. Patients with severe comorbidity received systemic chemotherapy less frequently and had a poorer overall survival (OS) especially within the first 4 months after first diagnosis of the HL. This indicates that comorbidities likely have an impact on survival. Levis et al. reported similar findings noting comorbidities in 35% of 105 older HL patients treated with VEPEMB [25]. A multivariate analysis of this cohort identified comorbidity as an independent prognostic factor for poorer survival. A retrospective analysis of older HL patients across several US medical centers was completed [26]. Among 95 older patients with untreated HL, 61% of patients had at least one

severe comorbidity, 26% were classified as "unfit," 17% had presence of a geriatric syndrome, and 13% had loss of activities of daily living (ADLs) at diagnosis. The presence of loss so far at diagnosis was a strong prognostic factor for survival in this data set.

Guinee et al. compared the outcome of patients aged 60–70 years and 40–59 years, respectively [27]. They investigated the time period between 1977 and 1983. As compared with younger patients, older HL patients had a twofold increased risk of dying due to HL, but even a fourfold increased risk of dying due to other reasons. Surprisingly, the response rates (RR) were not different between the two cohorts with an overall RR of 84% for the older patients and 88% for the younger patients. The strongest prognostic factor in the aforementioned US series was loss of ADLs at initial diagnosis [26]. On multivariate regression, ages ≥70 years and loss of ADLs were the strongest prognostic factors for predicted survival; moreover, patients with both factors present at diagnosis had 3-year OS of 0%.

A recent multicenter phase 2 study reported treatment of 48 elderly HL patients with two initial brentuximab vedotin doses, followed by standard AVD × six cycles with subsequent consolidative brentuximab vedotin for four doses [13]. In this prospective study, geriatric-based measures (e.g., comorbidity score and loss of instrumental ADLs) were strongly associated with patient outcome (see Fig. 16.2). Two-year PFS rates for HL patients treated on this study with high a Cumulative Illness Rating Scale-Geriatric (CIRS-G) comorbidity score (i.e., ≥10 vs. <10) were 45% vs. 100%, respectively ($P < 0.0001$). Furthermore, patients with loss of any instrumental ADL at baseline vs. not had 2-year PFS rates of 25% vs. 94% ($P < 0.0001$), which persisted on multivariable analyses.

To summarize, presence of comorbidities and compromised functional status are relatively common and they represent significant prognostic factors regarding outcome of older patients with HL. There remains a clear need for validation of an age-specific prognostic tool for older HL patients that incorporates comorbidity, frailty, and functional and biological parameters.

16.5.2 Therapy-Associated Toxicity

Therapy-associated toxicities have a major impact on the treatment and outcomes of older HL patients. The reduced tolerability of conventional chemotherapy results in more toxicities overall and more severe toxicities (including fatal outcomes), the inability to maintain the scheduled dose density, and a shorter survival for relapsing or progressing patients [4, 6, 7, 18, 28–30]. This was shown in the GHSG analysis, in which the reduced dose density and the increased mortality during therapy were identified as the major determinants for an inferior outcome of older patients [5]. Landgren et al. reported that older HL patients who received ABVD (Adriamycin, bleomycin, vinblastine, dacarbazine)-based chemotherapy with a relative dose intensity (RDI) >65% had significantly improved OS vs. RDI ≤65% ($p = 0.001$) [18]. However, a significant fraction of older patients are unable to consistently tolerate ABVD with RDI of >65%.

As in younger patients, the GHSG and other studies identified the most prominent toxicities as leukopenia, infections, and cardiopulmonary events [5, 8, 31, 32]. Early termination of the scheduled therapy in older patients had a negative impact on survival [5, 18]. The incidence of severe therapy-associated toxicities varies in the literature for commonly used polychemotherapy regimens ranging between 8% and 20% [4, 6–8, 27, 31]. Using COPP/ABVD, 19% acute toxic deaths were reported [32]; this number was 18% for MOPP/ABVD. In the randomized study comparing baseline-BEACOPP regimen with COPP-ABVD ($HD9_{elderly}$), the treatment-related mortality rates (TRM) among 75 newly diagnosed advanced-stage HL patients aged 66–75 years were 21% and 8%, respectively [31]. Other modified chemotherapeutic regimens designed specifically for older HL patients had a low toxicity, but also a low efficacy [28, 33, 34].

There had been a lack of data examining the tolerability with ABVD for older HL patients in

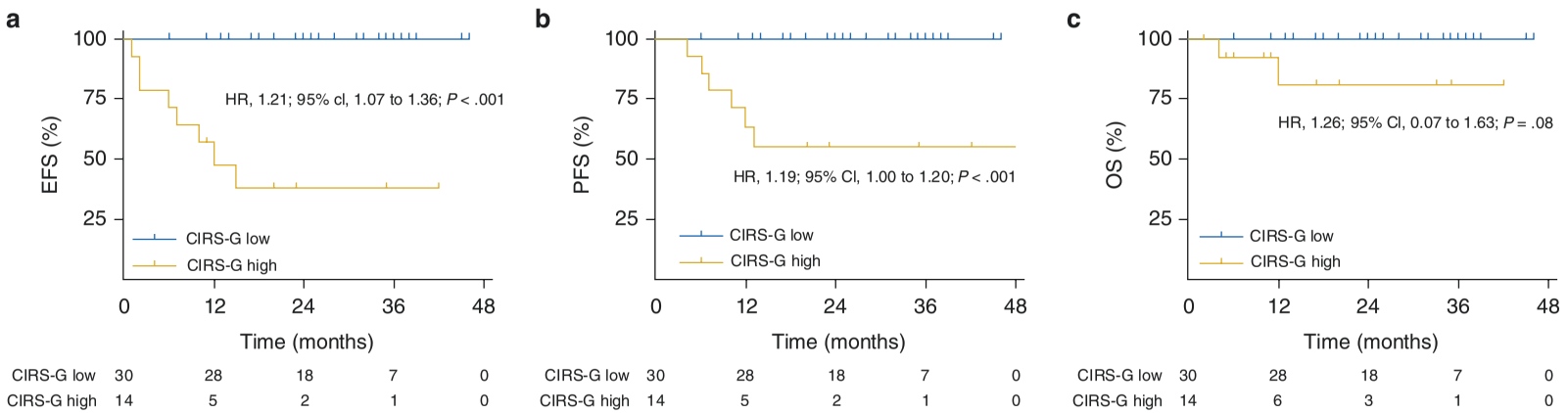

Fig. 16.2 Survival model for older Hodgkin lymphoma patientsKaplan–Meier curves for (**a**) event-free survival (EFS), (**b**) progression-free survival (PFS), and (**c**) overall survival (OS) for newly diagnosed older HL patients treated on phase II clinical trial of sequential brentuximab vedotin and AVD chemotherapy. Patients with a Cumulative Illness Rating Scale-Geriatrics (CIRS-G) score ≥ 10 vs. <10 had 2-year EFS rates of 38% (95% CI, 13% to 63%) vs. 100% (95% CI, 100% to 100%), respectively ($P < 0.001$); 2-year PFS rates of 45% (95% CI, 15% to 71%) vs. 100% (95% CI, 100% to 100%), respectively ($P < 0.001$); and 2-year OS rates of 81% (95% CI, 41% to 95%) vs. 100% (95% CI, 100% to 100%), respectively ($P < 0.02$). Reprinted with permission [13]

the contemporary era; however, two analyses addressed this question. Severe hematologic toxicities were significantly more frequent in older vs. younger HL patients treated on the randomized E2496 study [21]. Additionally, the incidence of bleomycin lung toxicity (BLT) among older HL patients was 24% with an associated BLT death rate of 18%. The vast majority of BLT cases occurred with ABVD. The incidence of BLT in the Chicago series was 32%, which was associated with a mortality rate of 25% [26]. Moreover, the incidence of BLT was 38% vs. 0% among patients who received colony-stimulating factor (G-CSF) vs. not, respectively ($P < 0.0001$). Retrospective analyses and preclinical data have suggested that the risk of BLT is increased when G-CSF is given concurrently [35]. Overall, the TRM rates for older vs. younger HL patients treated on E2496 were 9% vs. 0.3% ($P < 0.001$).

In more recent studies incorporating brentuximab vedotin into frontline therapy for untreated older patients, neurotoxicity has been examined. A multicenter prospective study examined extended dosing of single-agent brentuximab vedotin followed by expanded cohorts combing either bendamustine or dacarbazine (DTIC) for older HL patients deemed ineligible in the investigator's judgment for frontline conventional combination [36, 37]. In these two studies, the incidence rates of grade 3 neuropathy for single-agent BV and BV/DTIC frontline elderly HL studies were 30% and 27%, respectively. In a more recent clinical study utilizing brentuximab vedotin in more limited dosing and sequentially (before and after) AVD chemotherapy, the risk of grade 3 neuropathy was lower at 4% and grade 2 neuropathy was reversible in the majority of patients [13]. Collectively, all grades of neuropathy are important and there should be ardent efforts to closely track and mitigate the occurrence of this toxicity.

16.6 Therapy

16.6.1 Early Stages

In Europe, early stage is of comprised "early favorable" and "early unfavorable" subsets. In young patients, standard of care is a combined modality treatment using two to six cycles of ABVD plus involved field radiotherapy. Recent studies in younger early-stage HL have evaluated the use of PET-guided response-adapted radiotherapy reporting conflicting results. Moreover, these trials included only few, if any, older patients (Table 16.1). In the GHSG HD 8 trial, patients in the early unfavorable stage were randomized to four courses of chemotherapy (COPP/ABVD – cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, dacarbazine) and either involved field or extended field radiotherapy [38]. The analysis of the older subgroup of patients in this study demonstrated lower 5-year freedom from treatment failure (FFTF) and OS in older patients (FFTF 64 vs. 87%; $p < 0.001$ and OS 70 vs. 94%; $p < 0.001$). Importantly, older patients had a poorer outcome when treated with extended field radiation compared with involved field radiotherapy, 5-year FFTF (58 vs. 70%; $p = 0.034$), and OS (59 vs. 81%; $p = 0.008$), suggesting that EF radiotherapy should be avoided in older patients [39].

A recent analysis focusing on older patients treated within the GHSG HD10 [42] and HD11 [43] trials included 117 older early-stage HL patients treated with 2–4 cycles ABVD followed by IFRT [41]. Mean delay of treatment was twice as high in the older patients (2.2 vs. 1.2 weeks) and WHO grade 3 and 4 toxicities were also more frequent in this group (68 vs. 50%) as compared to younger patients. This resulted in higher treatment-related mortality in older patients. Despite lower dose intensity and higher toxicity, complete response was achieved in 89% of older patients; however, 3% had progressive disease, 11% relapsed, and 28% died within the median observation time of 92 months resulting in a low 5-year progression-free survival of 75% (see Fig. 16.3). Regarding older early favorable HL patients who received 2 cycles ABVD only followed by involved field radiotherapy, feasibility was higher and toxicity during chemotherapy was considerably lower with only 38% of patients experiencing WHO grade 2 to 4 toxicities. Overall, 96% of the patients receiving two cycles of ABVD achieved CR as final treatment

Table 16.1 Selected studies for older HL patients in early stages[a]

Author, year	*N*	Therapy	Outcome	Study comments
Kim, 2003 [29]	52	RT alone ($n = 37$), chemotherapy alone ($n = 9$), combined modality ($n = 6$)	10-year FFTF 71%, 5-year OS 55%, 10-year OS 31%	No significant difference among different treatment modalities; 8.6% second malignancy rate
Levis, 2004 [25]	48	3 cycles VEPEMB followed by IFRT	CR 98%, 5-year RFS 95%, DSS 97%, FFS 79%, and OS 94%	Dose intensity 85%; 5% infection rate, transfusion needed in 2%, hospitalization rate 8%
Landgren, 2006 [40]	68	RT alone—Median dose 40 Gy (IF $n = 28$; MF $n = 20$; TNI $n = 10$; other $n = 10$)	CR 82%; RR 42%	Lower CR rate vs. younger pts. 82% vs. 90% ($p = 0.05$); 16% developed second malignancy
Klimm, 2007 [39]	89	4 cycles COPP/ABVD followed by EFRT or IFRT (both 40 Gy)	5-year FFTF: EFRT 58% vs. IFRT 70%; 5-year OS: EFRT 59% vs. IFRT 81%	Toxicity increased with EF vs. IF (WHO grade 3–4: 27% vs. 9%);
Boll, 2013 [41]	117	4 cycles ABVD followed by 20–30 IFRT	5-year OS and PFS for older patients 81% and 75%, respectively	Mean treatment delay 2.2 weeks in older vs. 1.2 weeks in younger patients; WHO grade 3 and 4) in 68% older patients; TRM 6%

[a]Minimum study size of 45 patients
Abbreviations: *RT* radiation, *FFTF* freedom from treatment failure, *OS* overall survival, *CR* complete remission, *IFRT* involved field radiation therapy, *RFS* relapse-free survival, *DSS* disease-specific survival, *FFS* freedom from treatment failure, *RR* relapse rate, *TNI* total nodal irradiation, *MF* mantle field, *RT* radiation therapy, *IFRT* involved field radiation therapy, *EFRT* involved field radiation therapy, *TRM* treatment-related mortality

outcome. However, rates of progression or relapse (10%) and death (23%) were comparable in both treatment groups, and the 5-year estimates for overall survival (84%) and progression-free survival (79%) did not differ.

Levis et al. reported results of the VEPEMB schedule specifically designed for elderly patients treating 48 patients in stages IA–IIA matching the early favorable risk group [25]. The therapeutic approach was to administer three courses of VEPEMB chemotherapy plus involved field radiotherapy. The CR rate was 98% and 5-year FFS and OS were 79% and 94%, respectively. However, this FFS would be unacceptably low for early favorable HL in younger patients. A retrospective study by a Norwegian group investigated CHOP-21 (cyclophosphamide, vincristine, prednisone, and Adriamycin) in elderly HL patients [44]. Among 29 patients, 11 were stage I–IIA and 18 stage IIB–IV. Patients in early stages received two or four cycles of CHOP-21 (depending on the presence of risk factors) followed by involved field radiotherapy. The CR rate for early stages was 91%; 3-year OS and PFS were 91% and 82%, respectively. The number of patients is too small to allow a fair judgement of this regimen in the treatment of HL.

Three randomized prospective trials recently tested the omission of radiotherapy in patients with negative FDG-PET after ABVD in early-stage HL patients [45–47]. All three trials included only a minority of elderly patients. However, all three trials failed to show non-inferiority of the PET-adapted approach compared with the standard combined modality treatment. Similarly, in a recent multivariate large National Cancer Database analysis including 3795 older early-stage HL patients, the combination of chemotherapy and radiotherapy resulted in improved OS compared with chemotherapy only [48]. Therefore, the omission of radiotherapy in the early stage cannot be recommended in all patients and the expected risks of irradiation should be weighed on an individual basis with the possible gains in efficacy.

Based on currently available data, the GHSG recommends two cycles of A(B)VD followed by 20 Gy involved field radiotherapy for both young and elderly HL patients. Accordingly, four cycles of A(B)VD plus 30 Gy IF radiotherapy are

Table 16.2 Selected published studies for older HL patients in advanced stages[a]

Author, year	*N*	Therapy	Outcome	Therapy-associated death rate
Levis, 1994 [32]	26	ABVD, MOPP/ABVD	CR rate = 61% 8-year OS = 48% 8-year RFS = 75% 8-year EFS = 36%	23%
Levis, 1996 [28]	25	CVP/CEB	CR rate = 73% 5-year OS = 65% 5-year RFS = 47%	4%
Weeks, 2002 [7]	31	ChlVPP	5-year OS = 30% 5-year EFS = 24%	13%
	25	ChlVPP/ABV	5-year OS = 67% 5-year EFS = 52%	16%
Levis, 2004 [25]	57	VEPEMB	CR rate = 58% 5-year OS = 32% 5-year RFS = 66%	3%
Ballova, 2005 [31]	26	COPP/ABVD	CR rate = 77% 5-year OS = 50% 5-year HD-FFTF = 55%	8%
	42	BEACOPP baseline	CR rate = 76% 5-year OS = 50% 5-year HD-FFTF = 74%	21%
Kolstad, 2007 [44]	18	CHOP-21	CR rate = 72% 3-year OS = 67% 3-year PFS = 72%	7%
Halbsguth, 2010 [53]	60	BACOPP	CR rate = 85% 2-year OS = 76% 2-year PFS = 71%	12%
Boll, 2011 [54]	59	PVAG	CR rate = 78% 3-year OS = 66% 3-year PFS = 58%	2%
Proctor, 2012 [55]	72	VEPEMB	CR rate 61% 3-year OS = 62% 3-year PFS = 52%	4%
Evens, 2013 [21]	45	ABVD and Stanford V	CR rate = 64% 5-year OS = 58% 5-year PFS = 48%	9%
Forero-Torres, 2015 [36]	27	Brentuximab vedotin	CR rate = 73% 2-year OS NR 2-year PFS = ~30%	NR
Friedberg, 2017 [37]	42	Brentuximab vedotin and bendamustine or DTIC	CR rate = 62% 2-year OS NR 2-year PFS = ~50%	NR
Evens, 2018 [13]	48	Brentuximab vedotin *sequentially* before and after AVD	CR rate = 95% 2-year OS = 91% 2-year PFS = 84%	2%
Boll, 2018 [56]	25	Lenalidomide and AVD	CR rate = 95% 2-year OS = 91% 2-year PFS = 84%	NR

[a]Prospective clinical studies denoted in italics

Abbreviations: *OS* overall survival, *RFS* relapse-free survival, *EFS* event-free survival, *DFS* disease-free survival, *FFTF* freedom from treatment failure, *PFS* progression-free survival, *ODBEP* vincristine, doxorubicin, bleomycin, etoposide, and prednisolone, *VEPEMB* vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone, and bleomycin, *ChlVPP* chlorambucil, vinblastine, procarbazine, and prednisone, *COPP* cyclophosphamide, vincristine, procarbazine, and prednisone, *ABVD* doxorubicin, bleomycin, vinblastine, and dacarbazine, *BEACOPP* bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone, *BACOPP* bleomycin, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone, *PVAG* prednisone, vinblastine, doxorubicin, and gemcitabine, *DTIC* dacarbazine, *NR* not reported

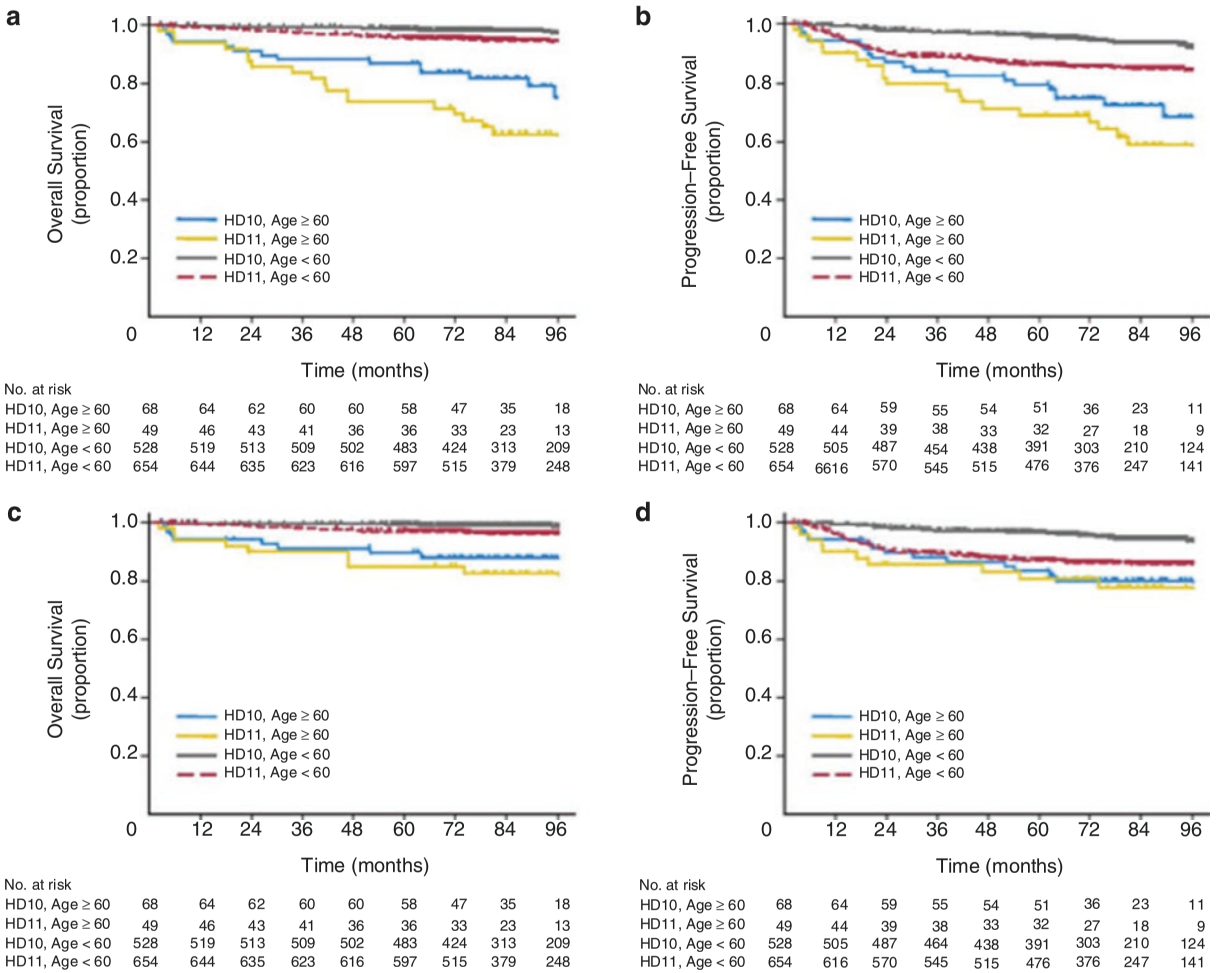

Fig. 16.3 Overall survival/progression-free survival patients in favorable early stage (HD10, GHSG) and patients in unfavorable early stage (HD11, GHSG) [41]. Kaplan–Meier plots of (**a**) overall survival, (**b**) progression-free survival, (**c**) time to HL-related death, and (**d**) time to HL-related failure according to stage and age group. HD10, favorable early-stage patients from German Hodgkin Study Group HD10 trial; HD11, unfavorable early-stage patients from German Hodgkin Study Group HD11 trial

recommended for early unfavorable stage HL in elderly patients. VEPEMB or CHOP may be considered as secondary therapeutic options. Due to potential severe toxicity, the use of bleomycin should be considered cautiously in older patients and bleomycin should not be applied beyond the second cycle to avoid cumulative toxicity [49]. In the case of preexisting pulmonary comorbidity, omitting bleomycin in this group of patients a priori is justifiable (i.e., AVD). If bleomycin is used, patients should be followed closely clinically with low threshold to discontinue it with the development of any clinical symptoms or sequelae suggestive of bleomycin lung toxicity.

16.6.2 Advanced Stages

16.6.2.1 Earlier Data

Although a superior outcome of younger HL patients can be reached by intensification of chemotherapy, ABVD can be regarded as possible for advanced-stage HL [50–52]. However, when ABVD is given with curative intent to patients over 60–65 years, chemotherapy-related toxicities are often prohibitive [5, 15, 18, 32]. This is mainly true for bleomycin. The 5-year OS for older patients treated on the ABVD-based randomized CALGB 8251 trial was 31% compared to 79% for patients aged less than 40 years ($p < 0.0001$) in the late 1980s. Levis et al. analyzed the outcome of 65 patients ages ≥65 years receiving a registry-recommended protocol of ABVD, MOPP (mechlorethamine, vincristine, procarbazine, prednisone), or ABVD/MOPP [32]. Eight-year event-free survival (EFS) and OS in these patients were 41% and 46%, respectively, both significantly inferior compared with patients ages <65 years [32]. Toxicity was prohibitive in this study with a TRM rate of 23%.

Anthracycline is likely an important component of therapy for older HL patients. The Nebraska Group compared ChlVPP (chlorambucil, vinblastine, procarbazine, and prednisone) with the hybrid ChlVPP/ABV (added Adriamycin, bleomycin, and vincristine) in a nonrandomized study including 262 previously untreated HL patients (see Table 18.2) [7]. Among patients age ≥ 60 years, the 5-year EFS was 31% and 5-year OS at 5 years was 39%, compared with 75% EFS and 87% OS for younger patients. In addition, older patients treated with ChlVPP had a poorer outcome as those treated with ChlVPP/ABV. The 5-year EFS were 24% vs. 52%, respectively ($p = 0.011$), and 5-year OS 30% vs. 67%, respectively ($p = 0.0086$).

The Italian group followed another strategy by developing less-intensive polychemotherapy regimens specifically for older patients (see Table 18.1). They started in the early 1990s with the CVP/CEB regimen (chlorambucil, vinblastine, procarbazine, prednisone, cyclophosphamide, etoposide, bleomycin) and subsequently used VEPEMB [28, 32]. CVP/CEB, a low-toxicity regimen, was administered to 25 patients and well tolerated. The CR rate at the end of treatment was 73%. However, the 5-year EFS and OS were disappointing with 32 and 55%, respectively.

The subsequent study investigated the VEPEMB regimen (see Table 16.1). Among 105 patients, 57 were in advanced stages of disease receiving six cycles of this regimen with additional radiotherapy to bulky disease or residual mass. VEPEMB was well tolerated and could be administrated to most patients, and only one patient died during treatment. After the end of treatment, 58% of patients were in CR; the 5-year FFS was 34% and OS 32% [25]. In an analysis of a prospectively randomized phase III study comparing this regimen with ABVD in 56 older HL patients (17 early-stage and 37 advanced-stage disease), the 5-year PFS rates were 48% vs. 70% ($P = 0.07$) and 5-year OS rates were 63% vs. 77% ($P = 0.25$) [57]. Though this was a small randomized study, the data do not support the use of VEPEMB outside clinical studies, since superiority to ABVD cannot be seen so far and only a minority of patients with advanced-stage disease might be cured using this schedule.

The GHSG more recently reported results of two phase II studies for untreated, older HL patients, using BACOPP (bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) and PVAG (prednisone,

vinblastine, doxorubicin, gemcitabine) [53, 54]. The CR rate with BACOPP was 85% with associated 3-year PFS and OS rates of 60% and 71%, respectively [53]. However, the regimen was associated with significant toxicity with 87% of patients experiencing grade 3–4 adverse events, 30% early termination, and TRM of 12%. PVAG was developed in part to eliminate the need for bleomycin or dacarbazine by substituting prednisone and gemcitabine [54]. The CR rate of this new regimen in elderly HL patients was 78% and the 3-year PFS and OS rates were 58% and 66%, respectively. Therapy was rather well tolerated and the TRM rate was 2%.

Kolstad et al. used CHOP (cyclophosphamide, Adriamycin, Oncovin, prednisone) for older HL patients [44]. They treated 29 patients with CHOP-21 using 2–4 cycles and involved field radiotherapy (IFRT) for early-stage and 6–8 cycles ± IFRT for advanced-stage disease. The CR rate was 93% and the 3-year PFS and OS rates for advanced-stage patients were 67% and 72%, respectively. Proctor et al. reported results from the Study of Hodgkin lymphoma In the Elderly/Lymphoma Database (SHIELD) project (www.shieldstudy.co.uk) [55]. They treated 103 older HL patients with VEPEMB, of which 72 patients had advanced-stage disease. Comorbidities and frailty were objectively assessed; only non-frail patients were eligible for the prospective study. For advanced-stage patients, the CR rate was 61% and 3-year PFS and OS rates were 58% and 66%, respectively. Therapy was generally well tolerated with a TRM rate of 3%. In prognostic factor analyses, achievement of CR strongly predicted survival. Factors associated with CR were comorbidity score (by modified ACE 27) and ADLs. In the same report, there was an additional observational group of older HL patients (frail and non-frail) treated according to physician discretion. Among 13 frail HL patients in this substudy, all died (12 from HL) with median OS of 7 months.

Findings on elderly patients from a subgroup analysis of the North American Intergroup trial E2496 were reported [21]. E2496 was a phase III study that randomized advanced-stage HL to ABVD or Stanford V; 45 patients were ≥60 years. There were no survival differences between ABVD and Stanford V for older HL patients. Toxicities were similar to other chemotherapy regimens used for older patients; however, the incidence of BLT was 24% with 91% of cases occurring with ABVD. Furthermore, the associated BLT death rate was 18%. Altogether, TRM was significantly higher for older vs. younger HL patients (i.e., 9% vs. 0.3%, $p < 0.001$). Moreover, outcomes were markedly inferior for older patients with 5-year FFS rates of 48% vs. 74%, respectively ($p = 0.002$), and 5-year OS rates of 58% and 90%, respectively, when compared to younger patients treated in this trial ($p < 0.0001$) (see Fig. 16.4).

16.6.2.2 Contemporary Data

Brentuximab vedotin has been integrated into the treatment of untreated older HL patients. An initial study examined single-agent BV for older HL patients deemed ineligible in the investigator's judgment for frontline conventional combination treatment [36]. The ORR was 92% with a complete remission (CR) rate of 72%. However, the relapse rate was high with 2-year PFS rates <40%.

This single-agent BV study was amended to combine concurrent bendamustine or DTIC [37]. The bendamustine arm was closed prematurely due to toxicity; response rates were good in the concurrent BV/DTIC arm; however, this approach did not appear curative in most patients (i.e., 2-year PFS rates of approximately 50%) and may be best considered where combination chemotherapy is not feasible.

In the aforementioned clinical study of brentuximab vedotin given before and after standard AVD therapy for untreated older HL patients [13], the choice of sequential therapy (vs. concurrent) was predicated on assumptions that (1) initial brentuximab vedotin therapy could establish earlier disease control and increase the likelihood of successful potentially curative therapy, (2) initial brentuximab vedotin therapy could minimize overlapping neurotoxicity with concurrent brentuximab vedotin/AVD, and (3) consolidation would decrease the risk of relapse. This approach also allowed assessment of the

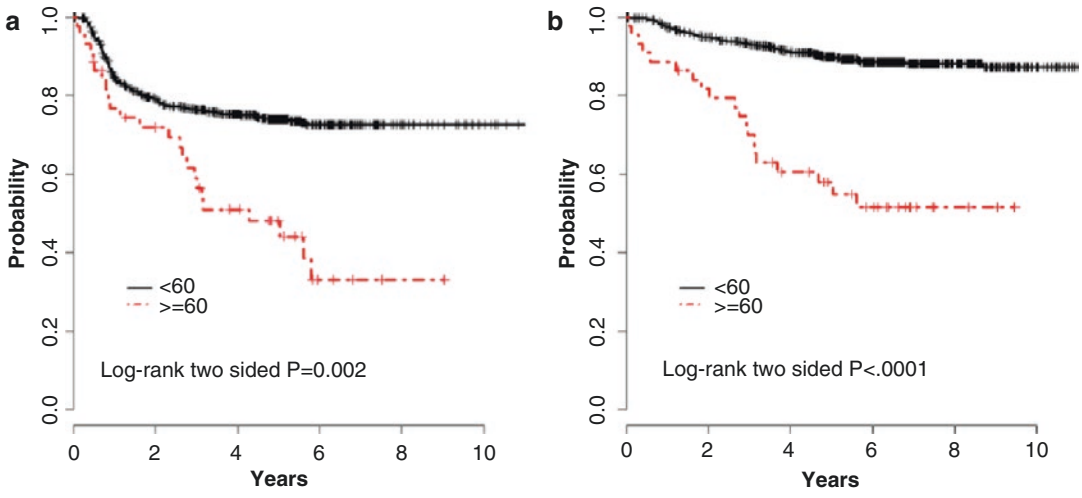

Fig. 16.4 Outcomes comparing older HL with younger patients. The (**a**) 3- and 5-year FFS for patients ages ≥60 years were 56% and 48%, respectively, compared with 76% and 74%, respectively, for patients ages <60 years ($p = 0.002$); while (**b**) the 3- and 5-year OS for patients ages ≥60 years were 70% and 58%, respectively, compared with 93% and 90%, respectively, for patients ages <60 years ($p < 0.0001$). Modified from original figure; reprinted with permission [21]

individual contribution of BV in untreated patients. The median age of patients was 69 years (range, 60–88), 81% stage III/IV and 19% stage II with bulky disease and/or B-symptoms, IPS 3–7 in 60%, median CIRS-G comorbidity score of 7 (52% with grade 3/4), and 12% having loss of instrumental ADL at baseline. Overall, 77% of patients completed the brentuximab vedotin prephase and 6 AVD cycles and 73% received at least 1 dose of brentuximab vedotin consolidation. The ORR and CR rates after the initial 2 lead-in doses of brentuximab vedotin were 82% and 36%, respectively, and 95% and 90%, respectively, after 6 AVD. Survival rates are depicted in Fig. 16.5. The most common grade 3/4 adverse events were neutropenia (44%), febrile neutropenia and pneumonia (8%), and diarrhea (6%). By intention-to-treat analysis, the 2-year PFS and overall OS were 84% and 93%, respectively. TRM for all patients was 2% (i.e., 1 case of pancreatitis, which occurred following the second lead-in dose of single-agent brentuximab vedotin) [58].

A recently published phase 1 study examined lenalidomide given concurrently (daily from days 1 to 21) with AVD chemotherapy for older HL patients [56]. Twenty-five HL patients with a median age of 67 years (range 61–76) were treated with escalating doses of lenalidomide, with DLT evaluation of 20 patients elucidating a recommended dose for phase II of 25 mg. Dose-limiting toxicities were mainly hematologic, but also included 3 thromboembolic events despite documented aspirin prophylaxis. The ORR were 79% for evaluable patients and 86% in patients treated with at least 20 mg lenalidomide. After 12 months' median observation time, the 1-year PFS and OS rates were 69% and 91%, respectively.

The GHSG and the Nordic Lymphoma Group presented recent data using brentuximab vedotin concurrently with cyclophosphamide, doxorubicin, and prednisone (B-CAP) for older HL patients with CIRS-G $\leq$ 6 [59]. Among 48 eligible advanced-stage patients, median age was 67 years (range, 60–84 years) and 50% had IPS 4–7. The ORR was 98% with a CR rate of 65%; with median follow-up of 15 months, the 1-year PFS and OS rates were 74% and 93%. Notably, there was no grade 3 neuropathy observed and the TRM was 2% (infection).

Finally, outcomes were recently analyzed across ages and treatment regimens for the pivotal phase 3 ECHELON-1 study that examined

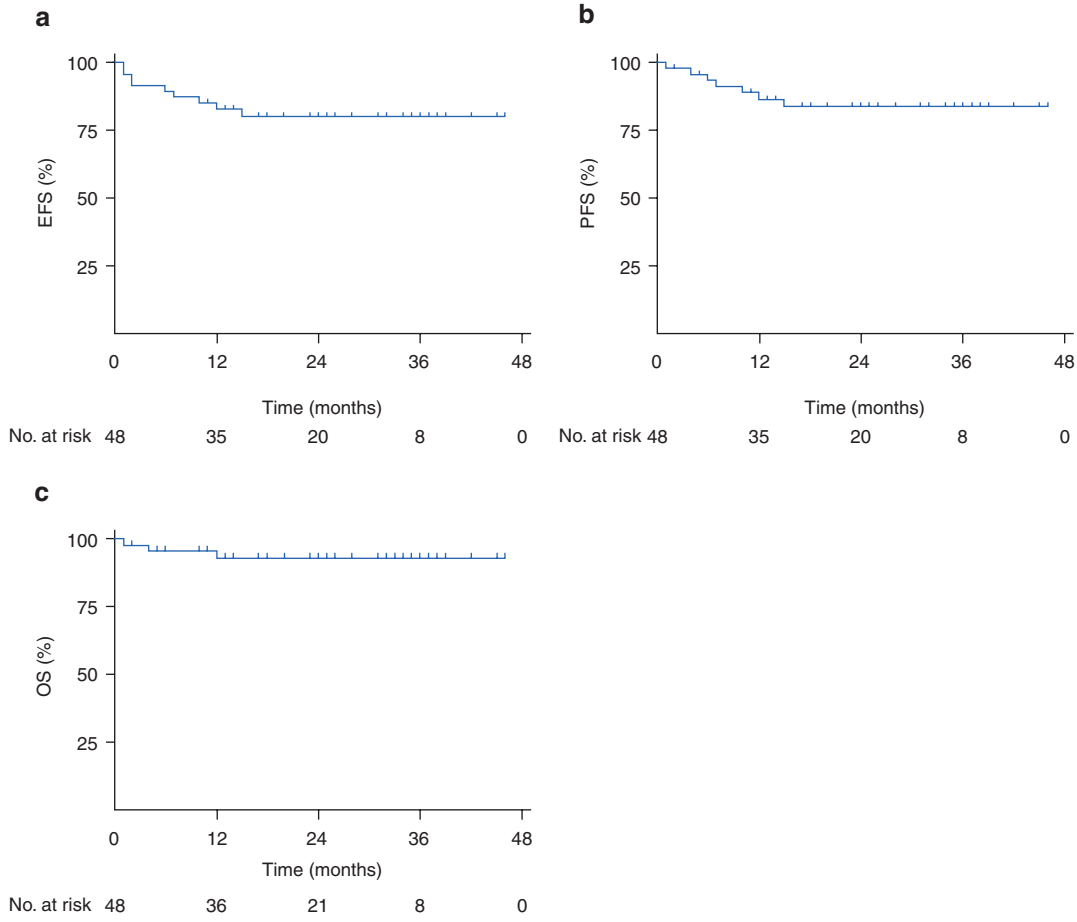

Fig. 16.5 Survival rates of patients treated on sequential brentuximab vedotin and chemotherapy study. Kaplan–Meier curves for (**a**) event-free survival (EFS, 80%; 95% CI, 65% to 89%), (**b**) progression-free survival (PFS, 84%; 95% CI, 69% to 92%), and (**c**) overall survival (OS, 93%; 95% CI, 80% to 98%) for 48 newly diagnosed older HL patients treated on phase II clinical trial of sequential brentuximab vedotin and AVD chemotherapy. Reprinted with permission [13]

the efficacy of brentuximab vedotin + doxorubicin, vinblastine, and dacarbazine (A + AVD) vs. ABVD in patients with previously untreated advanced-stage classical HL [60]. Overall, 186 of 1334 patients in the intent-to-treat population were ≥60 years (A + AVD, n = 84; ABVD, n = 102) and included in a subset analysis. With median follow-up of ~25 months, modified PFS (mPFS) per independent review facility (IRF) was similar between the 2 treatment arms for older patients (70.3% vs. 71.4%). For older patients with stage IV disease (n = 118), there was a numerical increase in median PFS per investigator with A + AVD vs. ABVD (74.0 months [95% CI, 59.5–84.0] vs. 59.9 months [95% CI, 45.6–71.5]; HR, 0.66 [95% CI, 0.34–1.26]; p = 0.20). In addition, the 2-year mPFS and PFS rates were higher in younger vs. older patients in both treatment arms. Furthermore, the TRM for older patients was 4% in the A + AVD arm and 5% with ABVD (all pulmonary related).

In conclusion, the use of anthracycline-based chemotherapy in the treatment of fit older patients with advanced HL appears to be important. In the treatment of older HL patients, at least partial or even complete omission of bleomycin from ABVD should be considered (i.e., AVD) as an

option for frontline therapy [55]. If bleomycin is utilized in older patients, there should be extreme caution overall and especially with the concurrent use of G-CSF. Dose intensification approaches, including BEACOPP variants, have not been successful in elderly patients, mainly due to an unacceptable increase in toxicity including high rates of TRM. Data incorporating brentuximab vedotin sequentially before and after AVD chemotherapy represent among the best-reported outcomes to date for untreated older HL patients. Furthermore, data from this study provided important prognostic guidelines based on geriatric assessments. Standard therapy for unfit/frail patients or ones with high comorbidities is less clear. Lower-intensity chemotherapy programs, including regimens that incorporate brentuximab vedotin, may be considered.

Objectives of future investigations should attempt to maintain these robust outcomes with less treatment (especially chemotherapy). Additionally, integration of other novel agents such as checkpoint inhibitors (e.g., NCT02758717, NCT03226249, NCT03033914, NCT03233347) and associated response-adapted trials should be evaluated, and concerted efforts should be given to prospectively integrate and potentially tailor therapy based upon geriatric assessments, especially for more frail and unfit older patients.

16.6.3 Relapsed Patients

Prospective randomized studies have not specifically evaluated the treatment of relapsed older HL patients. Therefore, treatment recommendations in this setting are largely based on personal experience and retrospective single-center analyses. Treatment options for relapsed or refractory HL in older patients include intensified treatment, poly-chemotherapy, radiotherapy in selected patients, single-agent (palliative) chemotherapy, and best supportive care.

With the development of novel drugs such as brentuximab vedotin having impressive single-agent activity, potentially less toxic alternative treatments are available for older patients in whom conventional treatment is not an option due to comorbidity [61–63].

The use of different treatment strategies is guided by patient preference, comorbidity/functional status, and the duration of response to first-line therapy. In patients with long-lasting remission after first-line treatment, polychemotherapy regimens such as PVAG, ABVD, CHOP, or the oral PECC (prednisolone, etoposide, chlorambucil, and CCNU) [64] are valid options. Furthermore, drugs with known single-agent activity in HL include alkylating agents (e.g., ifosfamide, trofosfamide, and procarbazine), gemcitabine, vinca alkaloids, and platinum derivates.

Smaller retrospective single-center studies have suggested that high-dose chemotherapy followed by autologous stem-cell support might be an effective treatment for selected patients with relapsed HL [65]. A recent, GHSG analysis examined 105 patients with a median age of 66 years [66]. Different second-line treatment strategies were used including intensified salvage regimens in 22%, conventional polychemotherapy and/or salvage-radiotherapy with curative intent in 42%, and palliative approaches such as single-agent chemotherapy and best-supportive care in 31% of the older HL patients. As patient characteristics were varied within the different treatment groups, a prognostic score applied using the risk factors (RFs) early relapse, clinical stage III/IV, and anemia identified patients with favorable and unfavorable prognosis. Median OS for the entire cohort of relapsing older HL patients was 12 months. Survival was significantly different within different risk groups (i.e., $\leq$ one RF, 3-year OS, 59%; 95% CI, 44% to 74%; $\geq$ two RFs, 3-year OS, 9%; 95% CI, 1% to 18%) (see Fig. 16.6). In low-risk patients, the impact of therapy on survival was significant in favor of the conventional polychemotherapy/salvage radiotherapy approach. In high-risk patients, OS was low overall and did not differ significantly between treatment strategies [66]. These results might be useful in guiding treatment decisions, while there remains a significant need to evaluate

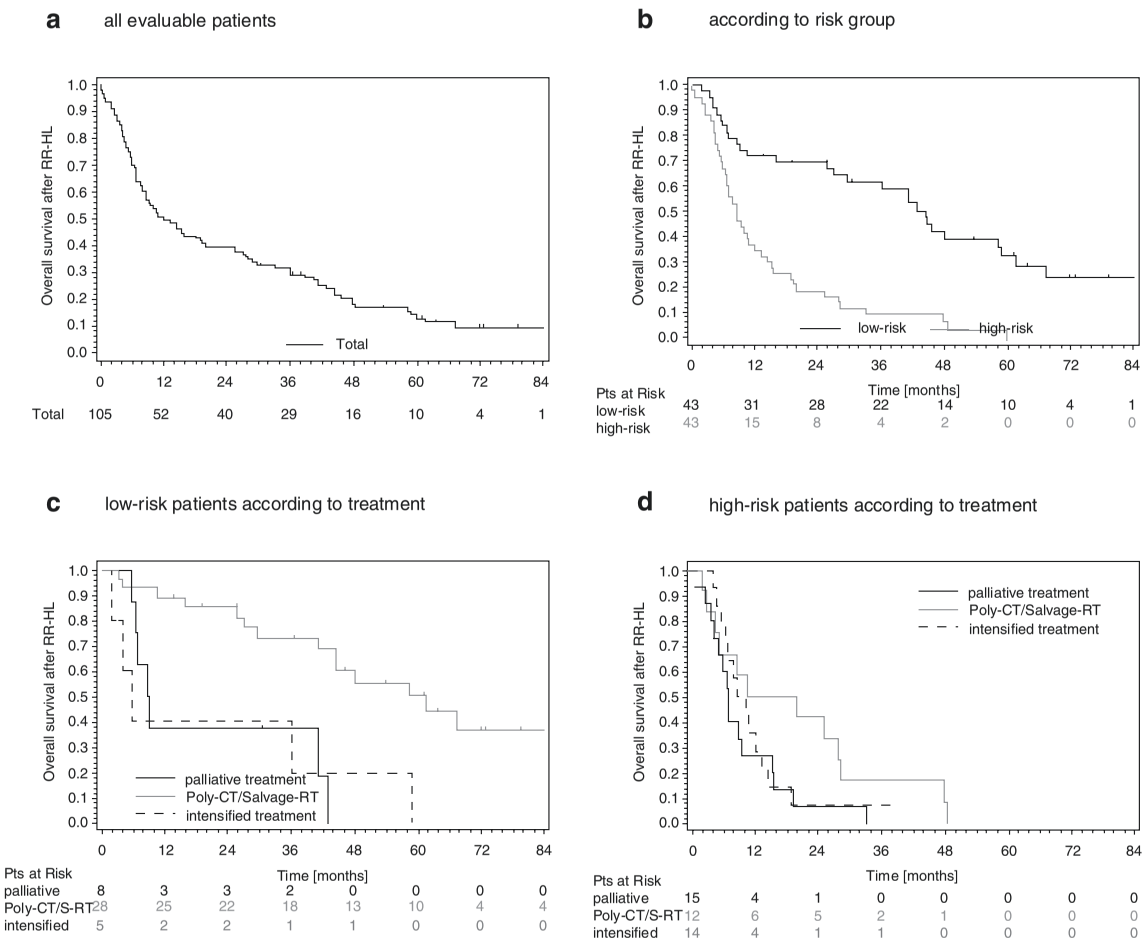

Fig. 16.6 Overall survival of older HL patients after relapse/progression. Kaplan–Meier plots of overall survival (OS) in (**a**) all evaluable patients (median OS, 12 months; 95% CI, 8 to 19 months; 3-year OS, 31%; 95% CI, 22% to 40%), (**b**) all evaluable patients according to risk group (high-risk patients, 3-year OS, 11%; 95% CI, 1% to 22%; low-risk patients, 3-year OS, 57%; 95% CI, 40% to 73%), (**c**) low-risk patients according to treatment (intensified treatment, 3-year OS, 20%; 95% CI, 0% to 55%; polychemotherapy [poly-CT]/salvage radiotherapy [RT], 3-year OS, 71%; 95% CI, 53% to 89%; could not be estimated for patients receiving palliative treatment), and (**d**) high-risk patients according to treatment. RR-HL, relapsed/refractory Hodgkin lymphoma. Modified from original figure; reprinted with permission [65]

novel compounds in older patients with relapsed/refractory HL.

Antibodies against PD-1 have shown remarkable efficacy in Hodgkin lymphoma and were well tolerated. Phase II trials for relapsed and refractory Hodgkin lymphoma patients have been conducted evaluating the anti-PD-1 antibodies nivolumab and pembrolizumab with similar results. Although only few elderly patients were treated within these trials, anti-PD-1 antibodies might provide a valid treatment option for relapsed or refractory elderly Hodgkin lymphoma patients [67, 68]. This new class of drugs are generally well tolerated and not associated with toxicity observed with chemotherapy.

16.7 Conclusions and Perspectives

Although outcomes have improved over time, survival rates for older HL patients remain disproportionately inferior compared to younger patients. Furthermore, HL in older patients remains a disease where standard treatment recommendations are difficult. Generally, treatment of older HL patients for all disease stages should be given with curative intent with treatment paradigms similar to younger patients. This includes abbreviated chemotherapy (2–4 cycles) and involved field radiation for early-stage disease and chemotherapy for 6 cycles for advanced stages. Intensive regimens such as BEACOPP are too toxic for older patients, while less intensive regimens such as CVP/CEB and ChlVPP are not effective enough.

Outside of a clinical trial, ABVD likely remains a standard regimen for older HL patients; however, caution should be given to potential severe treatment-related toxicities, especially bleomycin-related lung toxicity. Balancing the risk/benefit ratio, a priori omission of bleomycin may be considered in older patients (i.e., AVD), especially for patients over ages 65–70 years. Additionally, the impact of patient comorbidities and assessment of functional status should continue to be examined in prospective studies with this consideration of choice of therapy based on this. Finally, the integration of novel therapeutic agents into frontline treatment paradigms should continue to be evaluated.

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Nodular Lymphocyte-Predominant Hodgkin Lymphoma

17

Dennis A. Eichenauer and Ranjana H. Advani

Contents

17.1 Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare lymphoma entity representing about 5% of all HL cases [1]. Pathobiology and clinical course differ from classical HL (cHL). This chapter describes the pathologic and clinical characteristics, differential diagnoses, risk factors, and treatment options of NLPHL.

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17.2 Pathology of NLPHL

The pathologic key feature of NLPHL is a malignant cell population that was originally termed lymphocytic and histiocytic (L&H). These cells were reclassified in the WHO 2008 classification as lymphocyte predominant (LP)

A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_17

cells [2]. LP cells carry one large single-folded or polylobulated vesiculated nucleus. In contrast to Hodgkin and Reed-Sternberg (H-RS) cells seen in cHL, the number of nucleoli in LP cells is increased leading to the more descriptive term "popcorn cells" [3]. In rare cases, however, LP cells can resemble classical or lacunar-type H-RS cells.

While H-RS cells derive from germinal center (GC) B cells that normally would have undergone apoptosis, LP cells originate from GC B cells that were positively selected. Single-cell polymerase chain reaction assays demonstrated that LP cells typically contain rearranged immunoglobulin (Ig) genes and variably express Ig mRNA. The Ig heavy chain can show evidence of somatic hypermutation in line with the GC origin of LP cells. Different chromosomal abnormalities have been described in up to two-thirds of NLPHL cases. Although some genetic lesions were identified, little is known about the pathologic properties of LP cells. Constitutive activity of NF-κB, the JAK/STAT pathway, and the BCL-6 transcription factors seems to be involved. However, mutations in the genes coding for the NF-κB regulating factors IκBα and A20 are uncommon [4–7].

LP cells are embedded in a nodular or follicular background that is dominated by small B lymphocytes (Fig. 17.1). Rarely, a more diffuse growth pattern can be observed. Immunophenotyping is critical to establish the correct diagnosis of NLPHL. LP cells present a B-cell phenotype expressing CD20, CD45, and frequently EMA and CD79a but are negative for CD15, CD30, and EBV (Table 17.1).

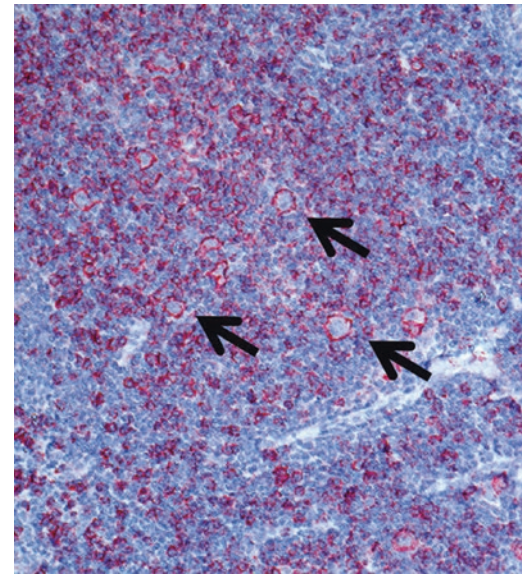

Fig. 17.1 Malignant LP cells (CD20 staining). Permission: Courtesy of S. Hartmann

Table 17.1 The immunophenotype of cHL and NLPHL

	NLPHL	cHL
CD20	+	±
CD30	−	+
CD15	−	+
CD45	+	−
CD79a	+	±
OCT-2	+	−
BOB-1	+	±
EMA	±	−
EBER	−	±

17.3 Differential Diagnosis

The discrimination between NLPHL and cHL or other related lymphoma entities can be difficult. A consortium of European and American expert pathologists that evaluated 426 cases initially classified as NLPHL highlighted this challenge. Using classical morphology and immunohistochemistry, 51% of cases were confirmed as NLPHL, 27% were reclassified as lymphocyte-rich cHL, and 5% as other cHL subtypes. The remaining 17% of cases were identified as non-Hodgkin lymphoma (NHL) (3%) and reactive lesions (3%) or were not assessable (11%) [1]. These findings underscore the need for immunohistochemistry and expert pathology review for the diagnosis of NLPHL.

17.4 Transformation to NHL

In contrast to cHL, NLPHL tends to transform into aggressive NHL. T-cell-rich B-cell lymphoma represents the most frequently observed histologic subtype at transformation.

A registry-based retrospective analysis comprising 164 patients initially diagnosed with NLPHL came from France. After a median follow-up of 9.5 years for survivors, 66 patients had lymphoma recurrence of which 19 had relapsed with transformation into aggressive NHL. The median time from initial NLPHL diagnosis to histologic transformation was 4.7 years; the cumulative 10-year transformation rate was 12% [8].

A retrospective study from Canada using the British Columbia Cancer Agency (BCCA) database included a total of 95 patients initially diagnosed with NLPHL. Transformation into aggressive NHL occurred in 13 of them; the median time to transformation was 8.1 years. The actuarial risks for the diagnosis of transformed lymphoma after initial diagnosis of NLPHL were 5, 7, 15, 31, and 36% after 5, 10, 15, 20, and 25 years, respectively. Interestingly, two clusters of transformation were seen. One cluster of transformation occurred less than 3 years after initial lymphoma diagnosis (5/13), while a second cluster occurred after 10 to 25 years (7/13). Transformation was more likely in patients with initial splenic involvement [9].

Given the significant risk for histologic transformation into aggressive NHL, obtaining a biopsy is mandatory in NLPHL patients presenting with suspected relapse.

17.5 Clinical Characteristics

A comprehensive analysis performed by the German Hodgkin Study Group (GHSG) compared characteristics and clinical outcome of 394 NLPHL patients and 7.904 cHL patients. Median age was 37 years for NLPHL patients and 33 years for patients with cHL. The proportion of male patients was higher in NLPHL with 75% compared to 56% in cHL. Most NLPHL patients had early favorable stages at diagnosis (63% in NLPHL vs. 22% in cHL), and patients with early unfavorable and advanced stages were less frequently seen (16 and 21% in NLPHL vs. 39 and 39% in cHL). The presence of B symptoms (9% in NLPHL vs. 40% in cHL) and risk factors such as involvement of 3 or more nodal areas (28% in NLPHL vs. 55% in cHL), elevated erythrocyte sedimentation rate (4% in NLPHL vs. 45% in cHL), large mediastinal mass (31% in NLPHL vs. 55% in cHL), extranodal involvement (6% in NLPHL vs. 14% in cHL), and elevated lactate dehydrogenase (16% in NLPHL vs. 32% in cHL) was also less common in NLPHL. After a median follow-up of 50 months, relapse rates in NLPHL and cHL were comparable (8.1% in NLPHL vs. 8.0% in cHL). However, the temporal distribution of disease recurrence differed between both HL subtypes. Late relapses occurred significantly more often in NLPHL (7.4% in NLPHL vs. 4.7% in cHL), whereas early relapses were more common in cHL (0.8% in NLPHL vs. 3.2% in cHL) [10].

17.6 Treatment of Early Favorable NLPHL

Patients with NLPHL in early favorable stages have an excellent prognosis. Different treatment modalities including watchful waiting, radiotherapy (RT) alone, combined-modality approaches, and anti-CD20 antibody therapy with rituximab have been evaluated in this patient group.

Generally, treatment of NLPHL in early favorable stages aims at inducing as little acute and late toxicity as possible. Particularly in children, treatment strategies focus on avoiding long-term side effects such as second malignancies, infertility, growth retardation, hypothyroidism, and damage of heart and lung. In an attempt to postpone treatment, watchful waiting after diagnostic lymphadenectomy was evaluated prospectively in a study from the Children's Oncology Group. A total of 52 pediatric patients with NLPHL affecting a single lymph node who had achieved a complete remission after surgery according to positron emission tomography (PET) and computed tomography (CT) were taken into account. The 5-year event-free survival rate was 77.1% so that chemotherapy or RT could be spared in a relevant proportion of patients [11]. Prospective data on watchful waiting after complete lymph node resection for adult patients are not available to date. Thus, RT alone represents the mainstay of treatment.

In their studies, the GHSG treated a total of 229 stage IA NLHPL patients with extended-field RT

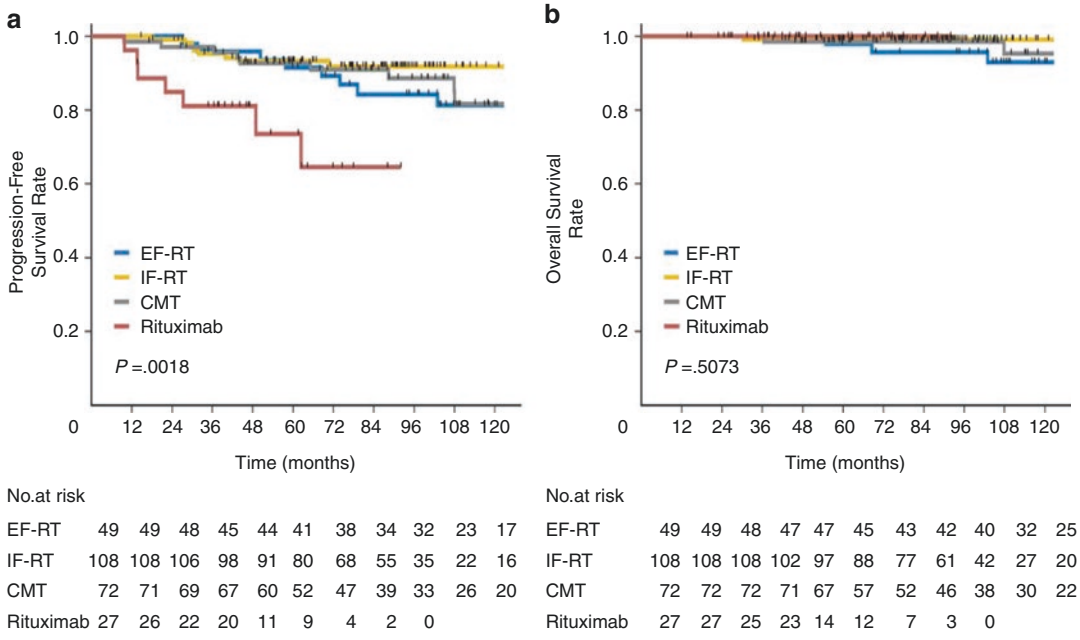

Fig. 17.2 Outcome (**a**, progression-free survival; **b**, overall survival) of patients with stage IA NLPHL after different first-line approaches (from Eichenauer et al., J Clin Oncol, 2015 [12])

(EF-RT) (49 patients), involved-field RT (IF-RT) (108 patients), and combined-modality approaches (72 patients), respectively. After a median follow-up of 110 months for the EF-RT group, 87 months for the IF-RT group, and 95 months for the combined-modality group, there were no significant differences in terms of progression-free survival (PFS) (8-year PFS rates: 84.3% after EF-RT, 91.9% after IF-RT, 88.5% after combined-modality treatment) and overall survival (OS) (8-year OS rates: 95.7% after EF-RT, 99.0% after IF-RT, 98.6% after combined-modality treatment) between the treatment approaches (Fig. 17.2). Increased toxicity was observed in patients who had been treated with combined-modality strategies [12]. Excellent long-term outcomes were also reported in another analysis including 113 patients with stage I/II NLPHL of whom 93 were treated with RT alone. Ten-year PFS and OS rates were 85 and 96% for stage I patients and 72 and 100% for stage II patients when treatment consisted of RT alone [13].

A retrospective study from Canada compared the clinical course of 32 early-stage NLPHL patients treated with RT alone between 1966 and 1993 with the course of 56 patients treated with two cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or ABVD-like chemotherapy followed by RT between 1993 and 2009. At 10 years, PFS and OS rates for patients treated with RT alone were 65 and 84%, respectively, whereas PFS and OS rates for patients who had received combined-modality treatment were 91 and 93%, respectively. However, these findings indicating a superior tumor control for patients treated with combined-modality approaches have to be interpreted with caution as the individuals included in the analysis had their treatment over a time interval of four decades and other factors could have had significant impact on the outcome. For example, supportive care may have varied considerably between individual patients. In addition, the combined-modality treatment group had a much shorter follow-up (5.7 years) than the RT-alone group (18.6 years). As most relapses in NLPHL occur late, the inferior outcome of patients treated with RT alone might thus at least in part relate to the longer follow-up in comparison with the patients who had combined-modality treatment [14].

Given the consistent expression of CD20 on the malignant LP cells, the GHSG conducted a phase II study evaluating the monoclonal anti-CD20 antibody rituximab in 28 patients with stage IA NLPHL. Patients received four weekly standard doses of the antibody (375 mg/m^2). All patients responded to treatment. However, after a median follow-up of 43 months, 25% of patients had relapsed indicating that tumor control with single-agent rituximab is inferior when compared with RT alone or combined-modality approaches [15].

On the basis of the data that are currently available, limited-field RT alone is recommended as standard of care for the treatment of stage IA NLPHL without risk factors by the European Society for Medical Oncology (ESMO) and the National Cancer Center Network (NCCN) [16, 17]. For stage IB and stage II NLPHL without risk factors, the ESMO recommends combined-modality approaches as applied in cHL. Results obtained with such strategies, i.e., a brief chemotherapy followed by limited-field RT, are excellent with 8-year PFS and OS rates of 83.2 and 95.1%, respectively [18]. The NCCN recommends RT alone for stage IIA patients, while chemotherapy or immuno-chemotherapy optionally followed by IF-RT should be given in stage IB/IIB NLPHL [17].

17.7 Treatment of Early Unfavorable and Advanced NLPHL

The treatment of patients with early unfavorable and advanced NLPHL is often identical to cHL. This is based on several retrospective analyses. According to an analysis from the GHSG, NLPHL patients with early unfavorable and advanced stages had 8-year PFS rates of 85.2 and 76.2% and 8-year OS rates of 98.6 and 87.4%, respectively, after ABVD-based chemotherapy for early unfavorable stages and different variants of the BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) protocol for advanced stages [18].

Promising data on the R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) protocol have recently become available. A retrospective study from the MD Anderson Cancer Center included 14 patients with advanced NLPHL who had treatment with this regimen. The overall response rate was 100%. The PFS estimates at 5 and 10 years were 85.7% each. No case of histologic transformation into aggressive NHL had occurred [19]. Although prospective data confirming these results are pending, the use of R-CHOP should be considered particularly in patients with advanced NLPHL who have splenic involvement and are thus at an increased risk of transformation into aggressive NHL.

A recent retrospective study from the Memorial Sloan Kettering Cancer Center evaluated active surveillance as initial strategy for NLPHL. The study included 163 patients, of whom 126 (77%) had received treatment with RT, chemotherapy, combined-modality approaches, or single-agent rituximab and 37 (23%) were followed with active surveillance. After a median follow-up of 5.7 years, the 5-year PFS rates were 97.2 and 76.5% for patients receiving treatment and active surveillance, respectively. Especially among the 121 patients with early stages, the 5-year PFS was better with active therapy (94.2% after treatment vs. 65.1% with active surveillance). However, there was no impact on OS with a 10-year estimate of 96.6% for the whole cohort and comparable rates for both groups. Only 24% of patients followed with active surveillance received therapy after a median of 5.1 years. Treatment-related mortality exceeded lymphoma-related mortality. Based on these results, the authors concluded that active surveillance may be a viable initial strategy, particularly for asymptomatic patients with low tumor burden, as most patients do not require therapy after many years of observation and those who progress may be effectively salvaged without compromising OS [20]. However, similarly to R-CHOP and in contrast to pediatric patients, these data on active surveillance have not yet been confirmed prospectively or in retrospective analyses from other groups.

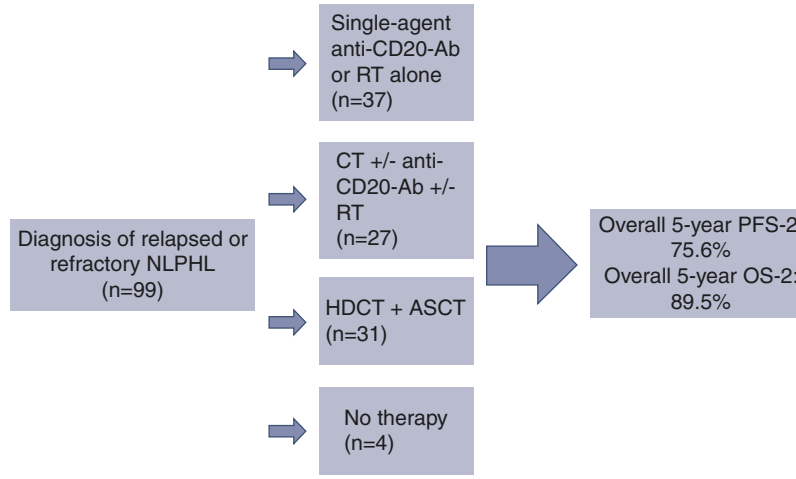

Fig. 17.3 Overall outcome of patients with relapsed or refractory NLPHL after different salvage strategies (from Eichenauer et al., Blood, 2018 [27])

17.8 Treatment of Relapsed NLPHL

A standard of care for relapsed NLPHL has not been defined to date. The available data indicate that different approaches ranging from single-agent anti-CD20 antibody treatment to high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) represent options in case of disease recurrence (Fig. 17.3).

In a phase II study conducted by the GHSG, 15 patients with relapsed NLPHL were treated with four weekly doses of rituximab at 375 mg/m^2. The ORR was 94%. After a median follow-up of 63 months, the median time to progression was 33 months, and the median OS was not reached [21]. Another phase II study by the Stanford group included 39 patients (18 patients with relapsed NLPHL and 21 patients with previously untreated NLPHL). Patients received four weekly doses of rituximab at 375 mg/m^2 either alone or followed by rituximab maintenance every 6 months for 2 years. All patients responded to treatment. After a median follow-up of 9.8 years for patients treated with rituximab alone and 5.0 years for patients receiving rituximab induction followed by rituximab maintenance, 5-year PFS estimates for previously treated patients were 36.4 and 71.4%, whereas the 5-year OS estimates were 90.9 and 71.4% after rituximab alone and rituximab induction followed by rituximab maintenance, respectively [22]. More recently, the second-generation anti-CD20 antibody ofatumumab was evaluated in a phase II study including 28 patients with relapsed NLPHL. The ORR was 96%. After a median follow-up of 26 months, the 2-year PFS and OS estimates were 80 and 100%, respectively [23]. Thus, single-agent anti-CD20 antibody treatment results in a durable remission in a relevant proportion of patients with relapsed NLPHL.

However, patients with NLPHL recurrence who present with high-risk features such as a short time interval between first-line treatment and the diagnosis of relapse are candidates for more aggressive salvage approaches, e.g., high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). The largest analysis evaluating this treatment modality came from the European Society for Blood and Marrow Transplantation. A total of 60 patients were included. The patients had a median of 2 prior lines of therapy; the median time interval between NLPHL diagnosis and ASCT was 21 months. After a median follow-up of 56 months, the 5-year PFS and OS rates were 66 and 87%, respectively [24]. Similar results were also obtained in smaller retrospective studies investigating the role of high-dose chemotherapy and ASCT in relapsed NLPHL [25, 26].

Taken together, there are different treatment options in relapsed NLPHL. Those include anti-CD20 antibody treatment and high-dose chemotherapy followed by ASCT, but also localized RT

and conventional chemotherapy. The optimal approach should be chosen individually based on patient characteristics such as the time interval between first-line treatment and the diagnosis of disease recurrence, previous therapies, and tumor burden at relapse [27].

17.9 Risk Factors

Due to the rarity of NLPHL, it has been difficult to recognize prognostic factors in this entity. However, some retrospective analyses could identify risk factors predicting a poorer outcome.

Within a large GHSG analysis including 394 NLPHL patients, advanced stages, hemoglobin of less than 10.5 g/dl, and lymphocytopenia were associated with an impaired freedom from treatment failure, while an age of 45 years or older, advanced stages, and hemoglobin of less than 10.5 g/dl were identified as negative prognostic factors for OS [10]. A smaller analysis assessing the long-term course of 88 NLPHL patients revealed advanced stages, presence of B symptoms at diagnosis, low serum albumin, and insufficient response to first-line treatment as risk factors for a worse outcome [28].

A prognostic score including the risk factors low serum albumin, male gender, and variant NLPHL histology was developed using data from 413 NLPHL patients treated within 9 prospective GHSG studies. On the basis of this score, 3 distinct risk groups with significant differences in terms of PFS and OS could be defined. Five-year PFS rates ranged between 68.7% and 95.2% and OS rates ranged between 88.3% and 98.7% [29]. Histologic NLPHL variants were characterized by the presence of lymphoma cells outside the B-cell nodules or B-cell depletion of the microenvironment and therefore corresponded to the growth patterns C, D, E, and F (C, extranodular LP cells; D, T-cell rich; E, T-cell-/histiocyte-rich large B-cell lymphoma-like; F, diffuse moth-eaten) as described by Fan and colleagues. In contrast, the growth patterns A and B (A, B-cell-rich nodular; B, serpiginous/interconnected) according to Fan et al. were considered typical [29, 30].

17.10 Summary and Conclusions

NLPHL which accounts for about 5% of all HL cases is characterized by pathologic and clinical features that substantially differ from cHL. Given the mostly indolent clinical course, RT alone represents the treatment of choice for NLPHL patients with localized disease. More advanced stages are often treated with approaches originally developed for cHL consisting of chemotherapy and/or RT. However, it is unclear whether these strategies represent the optimal treatment for NLPHL patients, especially for those with advanced stages. In relapsed NLPHL, single-agent anti-CD20 antibody treatment seems to be sufficient for a relevant proportion of patients as indicated by small phase II studies. However, treatment should be chosen individually as some patients with NLPHL recurrence appear to require more aggressive treatment.

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The Management of Hodgkin Lymphoma During Pregnancy

18

Veronika Bachanova and Joseph M. Connors

Contents

18.1 Introduction

The peak incidence of Hodgkin lymphoma (HL) coincides with reproductive years, and about 0.5–1% of all HL patients present with concurrent pregnancy. Lymphoma is the most common hematologic malignancy complicating pregnancy, with an estimated incidence of HL-associated deliveries of between 1 in 1000 and 1 in 3000 pregnancies [1, 2]. The medical challenge of concurrent HL and pregnancy stems from the need to manage the potentially life-threatening malignancy while giving the

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_18

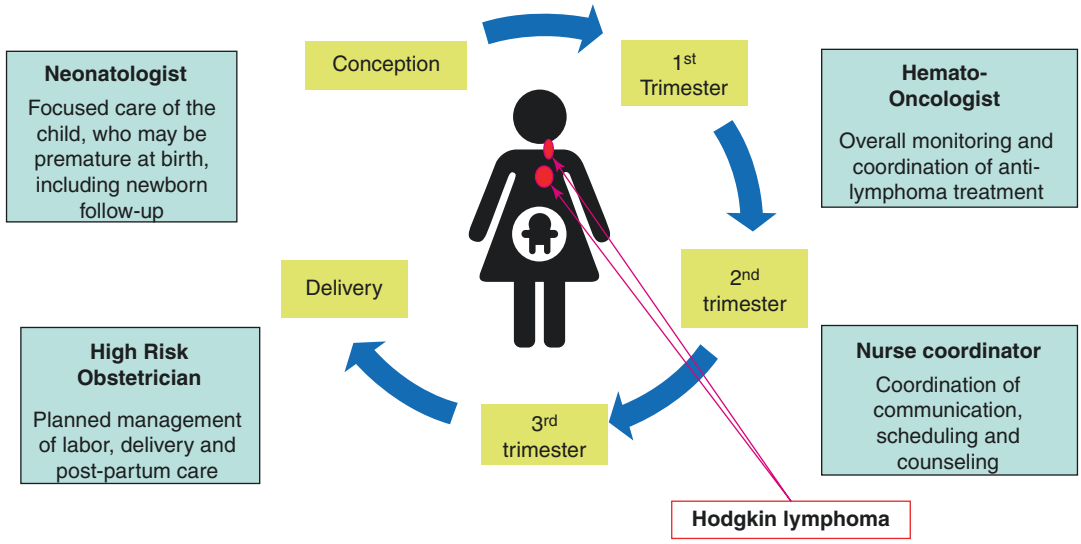

Fig. 18.1 Recommended algorithm for treatment of pregnancy-associated Hodgkin lymphoma (*HL*). *ABVD* doxorubicin, bleomycin, vinblastine, dacarbazine

developing fetus the best chance of reaching term fully intact. Essentially, two patients need to be managed: one with lymphoma and the other without, both of whom will be affected by the toxicity of any treatments. Religious, ethical, psychological, social, and cultural beliefs and attitudes of the patient and her partner, family, and physicians all can affect decision-making. Thus, management of the disease and pregnancy not only involves the therapeutic approach but also requires attention to alleviating fear and anxiety and supporting the patient's emotional and social well-being. Current clinical practice for treating HL during pregnancy is based largely on case series, retrospective reports, and expert opinions. Therefore, management of HL during pregnancy requires that the advising clinician must balance the provision of expertise and knowledge about treatment options and prognosis with respect for ethical principles, compassion, and acceptance of patient autonomy.

One of the main principles in treating patients with HL discovered during pregnancy is to provide care under the direction of a multidisciplinary team composed of a hemato-oncologist knowledgeable in the treatment of HL, an obstetrician experienced in the management of high-risk pregnancy, a pediatrician/neonatologist familiar with hematologic problems in the neonate, and a nurse coordinator who augments the communication and delivery of care (Fig. 18.1). The best results are possible if the decision-making is guided by a judicious mix of careful clinical judgment, the experience of involved team members, knowledge of the natural history of HL, and consideration of the patient's personal beliefs and desires [2–4]. A comprehensive review of the management of HL and coincident pregnancy recently published by Eyre et al. validates the effectiveness of this team approach and the specific recommendations described below [5].

18.2 Diagnostic Approach to HL during Pregnancy

Planning the diagnostic evaluation of HL in a pregnant patient should balance accurate disease assessment with the need to limit invasive procedures. The histopathologic diagnosis of HL should be based on tissue examination obtained by excisional or incisional tissue biopsy. The most common subtype encountered in pregnancy is nodular sclerosing HL. Following diagnosis, the initial evaluation should include a complete history and physical examination with thorough

palpation of all node-bearing areas and the abdomen, as well as careful documentation of B symptoms. Despite a higher rate of extranodal involvement of genital organs in non-Hodgkin lymphoma during pregnancy [6], non-lymphatic spread in the pregnant HL patient is rare and usually limited to the lung or liver [7]. Often complete staging is not necessary, and the guiding principle in managing the pregnant patient should be to restrict investigations to determining the cause of patient symptoms, noting the bulk and anatomic location of the dominant tumor masses, and estimating lymphoma stage. Standard laboratory tests should include hemoglobin, complete differential white blood cell count, platelet count, erythrocyte sedimentation rate (ESR), liver and renal function assessment, lactate dehydrogenase, and serum protein electrophoresis including albumin level. It is important to recall that pregnancy can affect the results of some of these tests, particularly ESR and alkaline phosphatase, and therefore, these tests must be interpreted carefully.

Radiologic staging should be limited to the minimum necessary to identify disease that seriously threatens the immediate well-being of the mother or child. Combined F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) scan is a standard imaging modality for staging HL under ordinary circumstances, but it employs ionizing radiation that is potentially harmful to an unborn fetus and should be avoided in pregnancy [7]. A single posteroanterior radiograph of the chest, with proper shielding, should be obtained to characterize the extent of mediastinal and pulmonary disease because overall radiation exposure is much lower than the dose associated with malformation during organogenesis [8]. Abdominal ultrasonography should be used to identify the extent and size of retroperitoneal nodal disease and provides sufficient detail for proper management [3]. Magnetic resonance imaging (MRI) without use of gadolinium has been used in place of CT scan with no potential toxicity to the fetus [9]. A recent study on 90 patients with lymphoma coincidental with pregnancy reported that MRI staging was performed on most patients without obvious negative consequences [2]; however, the amount of detail provided in excess of what can be found with ultrasonography is not necessary, and the safety of the intensive magnetic fields required and the exposure to gadolinium for contrast enhancement is not fully established. Bone marrow biopsy should be performed in patients with B symptoms or abnormalities in blood counts such as anemia, thrombocytopenia, or leukopenia; however, only 1 out of 40 had marrow involved in a recently published large case series [2]. For those patients in whom chemotherapy is planned, echocardiography may be used to assess left ventricular function. The goal of clinical and radiologic staging is to provide guidance about the pace of disease progression, to determine the cause of any specific symptoms such as cough, and to evaluate whether treatment can be deferred or whether immediate treatment is required because of symptomatic disease or organ dysfunction. Hence, tests should only be performed if decisions regarding immediate management will be influenced.

18.3 Outcomes of Mother and Child in HL Coincident with Pregnancy

The complexity of caring for pregnant patients with HL requires a multidisciplinary team of experts working together to develop an individualized management plan (Table 18.1). The therapeutic options for pregnant patients with HL depend on stage, symptoms, gestational age at diagnosis, fetal risks, and the patient's wishes regarding the continuation of pregnancy. Useful lay language explanations and guidance for patients have been developed by several advocacy groups and can be recommended to patients (e.g., https://lymphoma-action.org.uk/about-lymphoma-treatment-lymphoma/treatment-during-pregnancy). Although the evidence for managing pregnant HL patients comes from a few published case series and anecdotal descriptions, this evidence can provide useful guidance when complemented by careful clinical judgment and knowledge of the natural history of HL. The

Table 18.1 Characteristics of an ideal multidisciplinary team treating the pregnant patient with concomitant Hodgkin lymphoma

Obstetrician	Usually makes the diagnosis, arranges referral to hematologist/oncologist
	Brings experience in high-risk pregnancies (patients with active malignancy)
	Provides counseling regarding pregnancy termination (if recommended by the team and chosen by the patient)
	Establishes the timing and method of delivery
	Supervises effective postpartum contraception for a minimum of 2 years (greatest risk of relapse)
Hematologist/ medical oncologist	Performs oncologic history and physical examination and plans staging
	History searching for B symptoms or other symptomatic problems suggesting more advanced disease
	Physical examination for lymphadenopathy or organomegaly
	Complete blood cell counts
	Serum creatinine, alkaline phosphatase, lactate dehydrogenase, bilirubin, and protein electrophoresis (including albumin level)
	Chest radiograph, posteroanterior view only, with appropriate shielding
	Abdominal ultrasound for retroperitoneal lymphadenopathy
	Formulates overall therapeutic plan
	Administers chemotherapy if deemed necessary
	Provides supportive care for patients treated with chemotherapy to keep Hgb $\geq$100 g/L and platelet count $\geq 30 \times 10^9$/L and reviews safety of medications used for supportive care during pregnancy
	Coordinates delivery planning and chemotherapy administration to ensure that platelet count is $\geq 50 \times 10^9$/L at the time of delivery
	Arranges oncology follow-up after pregnancy to complete appropriate staging
Neonatologist	Has experience in high-risk pregnancies
	Has experience in childhood hematologic disorders
	Examines placenta and arranges histopathologic evaluation for presence of metastasis
	Coordinates newborn care at the time of delivery
	Delivers early postnatal care of newborn
	Registers newborn to central registry of children born to pregnant mothers with HL
	Counsels about breastfeeding
	Schedules long-term follow-up of newborn
Nurse coordinator	Coordinates communication among subspecialists
	Helps interpret complex communication with the patient

clinical challenge of managing pregnant HL patients lies in determining the effect of treatment delay on maternal survival versus the risk of previously undesired abortion, fetal malformation, and adverse perinatal outcomes associated with the use of chemotherapy and radiotherapy. Frequent communication with the patient and her family is crucial to ensure understanding and alleviate anxiety and fear.

A critical question to be considered when caring for a pregnant patient with HL is the effect of pregnancy on the survival of mother and infant. Evens et al. published one of the largest series, which included 40 HL and 50 non-HL cases occurring during pregnancy [2]. Data on the clinical course of the disease and pregnancy outcomes were gathered from 11 institutions that had treated these patients during the past decade. HL was diagnosed at a median of 23 weeks' gestation. Of the six patients diagnosed in the first trimester, three elected to terminate the pregnancy and three elected to defer treatment until later. Most patients were diagnosed in the second or third trimester, and all patients who decided to keep the pregnancy successfully reached term delivery. In a study by Lishner et al., 48 pregnant women with HL were matched to nonpregnant controls with HL [10]. They found that stage and clinical presentation, course of the disease, response to therapy, and overall survival were similar when

compared to age- and stage-equivalent nonpregnant controls. These findings are consistent with previous analyses in which no difference in survival was found among women who did not have a therapeutic abortion and those who did [11–13]. Several authors have observed that HL by itself does not appear to have an adverse effect on the course of pregnancy, fetal development, labor, or puerperium [2, 14, 15]. The primary conclusion to be drawn from these observations is that pregnancies encountered coincident with HL do not need to be terminated [16].

18.4 Treatment of Hodgkin Lymphoma during Pregnancy

18.4.1 General Therapeutic Principles

Most patients with HL and concomitant pregnancy require no immediate intervention. As a general rule, any treatment, such as radiation or chemotherapy, should be avoided during the first trimester unless severe symptoms are present or organ function is seriously compromised or threatened. Almost all chemotherapy agents have been documented to be teratogenic in animals or humans, although for some drugs only experimental data exist. Chemotherapy during the first trimester may increase the risk of spontaneous abortion, fetal death, and major malformation; the fetus is extremely vulnerable from the second to eighth week of gestation during which time organogenesis occurs. Even after primary organogenesis, several organs including the eyes, genitalia, hematopoietic system, and central nervous system remain vulnerable to chemotherapy and radiation therapy.

18.4.2 Early-Stage HL during Pregnancy

The majority of HL patients diagnosed during pregnancy have stage IA or IIA disease and are asymptomatic or minimally symptomatic. Treatment for these patients can be deferred, but close monitoring and follow-up through the entire pregnancy has to be ensured. In a recent multicenter series, 75% of patients had early-stage HL and more than a third deferred treatment until the postpartum period resulting in good outcomes for both the mother and child [2]. In the Stanford series, 11 out of 17 patients required no immediate treatment for HL concomitant with pregnancy [17]. The approach of watchful waiting has also been demonstrated to be safe in a small case series of 19 patients from Royal Marsden Hospital [18]. Many patients can be monitored throughout pregnancy until normal full-term delivery without treatment for lymphoma. Nevertheless, therapy is required if severe symptoms or organ dysfunction develops. Patients with stage IA–IIA HL with localized or stable disease who have chemotherapy safely deferred can complete appropriate staging and initiate treatment soon after delivery. In two recent studies, among HL patients opting to delay treatment until after delivery, the birth weight, mean gestational age, and method of delivery were similar to normal pregnancies [10, 15].

Based primarily on experience acquired prior to the development of highly effective chemotherapy, several studies demonstrated the efficacy of irradiation for symptomatic patients with cervical adenopathy, stage IB or IIB, or respiratory symptoms due to enlarging mediastinal masses. However, at most, radiation should be reserved for cases where it is absolutely necessary, and extreme caution should be taken to provide special shielding of the fetus with ten half-value layer shields [10, 12, 19, 20]. An inverted Y field is not an option at any time during pregnancy. Radiation therapy to lymph nodes in the axilla, mediastinum, and neck-mediastinum could lead to a dose of >10 cGy and therefore should not be recommended in the first trimester [21, 22]. It is important to recall that use of any therapeutic radiation during pregnancy, especially in advanced gestational age, results in direct or scattered exposure. The effects of fetal irradiation may become evident only many years later. For example, a known risk for the fetus from radiation in the second half of gestation is acquisition

of blood dyscrasias or leukemia later in life [23]. In addition, irradiation encompassing the mediastinum exposes breast tissue to scatter radiation and potentially increases the risk of later secondary breast cancer and other secondary malignancies [24].

Because radiation unnecessarily endangers the fetus, a better choice, if treatment is necessary, is systemic chemotherapy. If intervention is required, especially after the first trimester, selected symptomatic patients can be treated with single-agent vinblastine (Fig. 18.1). Vinblastine, first described for this use more than 40 years ago [25, 26], is a particularly attractive agent because of its high level of effectiveness against HL in treatment-naïve patients (>75% response rate) and modest acute toxicity. Although teratogenic effects have been reported in mice, neither teratogenic nor carcinogenic effects are apparent in humans at doses therapeutic for lymphoma. The combination of a high level of effectiveness, minimal acute toxicity, and low likelihood of a negative effect on the fetus makes vinblastine an attractive agent to suppress HL during pregnancy. Single-agent vinblastine used as monotherapy does not cross the placenta and has been safely used in patients in all trimesters, including during early gestation when the use of other agents is more often associated with fetal malformations and increased risk of spontaneous abortions and stillbirths [11, 12, 27–30].

18.4.3 Use of Chemotherapy for Symptomatic or Advanced-Stage HL in Pregnant Patients

Management of HL with advanced stage, bulky disease, visceral involvement, B symptoms, subdiaphragmatic disease, or rapid disease progression remains challenging during pregnancy. A recent large collection of cases of coincident HL and pregnancy demonstrated that this presentation is rare, and good outcomes for both the mother and fetus were achieved in most patients [2]. Alkylating agents (mechlorethamine, cyclophosphamide, procarbazine, and chlorambucil), antimetabolites (methotrexate), and multiagent regimens including these agents (e.g., MOPP [mechlorethamine, vincristine, prednisone, and procarbazine]) should be avoided during pregnancy because of a reported increased risk of spontaneous abortion, teratogenicity, carcinogenicity, and fetal malformations [10, 11, 17, 18, 27–30]. Rather than expose the fetus to the potential adverse effects of multiple agents, an alternative approach for advanced-stage symptomatic HL is to employ single-agent chemotherapy with vinblastine. Infrequent doses at intervals of several weeks or longer can be given to control HL until delivery at term, minimizing risks to the mother and child. Standard dosing of 6 mg/m^2 is unlikely to cause significant myelosuppression, but careful timing to avoid a blood cell count nadir near delivery is prudent. Progression despite vinblastine, which occurs infrequently, should be treated with full-dose ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, dacarbazine) because evidence of vinblastine resistance signifies aggressive disease requiring multiagent chemotherapy (Fig. 18.1). ABVD, the current standard of care in North America, has been used during pregnancy. Although experience is limited, obvious negative effects on the fetus have not been observed [3–5]. The largest US retrospective analysis on 40 HL patients reported 21 subjects treated with ABVD or AVD in the second and third trimester [2]. Overall, the response to therapy was excellent with a 96% overall response rate and 83% complete remission rate. Multiple variables were examined in this series to predict outcomes. For HL patients, multiparous status predicted improved progression-free survival (hazard ratio 0.07), and the presence of B symptoms at diagnosis predicted inferior progression-free survival (hazard ratio 10). No variable was predictive of overall survival.

We have managed 18 pregnant patients with coincident HL at the British Columbia Cancer Agency during the past 23 years using the approach described above. Eleven patients remained off treatment through term delivery, and 6 required vinblastine to control the disease. Fourteen of the 18 patients are still alive and

well, while 4 have died, 2 from HL and 1 each from acute myeloid leukemia and retroperitoneal sarcoma. All 18 delivered normal children who now range in age from 2 to 23 years (median 17). Although these children have not been systematically assessed, no overt abnormality has become apparent [3]. The conservative use of single-agent vinblastine, which has allowed normal-term delivery of children and effective management of the mother's HL and psychological stress, appears to be a reasonable approach to this rare problem of coincident pregnancy and HL.

Data on the use of more intensive regimens such as Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, and prednisone) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine) during pregnancy are not available; however, because both contain alkylating agents, they should be avoided. Recently, novel agents including the antibody-drug conjugate brentuximab vedotin and the checkpoint inhibitors nivolumab and pembrolizumab have been shown to be highly effective for classic Hodgkin lymphoma; however, no experience with administration of these agents during pregnancy has been reported. Thus, they are included in US FDA category D, possibly harmful in pregnancy. Until evidence of their safety becomes available, it is best to avoid their use in pregnancy, especially with acceptable, effective alternatives available.

18.5 Fetal Outcomes

Patients with HL in whom gestation progresses to term need planning of the timing and mode of delivery. Fetal maturity should preferably be the criterion to induce delivery. In a multidisciplinary setting, maximal effort should be made to delay delivery until at least 35–37 weeks. A coordinated, detailed peripartum plan developed by a neonatologist, an obstetrician with experience in high-risk pregnancies, and an oncologist/hematologist is required to minimize complications. In a recent large retrospective study from Evens et al., preterm complications among 31 patients with HL included induction of labor (40%), preterm delivery in 14 patients, C-section in six, low gestational age in four patients, and postpartum hemorrhage in two patients [2]. The median gestational age at delivery was 37 weeks (range 31–40 weeks). Preeclampsia and fetal demise or malformations were not observed in this retrospective series. Thus, there appeared to be no impact of antenatal chemotherapy on the frequency of these complications. The median birth weight of infants was 2688 g (range 1005–3628 g) with no difference based on receipt of antenatal chemotherapy. No malformations were detected in babies exposed to ABVD or ABV chemotherapy [2]. In a smaller series of 26 children with HL with a long follow-up of 3–19 years, children born to women who received chemotherapy for HL in the second and third trimesters are delivered healthy newborns without short-term or long-term neurological, developmental, or infectious complications or secondary malignancies [15]. However, the use of anthracyclines at doses exceeding 70 mg/m^2 per cycle has been associated with a 30-fold increase in severe fetal toxicity including death, malformations, and cardiac toxicity [31]. The ABVD regimen contains doxorubicin at a lower dosage (25 mg/m^2 per dose); however, caution and careful counseling are always required when ABVD is administered in the second and third trimester. For example, one series reported stillbirth of twins in an HL patient who started the ABVD regimen at 14 weeks of gestation [31]. In addition, multiagent chemotherapy used in the last trimester of pregnancy may often result in prematurity, lower birth weights, and neonatal myelosuppression, although none of these complications were reported in the 21 patients included in the most recently reported series [2, 32, 33]. In a recent European series of 176 neonates born to mothers with malignancy, of whom 13 had HL, binomial testing revealed a significant increase in small-for-gestational-age children in the group receiving treatment during pregnancy versus those not treated during pregnancy [34]. Therefore, caution has to be taken because the adverse outcomes associated with chemotherapy are likely

underreported and available evidence comes from limited, small, and heterogeneous clinical series and anecdotal descriptions [2, 10–13, 15, 17, 20, 25–27, 32, 35–37].

18.6 Planning the Delivery and Managing the Postpartum Period in Patients with HL

Postdelivery oncologic care is a critical step in managing HL in pregnancy. Breastfeeding must be discouraged in those patients who continue chemotherapy postpartum as most cytotoxic agents can be excreted into the breast milk. In the perinatal period, patients who had not received any therapy for HL during pregnancy should be fully restaged after delivery including PET/CT staging. Patients treated with radiation, single-agent vinblastine, or other chemotherapy can no longer be accurately staged and therefore should be treated with a full course of six to eight cycles of multiagent chemotherapy. Posttreatment PET/CT imaging has a strong predictive value for overall survival and should be considered to assess the depth of post-therapy remission.

18.7 Relapsed HL and Concomitant Pregnancy

Occasionally, the patient with history of HL presents with relapsed lymphoma and concurrent pregnancy. There are limited data to guide the therapeutic decisions for such a rare clinical situation (five cases reviewed in Eyre et al. [5]); however, we advise that care be guided by principles similar to those recommended for newly diagnosed HL and concurrent pregnancy. Individualized recommendations will depend on the initial HL stage, type of primary therapy used in the past, and the time from remission to relapse, as well as current symptoms, stage, and gestational age. Patients with minimal disease burden in the second or third trimester can often be managed by careful watching. Most patients who relapse with advanced HL or those who had received prior chemotherapy would be considered for treatment with salvage multiagent chemotherapy followed by high-dose myeloablative chemotherapy and autologous hematopoietic stem cell rescue. Brentuximab vedotin should be avoided in pregnancy because there is no experience with this agent during pregnancy and it caused embryo-fetal lethality in pregnant female rats [38]. Conservative management that allows the pregnancy to develop to term is often possible, and interventions for definitive therapy, such as autologous stem cell transplant, can be planned for soon after delivery. The decision to initiate treatment rests on careful and frequent monitoring of the patient and the pace of disease progression. If rapidly symptomatic disease develops in the first trimester, planned pregnancy interruption and subsequent standard treatment should be considered. Coordination of care with a transplant team is necessary to ensure timely postdelivery interventions.

18.8 Conclusions

The diagnostic and therapeutic approach to the patient with concurrent HL and pregnancy presents the challenge of managing two lives. The goal is to give the mother with HL the best chance of cure while preserving the healthy development of the fetus. The management of a pregnant patient with HL requires a multidisciplinary approach combining expertise in medical oncology, high-risk obstetrics, and neonatology, as well as effective communication with the patient and her family. A pregnant patient with HL should be staged by clinical examination and judicious use of nonradiation imaging such as ultrasound or MRI, balancing the need for accurate disease assessment with the need to minimize invasive procedures. The treatment strategy should be individualized based on symptoms, lymphoma stage, gestational age, and the patients' wishes [36]. Therapeutic options include treatment deferral or single-agent vinblastine with reservation of multiagent chemotherapy until the second or third trimester for those patients with advanced-stage disease and B symptoms. Finally, establishment

of a prospective central registry for patients with concurrent HL and pregnancy to allow data collection on long-term follow-up of children born to HL patients would enhance the care of patients with this uncommon complication of pregnancy and that of their children by providing a larger database of relevant information than is currently available.

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The Management of HIV-Hodgkin Lymphoma

19

Marcus Hentrich and Michele Spina

Contents

19.1 Introduction

Since 1996, the availability of combination antiretroviral therapy (cART) has led to improvements in immune status among HIV-infected persons, reducing AIDS-related morbidity and prolonging survival. However, despite the impact of cART on HIV-related mortality, malignancies remain an important cause of death [1–3]. While the incidence of the two major AIDS-associated malignancies—Kaposi's sarcoma (KS) and high-grade non-Hodgkin lymphoma (NHL)—has dramatically declined in the cART era, the risk of non-AIDS-defining malignancies (NADM) such

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_19

as Hodgkin lymphoma (HL), anal cancer, liver cancer, or lung cancer remains markedly elevated [4–6]. In patients with HIV-HL, curative-intent chemotherapy, modern cART, and supportive care have resulted in outcomes that are similar to that reported in HIV-negative HL [7–9].

19.2 Epidemiology

Compared with the general population, the incidence of HIV-HL is increased by approximately 10–15-fold with about 45–55 new cases per 100.00 person-years among HIV-infected patients [4–6, 10–18]. A summary of epidemiological studies reporting data on standardized incidence ratios is given in Table 19.1. The incidence of HIV-HL may have further increased in the decade after the introduction of cART. However, recent studies observed significant declining annual trends in hazard rate of HIV-HL in the range of −3.2% to −5% per year [19, 20].

Although in western countries patients with HIV-HL appeared to be approximately 4–5 years older than their HIV-negative counterparts, recent

Table 19.1 Studies providing standardized incidence ratios (SIR) for HL in persons with HIV/AIDS

Country	Period	*N*	HIV/AIDS	SIR	Reference
Switzerland	1985–2003	7304	HIV	17.3	Clifford [10]
				11.4 (HAART-nonuser)	
				36.2 (HAART-user)	
USA	1980–2002	31,7428	AIDS	9.4	Biggar [11]
				7.0 (1980–1989)	
				8.1 (1990–1995)	
				13.2 (1996–2002)	
France/Italy	1985–2005	8074	HIV	10.8	Serraino [12]
USA	1991–2002	57,350	HIV (initially AIDS-free)	5.6	Engels [13]
				2.8 (1991–1995)	
				6.7 (1996–2002)	
				4.5 (before AIDS)	
				15 (after AIDS)	
USA	1992–2003	54,730	HIV	14.7 (RR)	Patel [14]
				11.7 (1992–1995)	
				16.6 (1996–1999)	
				17.9 (2000–2003)	
UK	1983–2007	11,112	HIV	13.9	Powles [15]
				4.5 (1983–1995)	
				11.1 (1996–2001)	
				32.4 (2002-2007)	
USA	1984–2007	6949	HIV/AIDS	7.3	Seaberg [16]
Switzerland	1985–2006	9429	HIV/AIDS	9.2 (1985–1996)	Franceschi [4]
				21 (1997–2001)	
				28.1 (2002–206)	
USA	1996–2008	20,775	HIV	18.7	Silverberg [17]
Italy	1999–2009	5090	HIV	12.3	Calabresi [18]
France	1997–2009	84,504	HIV	33.5 (1997–2000)	Hleyhel [5]
				21.6 (2001–2004)	
				26.5 (2005–2009)	
USA	1996–2010	448,258	HIV/AIDS	7.7	Hernández-Ramirez [6]

HAART highly active antiretroviral therapy, *RR* standardized rate ratio

data from the United States and South Africa no longer indicate differences in the median age of HIV-positive and HIV-negative individuals with HL [21–23]. In high-prevalence areas such as South Africa, 29% of HL cases were reported to be attributed to HIV [23], while in the United States 4% of HL cases occurred in the setting of HIV [24]. Highest incidence rates are observed among African Americans with 17% of HL cases being HIV-related [24].

19.2.1 CD4 T-Cell Counts and Risk of HIV-HL

Median CD4 cell counts at HL diagnosis is roughly between 150 and 260 cells/μL [7–9, 11, 25–28]. However, data on the relationship of CD4 cell counts and the risk of HIV-HL are somewhat inconsistent. The risk of HIV-HL is highest with CD4 counts between 50 and 100 cells/μL [29–31]. In contrast, the US HIV/AIDS Cancer Match Study found that the incidence of HL decreased in persons with AIDS and falling CD4 cell counts [11]. This finding is in line with data from the German HIV-lymphoma cohort study showing that HL has become as common as non-Hodgkin lymphoma in patients with sustained viral suppression and limited immune deficiency defined as HIV RNA < 50 copies/mL for more than 12 months and CD4 cell counts of >200/μL [32]. However, an analysis of 16 European cohorts suggested that the risk of HL declined more recently and CD4 counts have increased with an adjusted hazard ratio of 0.27 for patients with more than 350 cells as compared to less than 50 cells/μL [30].

The first 6–12 months after initiating cART is the period with the highest risk of HIV-HL diagnosis [27, 31, 33, 34]. There is also some evidence of a higher risk within 12 months after cART initiation [35]. The increased risk within 6 months after initiating cART may, at least in part, be explained by the occurrence of an immune reconstitution inflammatory syndrome (IRIS) [35]. In one cohort, unmasking lymphoma IRIS, defined as lymphoma within 6 months after ART accompanied by a ≥0.5 $\log_{10}$ copies/mL HIV RNA reduction, was observed in 15% of HL cases [36].

Case-control studies showed a marked decline of CD4 cells by 100–168 cells/μL over 12 months prior to HL diagnosis [37, 38].

There is conflicting data on the relationship of HIV RNA and the risk of HIV-HL. While in the European Cohere database, HIV-1 viral replication was not associated with the risk of HIV-HL [30], a more recent study among HIV-infected veterans found that decreased HIV viral load was associated with lower risk of HL [39].

19.3 Pathology

There are differences in the pathology between HIV-HL and HL in the general population. First, the pathology is characterized by a high incidence of unfavorable histological subtypes such as mixed cellularity and lymphocyte depleted [7, 40]. Although a higher proportion of classical HL not otherwise specified (NOS) has been diagnosed in recent years [23, 24, 27], the MC predominance has not changed over the last decades [7–9, 11].

Second, HIV-HL exhibits special features related to the cellular background with the presence of fibrohistiocytoid stromal cell proliferation and the high number of neoplastic cells. These features may pose relevant difficulties in diagnosing and classifying the disease (Fig. 19.1). This finding contrasts with the rather low population of neoplastic cells usually found in HIV-unrelated HL [41]. Compared to HL in the HIV-negative setting, nodal CD4+ T-cells are decreased lacking CD4+ rosetting around HRS [42, 43].

Third, a high frequency of EBV association has been shown in HL (80–100%) tissues from HIV-HL [7, 44]. This contrasts to HIV-negative HL in which the EBV genome is observed in 20–50% only according to histological subtype and age at diagnosis. The EBV genome in HIV-HL has been reported to be episomal and clonal, even when detected in multiple independent lesions (Fig. 19.2). The elevated frequency of EBV association with HIV-HL indicates that

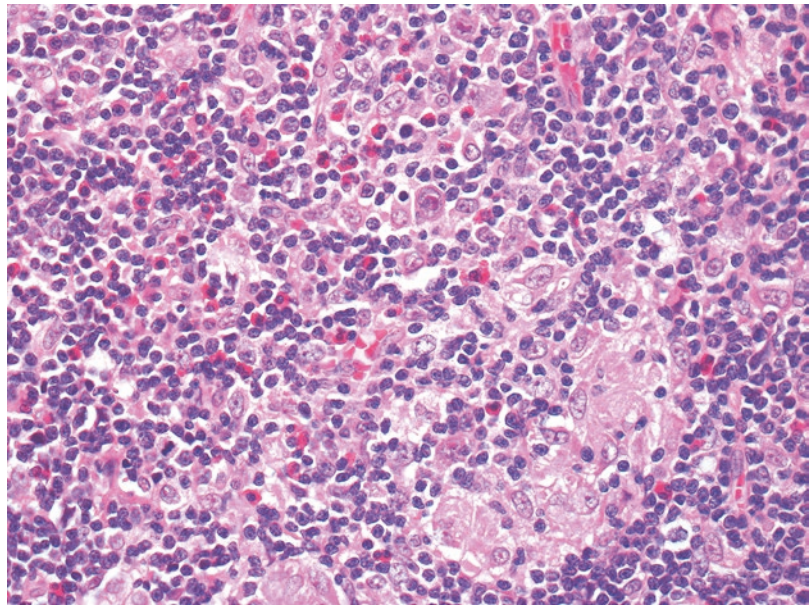

Fig. 19.1 Hodgkin and Reed-Sternberg (H/RS) cells with prominent central nucleoli in a case of HIV-HL (H&E, original magnification ×400)

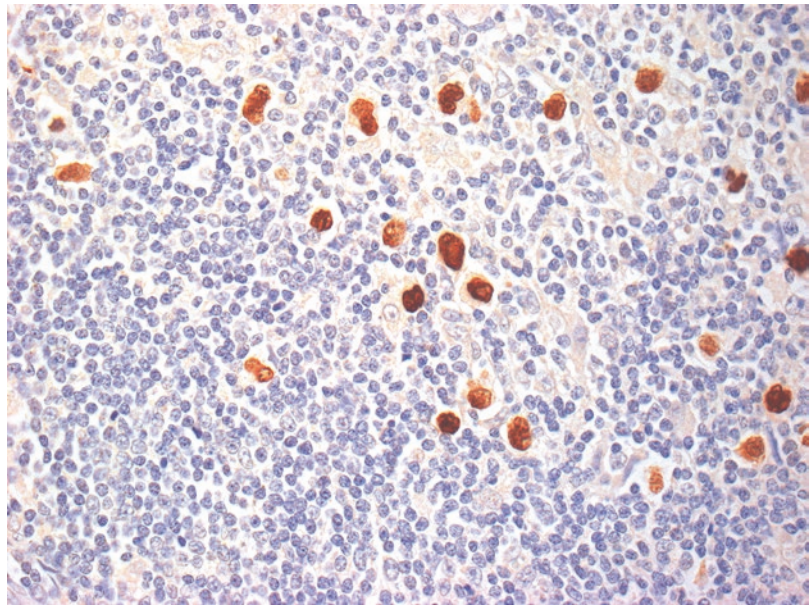

Fig. 19.2 In situ hybridization for EBV-encoded RNA (EBER) in H/RS cells of HIV-HL. The EBER signal is located to the nucleus. (original magnification ×400)

EBV probably represents a relevant factor involved in the pathogenesis of HIV-HL [45]. An etiologic role of EBV in the pathogenesis of HIV-HL is further supported by data showing that latent membrane protein 1 (LMP1) is expressed in the vast majority of HIV-HL cases [44, 45]. LMP1 and LMP2 are important for NF-KB and B-cell receptor signaling as well as for B-cell proliferation [44]. In addition, EBV infection induces an increase in T-regulatory cells and associated immunosuppressive cytokines (IL10) that may inhibit an immune response against EBV+ cells [46].

Finally, RS cells of classical HL of HIV-negative patients represent transformed B-cells originating from pre-apoptotic germinal center

(GC) B-cells [46]. Most HIV-related HL cases express LMP1 and display the BCL6−/CD138+/MUM1 IRF4+ (for multiple myeloma-1 interferon regulatory factor-4) phenotype, thus reflecting post-GC B-cells [47, 48]. The possible contribution of LMP1 to the loss of BCL6 expression seems plausible given that LMP1 can downregulate many B-cell-specific genes [49]. Loss of B-cell identity occurs during the normal differentiation of a GC B-cell into plasma cell or memory B-cell.

19.4 Clinical Presentation and Prognostic Factors

Approximately 65–80% of patients present with advanced stages or B-symptoms. Compared to HL in the general population, the bone marrow is more frequently involved and can be the only involved site of disease [23].

There is only limited evidence on the role of PET scans in the diagnosis of HIV-lymphoma. As ^{18}FDG can mark benign reactive nodes as seen in HIV infection, findings should be interpreted with caution. False-positive results may occur in ART-naive viremic patients and those with high HIV viral loads or low CD4 counts [50–55].

The routine diagnostic workup should include not only CD4 T-cell counts and HIV RNA but also hepatitis B and hepatitis C virus serology.

19.4.1 Prognostic Factors

Before the introduction of cART, results of chemotherapy and outcomes of patients with HIV-HL were not satisfactory [56–58]. This was mainly due to the poor tolerance of standard chemotherapy with high rates of opportunistic infections and toxic deaths. However, several cohort studies have shown that complete remission (CR) and overall survival (OS) rates were significantly higher in patients on cART as compared to those treated in the pre-cART era [59–63]. Factors independently associated with improved OS included response to cART, higher CD4 T-cell counts at HL diagnosis, and achievement of CR [61–63]. A large retrospective analysis of 596 HIV-HL patients from six European countries that included patients treated in the pre- and post-cART era found two parameters independently associated with OS: CD4 counts <200 cells/μL (HR 1.63) and IPS > 2 (HR 2.33) [64]. A multi-institutional retrospective study of 229 advanced HIV-HL patients who had received ABVD plus cART also showed CD4 cell counts <200/μL to be an independent adverse prognostic factor for PFS and OS [28].

Given the somewhat inconsistent data on the predictive power of the International Prognostic Score (IPS) in HIV-HL [7, 9, 25, 28, 65], treatment decisions should not be based on IPS.

An analysis from the National Cancer Database showed that among patients with HIV-HL who received chemotherapy, HIV status was not significantly associated with higher mortality in classical histological subtypes, while prognosis remained poor for those patients with undetermined histology, suggesting a more aggressive biology or other high-risk characteristics in this subgroup [66].

19.5 Management

19.5.1 Primary Chemotherapy

ABVD is the most common treatment for HIV-HL [28, 67–72]. In retrospective studies, ABVD (mainly 5–6 cycles) with concomitant cART resulted in CR rates of 74–89% and 5-year OS rates of 76–81% (Table 19.2). In comparative studies, no significant differences in the 5-year event-free survival (EFS) and OS were observed between HIV-positive and HIV-negative patients [8, 9, 72].

The use of the Stanford V regimen and concomitant cART resulted in CR rates of 81% and a 3-year OS rate of 51% in a prospective trial performed in the early cART era [25]. Although this represented a clear advantage compared to the pre-cART era, it was still below what is being reported in the general population.

Table 19.2 Results from retrospective studies on ABVD in HIV-HL in the cART-era

N	Recruitment period	Stage III/IV (%)	CD4 counts[a]	No cycles	CR rate (%)	OS	Toxic deaths	Comment	Reference
62	1996–2005	100	129/μl	6: 68% 8: 15% <6: 17%	87	76% (5-year) 65% (14-year)	5% ($n = 3$)	Concurrent cART in al pts	Xicoy [67] Xicoy [68]
93	1997–2010	80	185/μl	6	74	81% (5-year)	1% ($n = 1$)	Concurrent cART in 92/93 pts; no impact of HIV-status on OS	Montoto [8]
229	NR–2010	100	180/μl	5 (median, range 3-8)	83	78% (5-year)	NR	Concurrent cART in all pts	Castillo [28]
68	2008–2014	76	387/μl	3–4 (stage I/II)[b]	NR	94% (2-year)	NR	Concurrent cART in 67/68 pts; no impact of HIV-status on OS	Besson [9]
21	1995–2013	NR	182/μl	6–8	89	73% (10-year)	10% ($n = 2$)[c]	Concurrent cART in all pts; no impact of HIV-status on OS	Sorigué [72]

CR complete remission, *OS* overall survival, *NR* not reported
[a]Median, at HL diagnosis
[b]ABVD given to 65/68 pts, no. of cycles for stage III/IV not reported
[c]Death in induction

19.5.1.1 Stage-Adapted Approach

A stage-adapted treatment approach was investigated in another prospective trial [7]. Patients with early favorable HL received 2–4 cycles of ABVD followed by involved-field radiation, patients with early unfavorable disease were treated with 4 cycles of BEACOPP baseline or 4 cycles of ABVD, and patients with advanced HIV-HL received 6–8 cycles of BEACOPP baseline. In patients with advanced HIV infection, BEACOPP was replaced by ABVD; 94% received concurrent cART while on protocol therapy. The CR rate for patients with early favorable, early unfavorable, and advanced-stage HL was 96%, 100%, and 86%, respectively (Table 19.3). The 2-year OS of the entire study population was 90.7% with no significant difference between early favorable (95.7%), early unfavorable (100%), and advanced HL (86.8%). Treatment-related mortality in patients with advanced disease was 7% with three of four toxic deaths having occurred after the seventh cycle of BEACOPP. Thus, if the BEACOPP regimen is chosen, the number of cycles should be limited to six. In HIV-negative patients with HL, 6 cycles of the more intensified BEACOPP-escalated regimen proved superior to 8 cycles [73]. An overview of prospective clinical studies in HIV-HL in the cART era is given in Table 19.3 [7, 25, 74–76, 78].

Taken together, a stage-adapted treatment approach in HIV-HL is feasible and effective. Two cycles of ABVD followed by involved-field (IF) radiation therapy (RT) can be regarded as standard treatment for early favorable HL. As the use of 20-Gy and 30-Gy doses of RT proved equally effective in HIV-negative early-stage HL, the lower dose of 20-Gy RT should also be preferred in early-stage HIV-HL [77]. While the use of 4 cycles of ABVD followed by 30-Gy IF-RT

Table 19.3 Results from prospective studies on HIV-HL in the cART-era

Regimen	*N*	Recruitment period	Stage III/IV (%)	No cycles (median)	CR rate (%)	OS	Toxic deaths	Comment	Reference
Stanford V	59	1997–2001	71	Planned treatment in 69%[a]	81	51% (3-year)	2% (1/59)	2 deaths of OI 5-yr OS 54%	Spina [25, 78]
BEACOPP	12	1993–2002	92	6	100	75% (3-year)	17% (2/12)	cART in 4/12 pts	Hartmann [74]
VEBEP	73	2001–2008	70	NR	67	66% (3-year)	6% (4/73)	Results not yet fully published	Spina [75]
BEACOPP or ABVD	71	2004–2010	100	7	86	87% (2-year)	6% (4/71)	Fatal neutropenic sepsis in 3 of 4 pts beyond cycle 7	Hentrich [7]
ABVD or BEACOPP	14	2004–2010	Early unfavorable	4	100	100% (2-year)	0	1 relapse	
ABVD	23	2004–2010	Early favorable	2	96	96% (2-year)	4% (1/23)	1 fatal neutropenic sepsis after cycle 1	
ABVD	12	2010–2012	100	6 (PET2-) 2 (PET2+) + 6× BEACOPP	75	100% (2-year)	0	2-year PFS 83% with response-adapted treatment	Danilov [76]

VEBEP vinblastine, epirubicine, bleomycin, etoposide, prednisone; *NR* not reported
[a]12-week chemotherapy without dose reduction or delay in administration

may be considered standard of care for patients with early-stage unfavorable HL, six cycles of ABVD or BEACOPP baseline may be applied to patients with advanced-stage HIV-HL [69, 79].

19.5.1.2 PET-Adapted Approach

Although the predictive value of positive interim PET scans may be hampered by false-positive results in patients with HIV, data from a retrospective cohort study indicate a high negative predictive value of a ^{18}FDG-PET scan performed after 2–3 cycles of ABVD (PET2 or PET3) [80].

A response-adapted therapy based on early interim ^{18}FDG-PET was investigated in a US Intergroup Trial that included both HIV-positive and HIV-negative patients with HL [76]. Patients with stage III/IV classical HL who had CD4 cell counts ≥150/μL at registration or ≥250/μL at any time within 8 months prior to HL diagnosis received 2 cycles of ABVD followed by interim FDG-PET. Patients with a negative PET2 (Deauville ≤3) subsequently received four additional cycles of ABVD, while PET2-positive patients received 6 cycles of BEACOPP baseline. Ten of twelve (83%) HIV-HL patients who completed 2 cycles of ABVD achieved a negative PET2 status and two remained PET-positive with Deauville scores of four and five. With a median follow-up of 39 months, three patients developed progressive disease (all PET2-negative) resulting in an estimated PFS of 83% at 2 years.

In a study from South Africa that included 57 patients with HIV-HL, only 59.6% had a negative ^{18}FDG-PET (Deauville score 1–3) performed 8 weeks following completion of chemotherapy with ABVD. However, residual FDG avidity at sites of disease involvement identified during primary staging was not histologically confirmed and data on PFS and OS were not provided in this study [81]. The role of interim PET in HIV-HL should be further investigated in well-designed clinical trials.

19.5.1.3 Brentuximab Vedotin with Chemotherapy

Brentuximab vedotin (BV), an antibody-drug conjugate of the antimitotic agent monomethyl auristatin E targeting CD30, in combination with doxorubicin, vinblastine, and dacarbazine (AVD-BV) had superior efficacy to ABVD in the treatment of HIV-negative patients with advanced-stage HL [82]. In the setting of HIV, the combination of BV plus AVD is currently being investigated in AMC-085, a study by the AIDS Malignancy Consortium (NCT 01771107). Preliminary data on six patients showed grade 3 non-hematological toxicity in three patients and negative PET/CT scans in six of six patients following 6 cycles of therapy [83]. Thus, AVD-BV also seems feasible and effective in HIV-HL. The phase II portion of AMC-085 (51 subjects) is actively accruing in both the United States and France.

19.5.1.4 Combination Antiretroviral Therapy (cART)

Chemotherapy and concomitant cART have been shown to be feasible and effective during chemotherapy for HIV-HL. Furthermore, there is evidence that increased viremia during the 6 months after lymphoma diagnosis is associated with an increased risk of death between 6 months and 5 years after diagnosis [84]. Thus, cART should either be continued or initiated in parallel to chemotherapy according to current guidelines for the use of ART [69, 79, 85]. However, the potential of interactions between cytotoxics and antiretrovirals must be considered. Especially strong enzyme inhibitors such as ritonavir-boosted protease inhibitors or cobicistat should be avoided because of an increased risk of toxicity [86–90].

19.5.2 Relapsed and Resistant Disease

Patients with relapsed or refractory HIV-HL should be considered early for high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) [69, 79]. Peripheral blood stem cells can be effectively mobilized [91], and autologous stem cell transplantation (ASCT) has been shown to be a useful treatment in HIV-infected lymphoma patients with chemotherapy-sensitive relapse [92–95]. In a prospective phase II study on 40 patients with chemotherapy-sensitive relapsed/persistent HIV-lymphoma (of which 15 had HL), HDCT plus ASCT resulted in 1-year and 2-year OS probabilities of 87% and 82%, respectively [95]. One-year transplant-related mortality (TRM) was 5.2%. Retrospective studies did not show significant differences in survival between HIV-positive and HIV-negative lymphoma patients undergoing ASCT [93, 94]. Notably, ASCT in HIV-infected individuals does not worsen the initial immune impairment and does not enhance viral replication [96]. However, in a comparative analysis by the EBMT, TRM was 8% in HIV-positive compared to 2% in HIV-negative patients [93]. A more recent analysis of patients with HIV-lymphoma undergoing ASCT also found an increased TRM of 9% [97].

19.5.2.1 Brentuximab Vedotin

Case studies indicate that brentuximab vedotin alone is a valid treatment option in relapsed/refractory HIV-HL [98, 99]. In a patient with relapsed HIV-HL, BV given as bridging therapy prior to planned ASCT resulted not only in disease stabilization but also in a transient loss of detectable HIV-1 RNA [99]. Another case report presented a patient with relapsed HIV-HL who experienced a second complete remission after treatment with BV [98].

19.5.2.2 Checkpoint Inhibitors

Immune checkpoint inhibitors (ICIs) have dramatically improved the survival of patients with certain cancers and demonstrated high efficacy in HIV-negative patients with relapsed/refractory HL [100, 101]. The anti-programmed cell death protein 1 (PD1) agent nivolumab also proved safe and efficacious in a number of case reports on relapsed/refractory HIV-HL. Of five cases published in the literature, three achieved a complete remission and two a partial remission during treatment with nivolumab [102–105]. A review of 73 HIV-infected cancer patients treated with ICIs showed a 9% rate of grade 3 or higher

immune-related events [106]. Patients with HIV did not experience increased side effects, and HIV remained undetectable in 93% of patients (26 of 28) known to have undetectable viral load before treatment. Most patients had received either nivolumab (39.7%) or pembrolizumab (35.6%) [106].

Ongoing prospective clinical trials will further define the role of ICI therapy in patients with HIV-HL.

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Part IV

Relapsed and Refractory Disease

Relapsed and Refractory Hodgkin Lymphoma

20

Bastian von Tresckow and Craig Moskowitz

Contents

20.1 Introduction

High-dose therapy (HDCT) followed by autologous stem cell transplantation (ASCT) is the standard treatment for patients with relapsed Hodgkin lymphoma (HL). This is based on the results of two randomized controlled studies showing improved event-free survival (EFS) in the ASCT group compared to standard-dose salvage chemotherapy. There are a number of single-arm institutional and registry studies also showing an advantage for HDCT/ASCT [1, 2]. Many larger single-center studies have reported that HDCT/ASCT is the best treatment option for patients with primary refractory HL providing that the disease is chemosensitive to salvage chemotherapy (SC) [3–5]. Despite this evidence, many questions remain including the utility of pre-SC prognostic factors, type and number of salvage chemotherapy needed prior to HDCT, the use of pre-ASCT fludeoxyglucose-positron

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_20

emission tomography (FDG-PET) scanning to determine ASCT eligibility, the role of radiotherapy during ASCT, and the need to consider allogeneic transplantation in selected patients. The objective of this chapter is to provide hematologists/oncologists with an up-to-date review of these issues; however, we will restrict the data to refractory or relapsing HL patients who are eligible for HDCT.

20.2 Prognostic Factors in Relapsed and Refractory Hodgkin Lymphoma

Several studies analyzed risk factors in relapsed and refractory HL. Time to relapse after first-line therapy was confirmed as important risk factor in virtually all analyses. The observation that the duration of remission has a marked effect on the ability of patients to respond to subsequent salvage treatment dates back to 1979 [6]. This finding was later confirmed in larger analyses [7–9]. In 422 patients with relapsed or refractory HL registered in the German Hodgkin Study Group (GHSG) database, patients with early (<12 months) and late relapse (>12 months) had a 4-year overall survival (OS) of 44% and 72%, respectively. This difference in outcome between early and late relapsed patients is also present when only patients treated with HDCT and ASCT were analyzed [7–9]. The prognosis of patients with primary refractory disease is particularly poor, as demonstrated in a large prospective multicenter trial with 157 patients receiving HDCT and ASCT after failure of first-line therapy [10]. The 5-year OS estimates were 30% and 76% for patients with refractory or relapsed disease, respectively. Many other prognostic factors have been described for patients relapsing after first-line chemotherapy. These include age, sex, histology, site of relapse, stage at relapse, bulky disease, B-symptoms, performance status, extranodal relapse, anemia, and chemosensitivity to salvage chemotherapy in patients receiving HDCT and ASCT. However, the impact of these factors on outcome was less consistent than time to relapse.

The GHSG performed a larger retrospective analysis on 422 relapsed patients [7] suggesting that the prognosis of these patients can be estimated according to a number of risk factors. The most relevant factors were combined into a prognostic score (Table 20.1). This score included duration of first remission, stage at relapse, and the presence or absence of anemia at relapse. Early recurrence within 3–12 months after the end of primary treatment, relapse stage III or IV, and hemoglobin <10.5 g/dL in female or <12 g/dL in male patients contributed to a score with values 0–3 in order of worsening prognosis. This prognostic score allowed distinguishing between different prognostic groups. The actuarial 4-year freedom from second failure (FF2F) and OS for patients relapsing after chemotherapy with three unfavorable factors was 17% and 27%, respectively. In contrast, patients with none of the unfavorable factors had an FF2F and OS of 48% and 83% at 4 years, respectively. In addition, the prognostic score was also predictive for patient subgroups such as those relapsing after radiotherapy, for patients relapsing after chemotherapy who were treated with conventional treatment or HDCT followed by ASCT, and for patients under 60 years having a Karnofsky performance status ≥90%. This prognostic score used clinical characteristics that can be easily collected at the time of relapse separating groups of patients with clearly different outcomes.

This score was confirmed in the prospective European HDR2 trial that was conducted by the GHSG, EORTC, GEL/TAMO, and EBMT comparing two pre-HDCT regimens in 241 patients

Table 20.1 Prognostic score in relapsed Hodgkin lymphoma evaluated in 422 patients [7]

Factor		Groups with 4-year OS (%)
Duration of first remission	Early relapse vs.	47
	Late relapse	73
Stage at relapse	Stage III/IV vs.	46
	Stage I/II	77
Hemoglobin	F < 10.5 g/dL; M < 12.0 g/dL Vs. F > 10.5 g/dL; M > 12.0 g/dL	40 72

[11]. Stage III patients had a similar risk in terms of progression-free survival (PFS) compared to stage II patients in univariate analysis. Thus, the prognostic score was slightly modified in that only stage IV (and not stage III) was scored as additional risk factor. Moreover, both multiple relapses and early relapse were scored as risk factor. Patients with none of these risk factors (n = 117) had a PFS of 81% (95% CI, 72% to 87%) at 3 years (Fig. 20.1). Conversely, almost all patients in the small group of those having three risk factors (n = 14) relapsed or died within 3 years (PFS, 14%; 95% CI, 2% to 37%). Other analyses have identified extranodal disease [8, 12] and B-symptoms [8, 13] as risk factors. Moreover, in patients receiving HDCT and ASCT, chemosensitivity to salvage chemotherapy was described as an important prognostic factor in several reports [9, 12]. More recently, FDG-PET after salvage therapy has been established as prognostic tool that might overshadow classical risk factors (see Sect. 20.4) [14, 15].

Although a plethora of risk factors have been described in relapsed/refractory HL, there is currently no generally accepted risk-adapted treatment approach. The French Lymphoma Study Association (LYSA) has proposed a risk-adapted strategy based on the three risk factors—primary refractory disease, early relapse, and stage III/IV at relapse [16]. The lymphoma group of the Memorial Sloan-Kettering Cancer Center (MSKCC) used three risk factors (early relapse, extranodal disease, and B-symptoms) to stratify patients into three different treatment groups [8, 17]. Risk-adapted therapy with different SC and/or HDCT approaches should be further evaluated in prospective clinical trials.

To shed more light on the impact of different risk factors in relapsed/refractory HL and to better identify patients who might be candidates for intensification strategies, a large multinational cooperative study recently reassessed 23 patients with known risk factors who received ASCT [18]. In a retrospective analysis of 656 patients with a median follow-up of 60 months after ASCT, the multivariate analysis identified stage IV disease, time to relapse ≤3 months, ECOG performance status ≥1, bulk ≥5 cm, and inadequate response to salvage chemotherapy (<PR by CT) as significant and nonredundant risk factors for PFS. Validation in 389 independent international patients with evaluation of response to salvage therapy by functional imaging instead of CT confirmed the excellent discrimination of risk groups and significant prognostication of PFS and OS after ASCT (HR = 1.70 and HR = 1.63, respectively; $p < 0.0001$). Especially, patients with 3–5 risk factors had a dismal prognosis (HR = 4.8 for PFS in 690 patients treated predominantly in routine care, Fig. 20.2), and

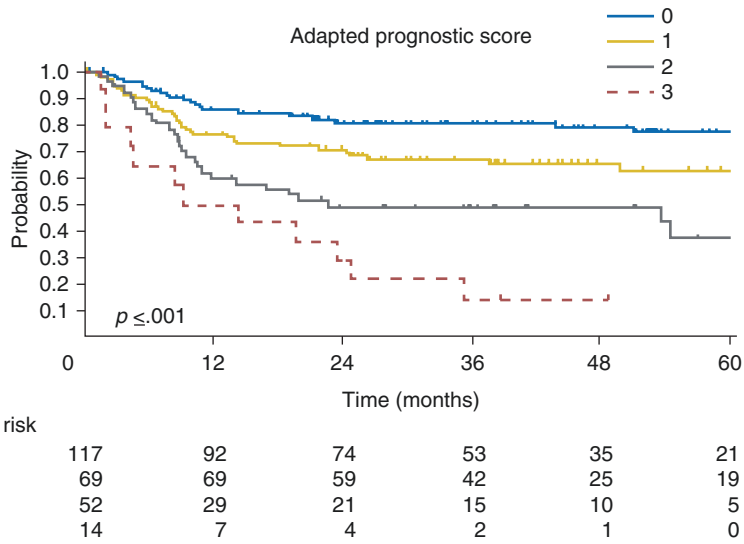

Fig. 20.1 Kaplan–Meier curves of progression-free survival in four groups of patients differentiated with an adapted prognostic score. Presence of stage IV disease, early or multiple relapse, and anemia summed up to a score ranging from 0 to 3 [11]

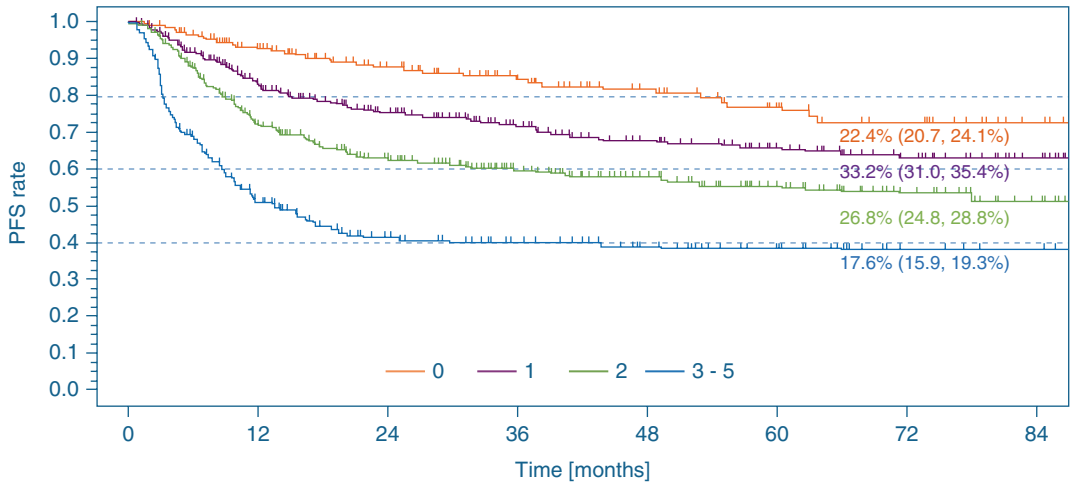

Fig. 20.2 Kaplan–Meier curves of progression-free survival (PFS) after autologous stem cell transplant (ASCT) in four risk groups of the risk score in patients treated predominantly in routine clinical care [18]

therefore, ultrahigh-risk patients can reliably be identified. This might allow for a more reasonable selection of patients for alternative salvage strategies in clinical trials or consolidation strategies (see Sects. 20.7 and 20.8) in routine care.

20.3 Salvage Therapy

Possibly the most important goal in the management of patients with relapsed or primary refractory HL is establishing chemosensitive disease with SC. It has been clearly demonstrated in multiple studies that chemorefractory disease to SC predicts for a poor long-term PFS [18, 19]. An effective salvage regimen must have a favorable toxicity profile, in addition to having a high response rate. Older regimens such as mini- or dexa-BEAM have limited utility in 2019 because of toxicity to hematopoietic stem cells, leading to an inadequate stem cell harvest [20–22]. The optimal choice of a salvage regimen is unclear, because different regimens have not been directly compared with one another and in general, as opposed to diffuse large B cell lymphoma, response rates are quite high approaching 80%. Unfortunately, the clinician is left to choose from a variety of reasonable salvage options without clear knowledge of the superiority of one regimen vs. another. At MSKCC, the ICE (ifosfamide, carboplatin, etoposide) chemotherapy regimen has been used since 1994 and has become the standard SC used in the United States [3, 8, 19]. ICE is regularly administered as an inpatient treatment for 2 cycles. In a series of prospective clinical trials, the complete response (CR) rate is approximately 50% and the overall response rate is 80%. An augmented dosing has been evaluated in patients with unfavorable risk factors [8, 17] with the following doses: ifosfamide 10 g/m^2 as a 48-h continuous infusion, etoposide 200 mg/m^2 for 3 doses, and carboplatin at an AUC of 5. It is likely that cytarabine-based regimens such as DHAP (dexamethasone, high-dose ara-C [=cytarabine], cisplatin), ESHAP (etoposide, methylprednisolone, high-dose ara-C [=cytarabine], cisplatin), and DHAX (dexamethasone, high-dose ara-C [=cytarabine], oxaliplatin) have similar response rates, and centers tend to be passionate concerning the type of salvage regimen that is employed. The GHSG and other European cooperative groups regard DHAP as standard SC [23, 24].

The other popular choice is to incorporate gemcitabine into the SC program. Gemcitabine-based regimens are better tolerated, show similar activity, and have the advantage of easier outpatient administration. GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin) was

evaluated in 91 patients with relapsed or refractory HL, and overall response rate (ORR) was 70%, albeit with a modest 19% CR rate based upon CT imaging [25]. Another program, IGEV (ifosfamide, prednisolone, gemcitabine, and vinorelbine), was administered to 91 patients of which 49 (54%) achieved a CR and 25 patients (27.5%) had a PR for an ORR of 81.3%, based upon PET imaging [26]. Lastly, Kuruvilla et al. compared GDP (gemcitabine, dexamethasone, and cisplatin) with mini-BEAM; response rates were similar but GDP was far less toxic [27]. A more recent report supports the tolerability and efficacy of GDP in patients with relapsed or refractory HL [28].

Depending upon prognostic factors, favorable risk patients are likely to have a high CR rate to any of these regimens and it is prudent to minimize toxicity if possible. Recently, several studies have incorporated brentuximab vedotin (BV) either sequentially or in combination with chemotherapy as part of a salvage strategy prior to ASCT [29–32]. BV comprises an anti-CD30 antibody conjugated by a protease-cleavable linker to a microtubule-disrupting agent, monomethyl auristatin E (MMAE). BV demonstrated substantial efficacy, including an objective response rate of 75% and complete remission (CR) rate of 34%, in a pivotal phase two study of patients with CD30-positive HL who had failed HDCT and ASCT therapy and is approved in this setting [33]. As a targeted therapy with minimal hematologic toxicity, BV may provide a unique opportunity to deliver therapy pre-ASCT. Two studies confirmed a single-agent response rate of >80% as first salvage treatment in transplant-eligible patients; however, the complete response rate is <40% [29, 30]. Sequential treatment with platinum-based salvage treatment to patients lacking a PET-negative response (Fig. 20.3) increases the CR rate to >80% [30]. Other studies have combined BV with either bendamustine, ICE, DHAP (Fig. 20.4), or ESHAP and all trials demonstrated feasibility and favorable results as compared to historical data [34–37]. Interestingly, patients achieving a CR to either single-agent BV, sequential BV and chemotherapy, or concomitant BV and chemotherapy all have similar 2-year PFS data post-ASCT: >80% of patients are progression-free. Clearly, single BV therapy

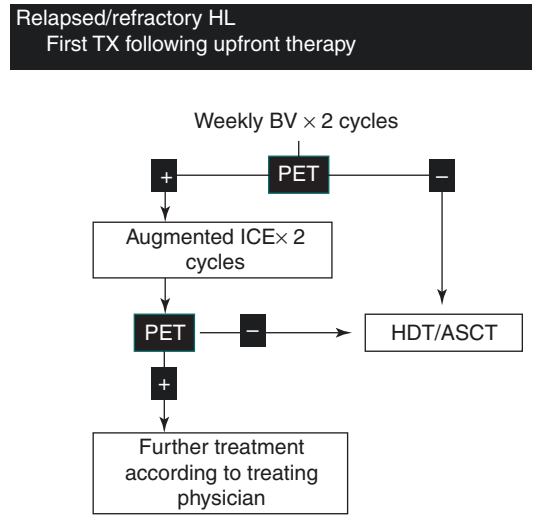

Fig. 20.3 Brentuximab vedotin as initial salvage therapy in relapsed/refractory HL. *HL* Hodgkin lymphoma, *TX* chemotherapy, *BV* brentuximab vedotin, *PET* positron emission tomography, *ICE* ifosfamide, carboplatin, and etoposide, *HDCT* high-dose therapy, *ASCT* autologous stem cell transplant [30]

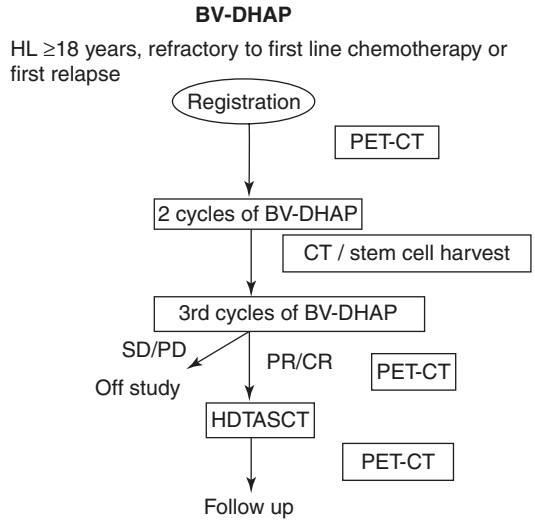

Fig. 20.4 Brentuximab vedotin-DHAP as salvage therapy in relapsed/refractory HL. *BV* brentuximab vedotin, *DHAP* dexamethasone, high-dose ara-C, Cisplatinum, *HL* Hodgkin lymphoma, *yr* year, *PET-CT* positron emission tomography/computed tomography, *SD* stable disease, *PD* progressive disease, *PR* partial remission, *CR* complete remission [35]

will have the least side effects, but the lowest CR rate and likely prognostic factor analyses should determine the optimal salvage program. BV might also be an alternative for patients not tolerating salvage combination chemotherapy due to lymphoma-associated morbidity and for patients not responding to conventional therapy. Therefore, BV as salvage therapy was assessed in a phase IV trial for patients with relapsed HL and a history of ≥1 prior systemic chemotherapy regimen who were deemed transplant-ineligible at trial entry. After treatment with BV, 47% of patients finally received HDCT [38].

Besides BV, the anti-programmed cell death receptor 1 (PD1) antibodies nivolumab and pembrolizumab were also evaluated as preparative therapy before curative HDCT due to their excellent tolerability and high efficacy [39, 40]. The chemotherapy-free combination of BV and nivolumab was tested in 62 patients who failed induction therapy in a phase 1/2 trial [41]. With an ORR of 82% and a CR rate of 61%, the tumor control rate was high; however, these numbers are in the range of what can be achieved with a combination of BV and chemotherapy. Another trial assessing different combinations of nivolumab, ipilimumab, and BV in multiple cohorts including transplant-naïve patients is currently enrolling in the randomized phase 2 part of the trial that compares nivolumab plus BV to a combination of nivolumab, ipilimumab, and BV (ClinicalTrials.gov Identifier: NCT01896999).

Importantly, no randomized phase III trials with BV or anti-PD1 treatment as part of the salvage program were conducted so far and therefore superiority of these newer strategies over conventional treatment has yet to be proven. Additionally, BV and anti-PD1 treatment are not approved for the use in first salvage therapy in relapsed HL. In summary, several reasonable salvage options were evaluated in prospective nonrandomized clinical trials, and the clinician is left to choose based on the characteristics of the individual patient, personal experience, availability of drugs, and the standards of a specific center.

20.4 Pre-ASCT FDG-PET

FDG-PET-CT has revolutionized the way oncologists manage HL. FDG-PET-CT imaging is more sensitive and specific than either modality alone, and in 2019, most HL patients have a combined FDG-PET-CT scan for staging and to determine remission status at the conclusion of a chemotherapy program [42]. It is also recommended that the CT component include intravenous and oral contrast which can be helpful for patients requiring subsequent consolidative radiotherapy. Some of the basic "rules" in PET scanning for HL is that it is always abnormal at diagnosis and normalization after therapy is highly predictive of a good outcome. However, controversy remains concerning its role for interim evaluation.

Since second-line treatment employs a comprehensive approach, the pre-ASCT PET in reality is an interim PET (iPET). Reporting should be similar to that of untreated HL, scores 1–3 are considered negative via the 5-point or Deauville scale, and 4/5 are positive [43]. The question that investigators face is should a patient who is deemed chemosensitive by CT but with an abnormal iPET be excluded from curative therapy? Thirty percent of patients achieve long-term EFS if there is tumor shrinkage after one course of salvage therapy despite an abnormal iPET.

Recent studies have reported that chemosensitive disease should be defined by pretransplant PET status; those patients with a negative scan have a 5-year EFS of approximately 75% compared to 30% for those patients with improvement of CT but with persistent PET positivity [14, 44, 45]. This data was confirmed by the MD Anderson group where 3-year PFS and OS rates were 69% and 87%, respectively, vs. 23% and 58%, respectively, for patients with positive functional imaging. MSKCC investigators recently reported the results of a large phase II second-line treatment program where iPET was prospectively evaluated. Patients that achieved normalization of the post-ICE PET scan were transplanted with the expected 77% long-term EFS. Patients achieving cytoreduction to ICE but with a persistently abnormal PET received a

second, non-cross-resistant salvage treatment with four doses of GVD administered biweekly. Interestingly, 50% of patients had a PET-negative response to GVD and these patients also had a 77% long-term PFS. Patients with a persistently positive PET scan after two salvage chemotherapy programs had only 22% 5-year EFS [46].

In our opinion, the goal of salvage chemotherapy should be a negative PET scan; however, owing to the lack of randomized trials, the best strategy for patients not achieving a negative PET after the first salvage program is currently unclear. A second, non-cross-resistant salvage program or tandem ASCT (see Sect. 20.7) seem to be reasonable options. It must be stressed that patients with nodal only HL at this point can still achieve a negative PET with involved or extended field radiotherapy, a reasonable approach in this patient population. The treatment decision should be based on pretreatment, risk factors and comorbidities of the individual patient.

20.5 Salvage Radiotherapy

As stated above, SC followed by HDCT/ASCT is standard therapy for transplant-eligible patients with HL. The incorporation of radiotherapy (RT) to selected sites integrated into the salvage program either before or after transplantation can improve EFS for a subset of patients. An increasing number of patients who failed primary treatment are RT naïve, and this number will only increase since the evolving trend in many centers is to use short-course chemotherapy alone for early-stage HL. An important argument in support of incorporating RT into high-dose salvage programs is that the pattern of relapse after HDCT is similar to that after primary therapy, i.e., in sites of moderately bulky nodal involvement.

The issues of optimal timing of RT—pre- or post-HDCT/ASCT—is center dependent. At MSKCC, involved field RT (IFRT) is administered prior to HDCT as part of the salvage program for further tumor reduction, and interestingly, at times it is the IFRT that normalizes the pre-ASCT PET scan. From 1985 to 2008, it was MSKCC policy to employ both IFRT and total lymphoid irradiation (TLI) for RT-naïve patients without extranodal involvement. A cohort of 186 patients of which 53% had primary refractory disease to ABVD was recently updated. These patients received involved field RT (IFRT) at 18 Gy followed by total lymphoid radiation at 18 Gy as part of the conditioning regimen; the 5- and 10-year OS were 68% and 56%, and the 5- and 10-year EFS were 62% and 56%, respectively [47]. This data was confirmed by the group at Northwestern where TLI was found to be an independent predictor for improved EFS on multivariate analysis [48]. Within the GHSG, RT in case of residual disease after HDCT and ASCT is preferred aiming at a dose-dense salvage and high-dose chemotherapy.

Currently, the use of RT can help a substantial number of patients in the salvage setting. Since nodal only relapses are common, the avoidance of RT in this setting makes little sense in patients whose major cause of death will clearly be HL if HDCT/ASCT is not successful.

20.6 HDCT Regimens

Similar to SC regimen selection, the choice of the HDCT regimen before ASCT is not evidence-based: no randomized controlled trials comparing different regimens have been conducted, and the choice of regimen is mostly made on personal experience. Historical comparisons of different regimens are limited by high patient heterogeneity in terms of pretreatment, risk factors, and comorbidity [49]. Because BEAM (BCNU [=carmustine], etoposide, cytarabine, melphalan) was used in both of the randomized controlled trials that established ASCT in relapsed/progressive HL [1, 2] and yielded excellent results in the large HDR2 trial, this is the HDCT regimen of choice for most groups. CBV(−Mx) (cyclophosphamide, carmustine, etoposide, mitoxantrone) and (sub)total lymphoid irradiation ([S]TLI)-based conditioning regimens are frequently used alternatives [46, 50]. Phase I/II trials with modified HDCT regimens aiming at a reduced toxicity of BCNU using bendamustine [51] or

gemcitabine/vinorelbine [52] have been published, but owing to the lack of randomized trials, these approaches currently remain experimental.

The addition of sequential HDCT after SC was evaluated as a potential alternative to the commonly used multiagent HDCT regimens. Based on the challenging results of a phase II trial [53], sequential HDCT was tested in the prospective GHSG, EORTC, GEL/TAMO, and EBMT HDR2 trial. Patients with histologically confirmed early or late relapsed HL and patients in second relapse with no prior HDCT received two cycles of DHAP. Patients achieving at least SD after DHAP were randomized to receive either BEAM followed by ASCT (arm A of the study) or high-dose cyclophosphamide, followed by high-dose methotrexate plus vincristine, followed by high-dose etoposide, and a final myeloablative course with BEAM (arm B of the study). A total of 284 patients with relapsed HL were included in this largest randomized trial performed in this setting so far; 241 patients were randomized after DHAP. The intensified experimental arm showed significantly longer mean treatment duration and higher toxicity before BEAM. Mortality was nearly identical in both arms (20% and 18%) and there were no differences in terms of PFS and OS. The respective 3-year rates for the standard arm and the intensified arm were PFS 72% vs. 67% and OS 87% vs. 80%. In conclusion, both regimens tested showed equally favorable results in outcome and survival. Since further intensification did not improve results, two cycles of conventional SC followed by HDCT and ASCT remain the standard of care for patients with relapsed HL.

20.7 Tandem HDCT/ASCT

The prognosis of high-risk patients with relapsed HL and especially the prognosis of refractory patients remain unsatisfactory despite HDCT and ASCT. Tandem autologous transplant is a potential strategy to improve the prognosis of these patients. In the French H96 prospective multicenter trial [50], 150 high-risk patients (primary refractory disease, $n = 77$, or two or more of the following risk factors at first relapse: time to relapse <12 months, stage III or IV at relapse, and relapse within previously irradiated sites, $n = 73$) were assigned to tandem ASCT. In the intent-to-treat analysis, the respective 5-year FF2F and OS estimates were 46% and 57%, with similar outcomes in primary refractory and high-risk relapsed patients. The 45% 5-year OS in patients with chemotherapy-resistant disease who completed tandem transplant compares favorably with previously reported 5-year OS rates of 30%. In the long-term follow-up analysis, these relatively favorable results were confirmed: 10-year FF2F and OS in the high-risk patients were 40% and 47%, respectively [54]. Additionally, two other analyses also suggested a benefit of tandem ASCT in high-risk relapsed/refractory HL patients [17, 55].

Moreover, a series of 111 consecutive patients who had relapsed or refractory HL achieving CR (PET negative) or PR (PET positive) after SC was reported; these patients underwent single or tandem ASCT [15]. In line with other analyses, outcomes were significantly better in patients with negative PET compared to patients who were PET positive after salvage with PFS and OS rates of 79% vs. 23% and 90% vs. 55%, respectively. In the PET-positive subgroup, tandem transplant improved 5-year PFS from 0% to 43% ($p = 0.034$) compared to single ASCT. In summary, tandem ASCT is an alternative for high-risk relapsed and primary refractory patients and for patients not sufficiently responding to SC.

20.8 Posttransplant Therapy

As stated above, single institution studies suggest nearly 2/3 of patients with a negative pre-ASCT pet scan are cured with ASCT, but registry and cooperative studies report that approximately 50% of patients can be cured after auto-HSCT, and most patients with unfavorable risk factors progress after transplant. Prior to the availability of checkpoint inhibitors, the median survival of ASCT failures was approximately 30 months. The AETHERA trial is a phase 3, randomized, double-blind, placebo-controlled, multicenter study initiated to

answer the question if there was benefit of giving post-ASCT therapy with BV to patients with an initial remission duration of <1 year or extranodal disease at the time of salvage therapy [56]. A total of 165 and 164 patients were randomized to receive either BV or placebo after high-dose therapy and stem cell infusion, respectively. At 5 years' follow-up, patients randomized to BV had a significantly longer PFS than patients who received placebo. Median 5-year PFS with BV was not reached and was 15.8 months with placebo. The 5-year PFS (95% CI) rate was 59% (51–66) with BV vs. 41% (33–49) with placebo (HR = 0.521; 95% CI, 0.379–0.717; Fig. 20.5). The data is very straightforward: one in five patients destined to be ASCT failures were now cured.

There were many lessons learned from this study: (1) A survival difference will not be achieved because of two main issues—crossover design where patients with progressive disease on the placebo arm were able to receive BV free of charge and more importantly checkpoint inhibitors became available and overall survival in patients where ASCT fails might be greater than 10 years as opposed to 30 months. (2) Five risk factors predicted outcome on the study: <CR pre-ASCT, extranodal disease, B symptoms at the time of salvage, the requirement of >1 salvage regimen to achieve ASCT eligibility and remission duration of less than 1 year. Only patients with at least two of these risk factors benefitted from maintenance. (3) PET imaging was not required and when done were not reviewed centrally; it is clear from other datasets however that patients with nodal only disease at the time of salvage in CR as defined by a negative pre-ASCT PET do extremely well with ASCT, and post-ASCT BV is likely of little benefit in the absence of other high-risk features. (4) At 5 years, BV-induced peripheral neuropathy resolved in 90% of patients. (5) All patients were BV naïve and the use of post-ASCT BV in this setting was not studied. The general recommendations in this situation requires common sense: if patients had a suboptimal response to BV prior to ASCT, defined as < partial response, administering BV again makes little sense.

Secondary malignancies occurred in six and three patients in the BV and placebo arms, respectively; they included myelodysplastic syndromes ($n = 2$), acute myelogenous leukemia,

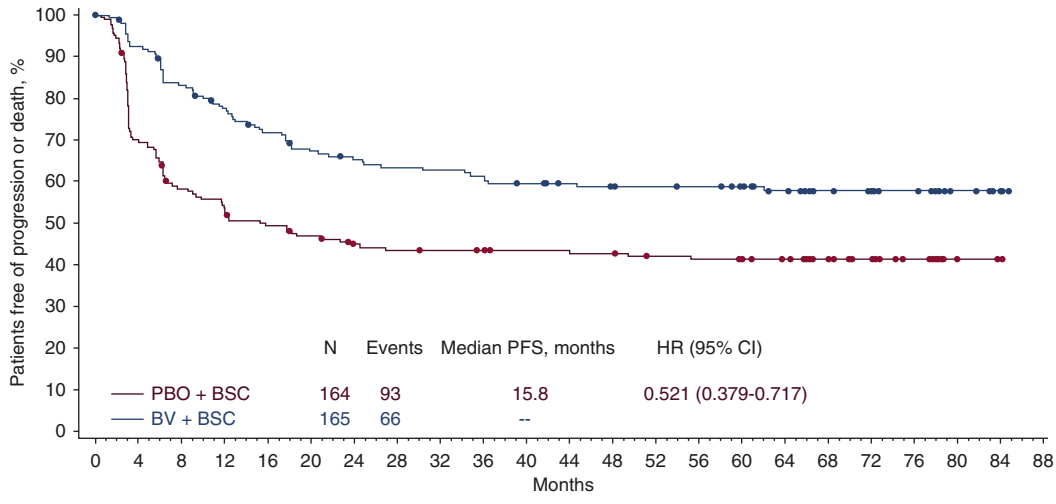

Fig. 20.5 AETHERA trial: Patients with increased risk of relapse after autologous stem cell transplantation received brentuximab vedotin (BV) or placebo as consolidation. All patients additionally had best supportive care (BSC). Progression-free survival (PFS) per investigator at 5 years [56, 57]

pancreatic, lung, and bladder cancer ($n = 1$ each) in the BV arm and mantle cell lymphoma, acute myelogenous leukemia, and myelodysplastic syndromes in the placebo arm ($n = 1$ each).

In summary, patients who received BV as early consolidation maintained a PFS benefit at 5 years and, despite a high rate of subsequent BV therapy in the placebo arm after relapse, also had a longer time to next salvage treatment [57]. Patients who received BV consolidation also required fewer therapies, including subsequent transplants. Lastly, PN continued to improve and/or resolve in 90% of patients. A final analysis of overall survival is expected in 2020.

20.9 Allogeneic Transplantation after Reduced Conditioning in Hodgkin Lymphoma

In most cases, allogeneic transplantation is not recommended for patients with HL. The reduced relapse rate associated with a potential graft-versus-tumor effect is offset by lethal graft-versus-host toxicity. Nevertheless, patients with first-line therapy failure or relapsed patients with additional risk factors such as insufficient response to SC face a poor prognosis after HDCT and ASCT. Therefore, the role of allogeneic transplant should be further evaluated within clinical trials in these patients. While allogeneic transplant after myeloablative conditioning led to poor results because of the exceedingly high non-relapse mortality, several retrospective analyses have suggested that dose-reduced allogeneic transplant (RIC-allo) could be an option for HL patients relapsing after ASCT. The largest multicenter phase 2 prospective clinical trial of RIC-allo in relapsed or refractory HL so far reported favorable results in a subset of patients [58]. The role of allogeneic transplant in HL is discussed in detail in Chap. 21.

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Allogeneic Transplantation for Relapsed Hodgkin Lymphoma

21

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Contents

21.1 Introduction

Hodgkin lymphoma (HL) is highly responsive to conventional chemotherapy (CT). Close to 90% of patients even with advanced disease are cured with modern treatment which is often followed by radiation [1, 2]. Patients who are refractory or relapse after first-line therapy do significantly worse. High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) is the standard of care for medically fit patients with relapsed HL [3, 4]. The results of ASCT,

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_21

however, vary significantly depending on a number of prognostic factors—the most important of which are the time interval between first-line treatment and relapse, the clinical stage at relapse, and the sensitivity of the tumor to salvage CT [5–9]. The most recent analysis on prognostic factors indicates that accurate and reliable risk stratification in patients with relapsed/refractory HL who successfully undergo ASCT can be achieved with five easily available clinical risk factors: stage IV disease, time to treatment failure of ≤3 months, bulky disease ≥5 cm, ECOG status ≥1, and nonresponse to salvage treatment, either measured as achieving less than partial remission (PR) by CT scan or PET positivity [10]. In the setting of high-risk disease, consolidation therapy with brentuximab vedotin (BV) single dose up to 16 cycles after ASCT has demonstrated to significantly improve progression-free survival (PFS) in this subgroup of patients with the potential to avoid exposure to subsequent toxic therapies [11]. Despite all these efforts, a significant proportion of patients with relapsed or refractory HL fail to achieve a continuous complete remission (CR) after ASCT; these patients might be candidates for other treatment strategies such as allogeneic stem cell transplantation (allo-SCT).

21.2 Myeloablative Allogeneic Stem Cell Transplantation in Hodgkin Lymphoma: A Historical Perspective

The first reports on allo-SCT in patients with HL appeared in the mid-1980s [12, 13]. Two large registry-based studies published in 1996 gave disappointing results. Gajewski et al. analyzed 100 HL patients allografted from HLA identical siblings and reported to the International Bone Marrow Transplant Registry (IBMTR) [14]. A significant proportion of these patients was not in remission before transplant and had a poor performance status (PS) as well as active infections before transplantation. Almost 50% of the patients received total body irradiation (TBI)-containing regimens. The 3-year rates for overall survival (OS), disease-free survival (DFS), and the probability of relapse were 21%, 15%, and 65%, respectively. The major problems after transplantation were persistent or recurrent disease as well as respiratory complications, which accounted for 35–51% of deaths. Acute and/or chronic graft-versus-host disease (GVHD) did not significantly reduce the risk of relapse. At the same time, a case-matched analysis including 45 allografts and 45 autografts reported to the European Group for Blood and Marrow Transplantation (EBMT) was performed by Milpied et al. [15]. The matching criteria were sex, age at time of transplantation, stage of disease at diagnosis, bone marrow involvement at diagnosis and at transplantation, year of transplantation, disease status at time of transplantation, time from diagnosis to transplantation, and conditioning regimen with or without TBI. The 4-year actuarial probabilities of survival, PFS, relapse, and non-relapse mortality (NRM) were 25%, 15%, 61%, and 48% and 37%, 24%, 61%, and 27% after allo-SCT and ASCT, respectively. The toxic death rate at 4 years was significantly higher for allo-SCT patients ($p = 0.04$). Even for patients with sensitive disease at the time of transplantation, the 4-year actuarial probability of survival was 30% after allo-SCT and 64% after ASCT ($p = 0.007$). This difference was mainly due to a higher NRM rate after allo-SCT (65% vs. 12%, $p = 0.005$) that was basically associated with the development of acute GVHD after transplantation and/or concomitant infectious episodes. Although a GVHD ≥grade II was associated with a significantly lower risk of relapse, it was also associated with a lower OS rate.

A number of reports confirmed the registry data: allo-SCT resulted in lower relapse rates but significantly higher toxicity with no improvement over ASCT when PFS or OS were considered [16–18]. Although the poor results after myeloablative conditioning could at least partly be explained by the very poor risk features of many individuals included in these early studies, the high procedure-related morbidity and mortality prevented the widespread use of allo-SCT.

21.3 Reduced-Intensity Regimens

Given the high NRM seen in adults with HL following myeloablative allo-SCT, the use of reduced-intensity (RIC) or nonmyeloablative conditioning regimens was found to be an attractive therapeutic option. The goal of these therapies was to reduce regimen-related toxicity while still providing sufficient immunosuppression to facilitate donor engraftment and a subsequent graft versus lymphoma (GVL) effect. The aim of all these regimens was to shift the balance from the antilymphoma activity of the conditioning regimen to the immune cells transferred with the donor graft which may mediate a GVL response. The marked reduction in upfront toxicity of these regimens has extended the applicability of allo-SCT to older patients, those with comorbidities, and patients who had previously failed a prior ASCT (Fig. 21.1).

There are many reports detailing the outcomes of RIC transplants of patients with relapsed HL [19–31]. These results can be difficult to compare due to the difference in patient populations and conditioning regimens; however, in general, the NRM has been impressively reduced when com-

Fig. 21.1 Number of allo-SCT reported to the EBMT Lymphoma database over time (EBMT Lymphoma database, with permission). (**a**) Evolution of numbers of allo-SCT over time (reduced intensity conditioning regimens (RIC) vs. myeloablative conditioning protocols (MAC)). (**b**) Allo-SCT activity over time: type of donors (HLA identical sibling donor (Hla-id sib) vs. matched unrelated donor (MUD) vs. haploidentical stem cell donor (Haplo-SCT) vs. cord blood transplants (CBT))

pared to myeloablative conditioning regimens. This reduction in transplant mortality was confirmed by the lymphoma working party (LWP) of the EBMT which compared HL patients having standard myeloablative conditioning to those having RIC between 1997 and 2002 [19]. Transplant-related mortality was 48% at 3 years in the myeloablative group and 24% in the RIC group ($p = 0.003$).

Although RIC has allowed allo-SCT to be performed more safely, relapse is now the most common cause of treatment failure. Conditioning intensity/antilymphoma activity may be an important factor in determining relapse rates. This may be secondary to the requirement for a lengthy period of clinical remission to allow the incoming donor immune system to eradicate residual disease. An early GVL response is often delayed by the use of immunosuppressive drugs to prevent GVHD following T-cell-depleted transplantation or by the use of a T-cell-depleted graft which often necessitates the use of posttransplant donor lymphocyte infusions (DLI). Some of the truly nonmyeloablative (NMA) regimens have been associated with particularly high relapse rates [20, 21]. This concept of regimen intensity being important is also supported by the EBMT analysis which showed a 32% relapse rate following myeloablative conditioning compared to 58% with reduced-intensity regimens [19]. Furthermore, within the reduced-intensity group, there was a higher relapse and lower OS rate in patients who were conditioned with low-dose TBI which is one of the regimens with the least toxicity ($p < 0.04$). Other studies have also shown better outcomes using more intensive regimens such as the combination of fludarabine and melphalan when compared to less intensive regimens [22]; the BEAM-alemtuzumab regimen has also demonstrated good disease control [23]. Finally, overall results have improved over time: in an updated retrospective analysis of the LWP of the EBMT comparing RIC with myeloablative procedures [32], NRM was not different between MAC and RIC. Due to a higher relapse rate of RIC in front of MAC, both PFS and OS were better for those patients being allografted with myeloablative procedures than with RIC protocols.

There is mounting evidence that successful allogeneic transplantation for HL needs a combination of effective salvage CT and a moderately intensive pretransplant conditioning regimen to keep the disease under control for several months allowing the withdrawal of immunosuppression and/or the use of DLI to mount an effective GVL response.

21.4 Prognostic Factors of Long-Term Outcome for Allogeneic SCT

The introduction of RIC regimens in the allogeneic field allowed a significant reduction in the NRM associated with the procedure in HL patients [19]. The identification of independent prognostic factors better allowed to guide physicians in the choice of therapy for individual patients. However, the reported experience of RIC-allo in HL has been limited by the number of patients included [19–31], making it difficult to identify independent predictors of outcome. The largest prospective study published to date includes 78 patients with relapsed/refractory HL, most of them being treated with an allo-SCT due to a relapse after an ASCT [33].

The LWP of the EBMT performed a retrospective analysis comprising a population of 285 patients with relapsed or refractory HL treated with reduced-intensity allo-SCT in order to try to identify prognostic factors for long-term outcome [34]. Sixty patients died of NRM at a median of 91 days (range 1 day–20 months) following transplantation. The cumulative incidence estimates a NRM at 100 days and 1 and 3 years posttransplant were 10.9%, 19.5%, and 21.1%, respectively. In multivariate analysis, NRM was associated with PS, chemorefractory disease at transplantation, age greater than 45, and transplantation before 2002. Identifying poor PS, chemorefractory disease, and older age as adverse risk factors for NRM, patients with no adverse risk factors had a 3-year NRM rate of 12.5% compared with 46.2% for those with two or three risk factors. With a median follow-up of 26 months (range 3–94 months), 126 patients

remained alive and 159 have died. The Kaplan-Meier estimates of OS and PFS at 1, 2, and 3 years were 67% and 52%, 43% and 39%, and 29% and 25% respectively. In multivariate analysis, patients in CR or with chemosensitive disease, those with a good PS, transplants other than sex-mismatched male recipients, and CMV−/− transplants had a significantly better OS. For PFS good PS, CR, or chemosensitive disease at transplantation and transplants other than male recipients from female donors was associated with a significantly better PFS in the multivariate analysis. Considering chemorefractory disease and poor PS as risk factors for a poor PFS and OS, patients with neither of these risk factors have a 3-year PFS and OS of 42% and 56% compared to 8% and 25% for patients with one or two of these risk factors. In an analysis restricted to patients who had relapsed after prior ASCT, relapse within 6 months of the autograft was associated with a significantly poorer disease progression rate (RR = 1.9 (1.2–3.1) p = 0.01) and PFS (RR = 1.9 (1.2–2.9) p = 0.003) following reduced-intensity allo-SCT. Reduced-intensity allo-SCT is an effective salvage strategy for patients with good risk features who relapse after ASCT (Fig. 21.2), and those outcomes are similar for both sibling and matched unrelated donor (MUD) transplants. Conversely for patients with chemorefractory disease or PS, the overall outcome is poor, and nowadays these patients should not be considered candidates to receive this treatment strategy.

These results are in agreement with what was also published in smaller series of patients. The UK Cooperative Group reported that disease status before allo-SCT was the strongest prognostic factor for PFS and OS, the results being significantly better for those patients allografted in CR [25]. In the HDR-Allo trial [33], chemosensitivity was the most important prognostic factor (HR = 2.3; 95% CI = 1.3–3.1; P = 0.001) for PFS. Patients allografted in CR had the best outcome, with PFS rates at 1 and 4 years of 70% (95% CI = 67–73) and 50% (95% CI = 47–53), respectively. Refractory disease and a poor PS were associated with a significantly worse OS (HR = 1.9, 95% CI = 1.0–2.7, and P = 0.001 and HR = 2.5, 95% CI = 1.3–4.2, and P = 0.01, respectively) in the same study. Disease status was the strongest factor predicting for survival in virtually the rest of the retrospective analyses published in the literature [19–24, 26–31, 36].

21.5 Evidence for Graft Versus Hodgkin Lymphoma

Despite the theoretical reliance of reduced-intensity RIC transplantation on a GVL effect, there are relatively few studies which convincingly demonstrate this activity in patients with HL. Many of the myeloablative transplants done in adults had such a high NRM that it would have been almost impossible to see a GVL effect if one had existed. In the context of RIC transplantation, there is some evidence of a reduction in relapse in association with GVHD. Conversely, the apparent lack of impact of T-cell depletion on relapse risk is unexpected. This finding might simply be a function of the relatively small numbers of patients reported or it is possible that the in vivo monoclonal antibody used to facilitate T-cell depletion may have anti-Hodgkin lymphoma activity.

The most convincing evidence of GVL activity in HL comes from the use of DLI to treat patients who relapse following allo-SCT (Table 21.1). Response rates to DLI have been reported to be between 15% and 60%, with CR seen in around 30% of patients. Many of these patients had received concurrent CT or radiotherapy but responses have been seen to DLI alone and some of these have been durable. There appears to be a higher response rate in the two series coming from the UK [25, 38] and it is not known whether the high incidence of mixed chimerism seen in patients who received alemtuzumab promotes GVL responses as it does in some animal models. The optimal T-cell dose for GVL remains unclear, although many groups use an escalating dose schedule to try and reduce the risk of severe graft-versus-host disease. Unlike follicular lymphoma, there is preliminary evidence that in relapsed HL, GVL responses are unlikely in the absence of GVHD. However,

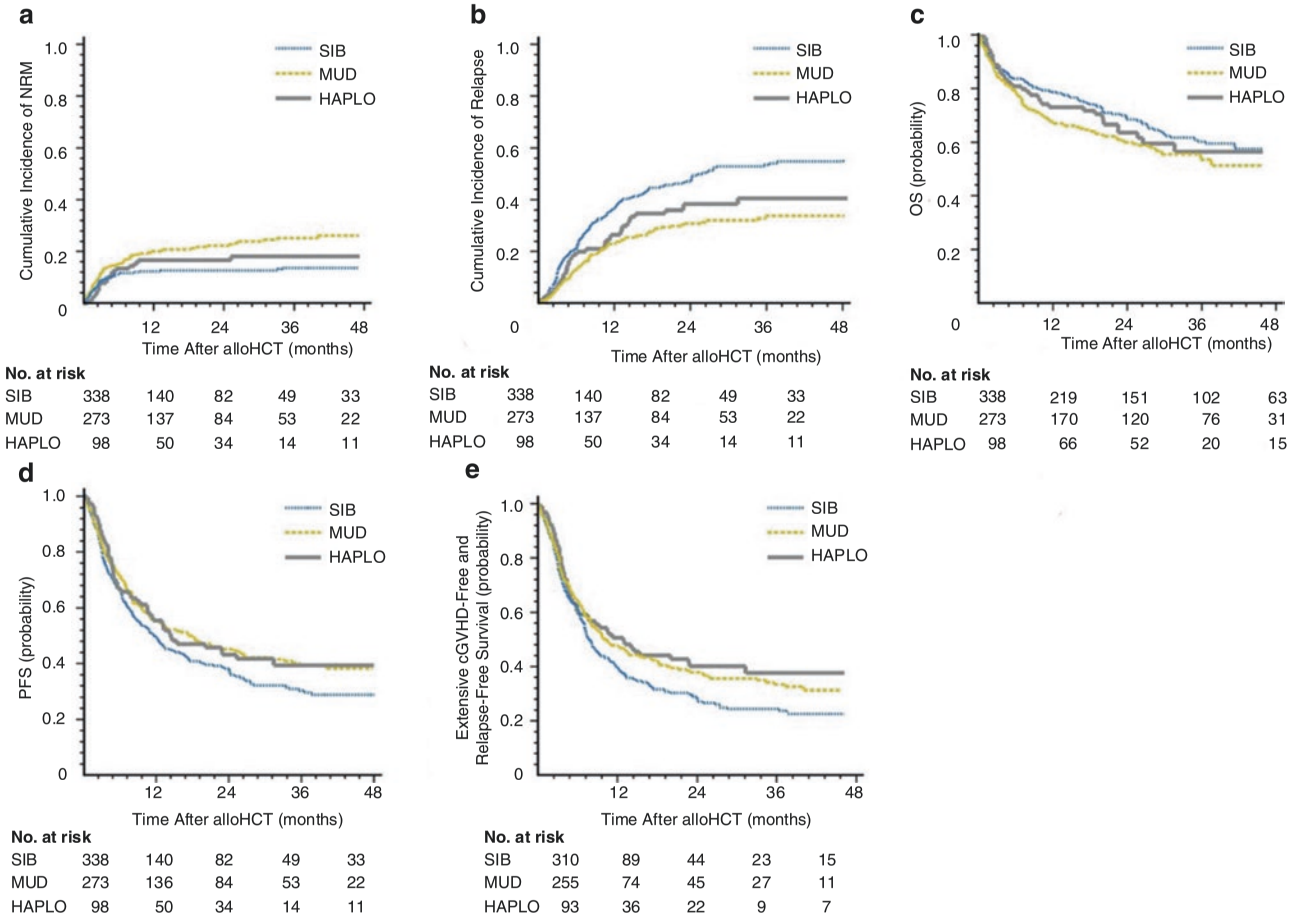

Fig. 21.2 Long-term outcomes of haploidentical donor stem cell transplantation vs. HLA identical sibling donor and matched unrelated donors. (**a**) Cumulative incidence of nonrelapse mortality (NRM) in recipients of sibling donor (SIB), match unrelated donor (MUD), and haploidentical donor (HAPLO) transplantations (overall, $P = 0.23$). (**b**) Cumulative incidence of relapse and/or progression in recipients of SIB, MUD, and HAPLO transplantations (overall, $P < 0.001$). (**c**) Kaplan-Meier estimate of overall survival (OS) in recipients of SIB, MUD, and HAPLO transplantations (overall, $P = 0.118$). (**d**) Kaplan-Meier estimate of progression-free survival (PFS) in recipients of SIB, MUD, and HAPLO transplantations (overall, $P = 0.086$). (**e**) Kaplan-Meier estimate of combined incidence of extensive chronic graft-versus-host disease (cGVHD)-free and relapse-free survival in recipients of SIB, MUD, and HAPLO transplantations (overall, $P = 0.04$). (Martínez C et al. [35], with permission)

Table 21.1 Donor leukocyte infusions for relapse

Study and regimen	Reference	Patient number	CR/PR	Response at last follow-up
UK	[25]	24	14/5	12 CR/2 PR at 2+ years
Houston	[36]	14	3/3	1 PR at 3+ years
GEL/TAMO	[26]	20	6/5	None ongoing
SFGM/TC	[37]	30	3/5	Not reported
EBMT	[19]	41	13/4	Not reported
UK	[38]	24	14/5	9 out of 19 patients

CR complete remission, *PR* partial remission

when DLI are given for mixed chimerism, there appears to be a GVL effect that is independent of GVHD [38]. There are a number of factors that may increase the toxicity of DLI including: increasing age of the patient, HLA mismatching, use of unrelated donors, and short time interval from transplant to DLI infusion. Although the DLI responses are impressive in some patients, the majority of patients will not achieve long-term benefit from DLI and further study is needed to optimize this potential effect. Recent data indicate some potential benefit of the use of BV before DLI in order to exert some immunomodulatory effect that would enhance the effectiveness of donor lymphocytes [39] or to simply act as an effective antitumoral strategy [40].

21.6 Role of Allogeneic SCT in Autograft Failures

Allogeneic stem cell transplantation is considered an adequate treatment strategy for patients who relapse or progress after ASCT [41]. Nevertheless, the potential benefit of allo-SCT in front other non-transplant-based strategies has never been demonstrated in a prospective randomized clinical trial, and the evidence of a potential benefit of this therapy in front of others is based on our knowledge on small phase II prospective clinical trials [33] and single center or multicenter retrospective analysis [19–31, 36].

Although there are no randomized trials comparing the results of CT ± radiotherapy in patients who relapse post autograft, comparisons have been made with the outcomes of historical controls. The UK group identified a group of patients who had relapsed following a BEAM autograft, who were chemosensitive at relapse and had survived at least 12 months from relapse, and who would therefore have been eligible for a RIC transplant [42]. This was a highly selected group representing 44% of all relapses who were predicted to have the best survival. These conventionally treated patients were compared to more recently treated patients who received a reduced-intensity allograft. Despite the selection of a control group with a relatively good prognosis, both OS from time of diagnosis and time of autograft were significantly improved following allogeneic transplant, when compared to the historical control group. The estimated current PFS for the allografted patients was 34% at 5 years and 42% if in chemosensitive relapse at the time of transplant, suggesting the early promising results might translate into a favorable long-term outcome. A donor versus no donor comparison performed by Sarina et al. [43] indicated that, in patients relapsing after ASCT, if there was a donor available and they were able to proceed to allo-CST, both PFS and OS were significantly better than in the non-allografted population of patients, thus suggesting that allo-SCT was partially able to overcome the negative impact of disease relapse after the autologous procedure. Nowadays, the role of allo-SCT in this setting is increasingly being challenged, at least in some subgroups of patients, by the advent of new drugs: BV and checkpoint inhibitors (see Sect. 21.9 of this chapter).

21.7 Moving Allogeneic Stem Cell Transplantation to Earlier Stages of the Disease

The more recent investigation of a response-adjusted transplantation algorithm identifies a potential strategy for evaluation of allo-SCT in

those deemed to be at high risk of failure of ASCT, targeting the intensification to those who have residual FDG-avid disease following salvage therapy [44]. The 3-year PFS of 68% in this high-risk group was encouraging, with 80% current PFS following DLI. These results constituted the basis for a phase II prospective clinical trial (CRUK-PAIReD, EUDRACT-2008-004956-60) already closed for recruitment that analyzes long-term outcome of relapsed/refractory HL patients that do not achieve a metabolic CR with first-line salvage chemotherapy and undergo an allo-SCT with BEAM protocol as conditioning regimen and the use of Campath-1H as GVHD prophylaxis. Final results of this trial have not been published in full so far. However, the lack of clear evidence of the potential benefit of allo-SCT as first transplant as well as the incapacity to be able to identify a subgroup of patients mostly benefiting from this approach together with the introduction of new drugs in the treatment armamentarium of these patients renders the role of allo-SCT quite blurred in this setting.

21.8 Role of Allogeneic SCT in the Pediatric Population

Information regarding the role of allo-SCT for HL in the pediatric population is very limited. Children undergoing allogeneic transplantation have been occasionally included in series of adult patients [16–19], whereas exclusively pediatric series were limited to fewer than ten patients [45].

The most extensive analysis of allo-SCT in the pediatric population comes from the LWP of the EBMT, and it comprises a group of 91 children and adolescents 18 years or younger treated with an allograft (myeloablative, $n = 40$; reduced intensity, $n = 51$) for relapsed or refractory HL [46]. NRM at 1 year was 21%, with comparable results after RIC or myeloablative allo-SCT. Probabilities of relapse at 2 and 5 years were 36% and 44%, respectively. Reduced-intensity conditioning allo-SCT was associated with an increased relapse risk compared with myeloablative transplantation, which was most apparent beginning 9 months after allo-SCT ($p = 0.01$). PFS was 40% and 30% and OS was 54% and 45% at 2 and 5 years, respectively. Beyond 9 months, PFS after RIC allograft was lower compared with myeloablative protocols ($p = 0.02$). The development of GVHD did not have any impact on PFS after allo-SCT. Of note, the 26 patients with sensitive disease and good PS who underwent transplantation between 2002 and 2005 showed a PFS of 60% (95% CI = 33–87%) and OS of 83% (95% CI = 67–98%), respectively, at 3 years. Fifteen of these patients (58% of the group) had previously failed ASCT. This retrospective analysis in a pediatric population of patients again raises the question of the exact dose intensity needed in HL patients. Because relapse now is the major problem after allogeneic transplantation for HL in pediatric as well as in adult patients, it may be wise to use myeloablative or "intermediate" conditioning at least in those children and adolescents who have a good PS. Nowadays, the improvement in first-line therapies also in the pediatric population as well as the introduction of BV [47] and eventually checkpoint inhibitors in this setting [48] has significantly reduced the need to allo-SCT in this specific group of patients.

21.9 Alternative Donor Transplants

In Europe and North America, only around a third of patients will have an HLA-matched sibling donor; therefore the use of alternative donors is essential to expand the number of patients eligible for the procedure. The advent of molecular techniques has improved the accuracy of tissue typing reports but the associated increase in HLA polymorphism has made finding an exact molecularly matched donor more difficult. However, the increase in unrelated donor numbers, the availability of cord blood, and the development of efficacious GVHD prophylaxis in haploidentical transplantation have significantly allowed a rise in the number of alternative donor transplants to be performed.

The transplant outcomes using unrelated donors appear similar to those reported using sibling donors [19, 25, 36, 49]. Not surprisingly, rates of GVHD may be higher and many groups have used T-cell depletion strategies with either alemtuzumab or ATG to reduce the incidence of this complication. Interestingly, unrelated donor transplants in patients with HL appear to have a similar overall survival and PFS to sibling donor transplants [19, 25]. Therefore, consideration of an unrelated allogeneic transplant is an adequate alternative for patients that do not have a HLA identical sibling donor [41].

The published experience with cord blood donors in HL is much more limited, but some retrospective analyses indicate that it may be feasible [50, 51]. A Eurocord-Netcord study showed a 30% PFS at 1 year in patients with relapsed HL [52]. A more recent retrospective analysis from Eurocord and EBMT Lymphoma and Cellular Therapy & Immunobiology Working Party that included 113 patients [53] demonstrates a 4-year PFS and OS of 26% and 46%, respectively, with significantly better results in those patients undergoing transplant in CR. A recently published French study showed that use of a cord blood donor was associated with inferior survival [37]. Because of the questionable results of cord blood transplants in terms of relapse rate after the procedure and high NRM but mostly because of the widespread use of haploidentical donors, the use of cord blood as stem cell source in patients with relapsed/refractory HL is almost nonexistent.

Finally, the introduction of posttransplantation cyclophosphamide (PT-Cy) for GVHD prophylaxis following NMA conditioning regimen has ameliorated survival and toxicity rates of haploidentical transplantation in hematologic malignancies [54]. In 2008, Burroughs et al. compared the outcome of NMA allo-SCT for 90 patients with relapsed HL based on donor cell source (38 matched related, 24 unrelated, 28 HLA-haploidentical related donors). Interestingly, the authors found no significant differences in grade III–IV aGVHD or cGVHD among the three groups, confirming a role for selective depletion of alloreactive T cells induced by PT-Cy in reducing the risk of GVHD in haploidentical transplants. Moreover, they reported no differences in 2-year OS (58% vs. 53% vs. 58%) with better 2-year PFS rates (51% vs. 23% vs. 29%) and lower 2-year cumulative incidence (CI) of relapse/progression (40% vs. 56% vs. 63%) in HLA-haploidentical related compared to matched related and unrelated recipients [21]. Subsequently, other groups reproduced promising outcomes for haploidentical allo-SCT, with reasonable grade II–IV aGVHD rates (range 23–39%) and low incidence of cGVHD (range 9–19%) [55–57]. Recently, the French Society of Bone Marrow Transplantation reported a significantly higher probability of GVHD-free relapse-free survival (GRFS) in HL patients who underwent allo-SCT with RIC or NMA conditioning from a haploidentical related donor, when compared with mismatched unrelated and cord blood donors (52% vs. 31% vs. 22%), indicating that haploidentical donors may be a valuable stem cell source in the absence of an HLA-matched donor [58]. Thereafter, the largest retrospective series of 709 adult HL patients recently published by the LWP of the EBMT reported similar survival outcomes in PT-Cy-based haploidentical allo-SCT compared with HLA-matched related and unrelated allo-SCT (1-year CI of NRM 17% vs. 13% vs. 21%; 2-year CI of relapse/progression 39% vs. 49% vs. 32%; 2-year OS 67% vs. 71% vs. 62%; 2-year PFS 43% vs. 38% vs. 45%), with a risk of chronic GVHD lower than that observed in matched unrelated transplants (1-year CI 26% vs. 41%), confirming the significant role of haploidentical allo-SCT in HL patients six [35] (Fig. 21.2).

21.10 Role of Allogeneic Stem Cell Transplantation in the Era of New Drugs

Brentuximab vedotin (BV) is an antibody-drug conjugate that selectively delivers monomethyl auristatin E, an antimicrotubule agent, into CD30-expressing cells. In phase I studies, BV demonstrated significant activity with a favorable safety profile in patients with relapsed/refractory CD30-positive lymphomas. The

interesting results seen in the phase I trial lead to a phase II that evaluated the efficacy and safety of BV. The drug was given at doses of 1.8 mg/kg by intravenous infusion every 3 weeks up to a maximum number of 16 cycles in 102 patients with relapsed or refractory HL after ASCT [59]. Overall response rate (ORR) was 75% with a CR in 34% of patients. The median PFS for all patients was 5.6 months, and the median duration of response for those in CR 40.5 months. After a median observation of 3 years, 31 patients were alive and free of documented progressive disease. The drug was quite well tolerated: the most common treatment-related adverse events were peripheral sensory neuropathy, nausea, fatigue, neutropenia, and diarrhea. Subsequently, the use of BV has been anticipated in the clinical setting of selected high-risk HL patients with primary refractory, initial remission duration shorter than 1 year, and extranodal or advanced-stage disease at relapse. In these patients BV was administered as consolidation after ASCT for up to 16 cycles, with a significant improvement in PFS and no additional toxicities other than peripheral sensory neuropathy as compared to patients who received no consolidation (42.9 vs. 24.1 months) [11]. This observation prompted the approval of BV by FDA and EMA in patients at high risk of relapse or progression after ASCT. At 5-year follow-up the survival advantage of consolidation BV has been confirmed with 5-year PFS of 59% vs. 41% [60].

BV has also been used in the pre-allo-SCT setting, as a "bridge to allo," and in the post-allogeneic setting to treat patients with relapsed/progressive disease after the allogeneic procedure. In 2012 Chen et al. [61] published their experience on 18 patients with multiply relapsed HL undergoing a RIC/allo-SCT after being treated with BV as salvage therapy. NRM and acute and chronic GVHD preferred incidence after the allogeneic procedure were not significantly different from what was previously described. With a median follow-up of only 12 months, PFS was 100%. In a retrospective analysis comparing outcomes after allo-SCT in relapsed/refractory HL patients, Chen et al. [62] also showed that the administration of BV as a bridge to transplant significantly increased the percentage of patients achieving a CR. Indeed, disease status at transplantation is a known significant prognostic factor for both long-term OS and GRFS [28]. Recently the LWP of the EBMT compared the outcomes of 210 patients who received BV prior to allo-SCT with that of 218 patients who did not receive BV. Differently from previous reports, in multivariate analysis pre-allo-SCT BV had no impact on aGVHD, NRM, CI of relapse, PFS, or OS, but significantly reduced the risk of cGVHD (hazard ratio = 0.64). Nevertheless, it must be noted that, while there were no differences between the two groups in disease status prior to ASCT, the population who received BV as pre-allo-SCT salvage was more heavily pretreated (median previous lines of treatment 4 vs. 3 of patients who did not receive BV). This might indicate that BV has a role in inducing favorable disease responses in otherwise refractory patients, therefore improving allo-SCT outcome [63] (Fig. 21.3). Moreover, the role of BV after allo-SCT has been reported in a recent registry study published by the LWP of the EBMT demonstrating encouraging results with ORR 76% (CR 29%) and with 34% of patients alive and in CR after a median follow-up of 33-month outcome [64].

The increasing anticipate use of BV before ASCT in clinical trials and the introduction of anti-programmed death 1 (PD-1) checkpoint inhibitors in the post-ASCT setting will most certainly change the treatment paradigm of these patients, either avoiding the allogeneic procedure in some patients or by increasing the group of potential candidates to allo-SCT. Recently, the PD-1 blocking antibodies nivolumab and pembrolizumab were shown to have significant therapeutic activity with an acceptable safety profile in patients with R/R classical HL. Based on the results of the phase II studies Checkmate 205 and Keynote 087, nivolumab and pembrolizumab have been approved by EMA and FDA for patients who failed ASCT and pre- and/or post-ASCT BV [65, 66]. The role of allo-SCT in cHL has become less clear after nivolumab and

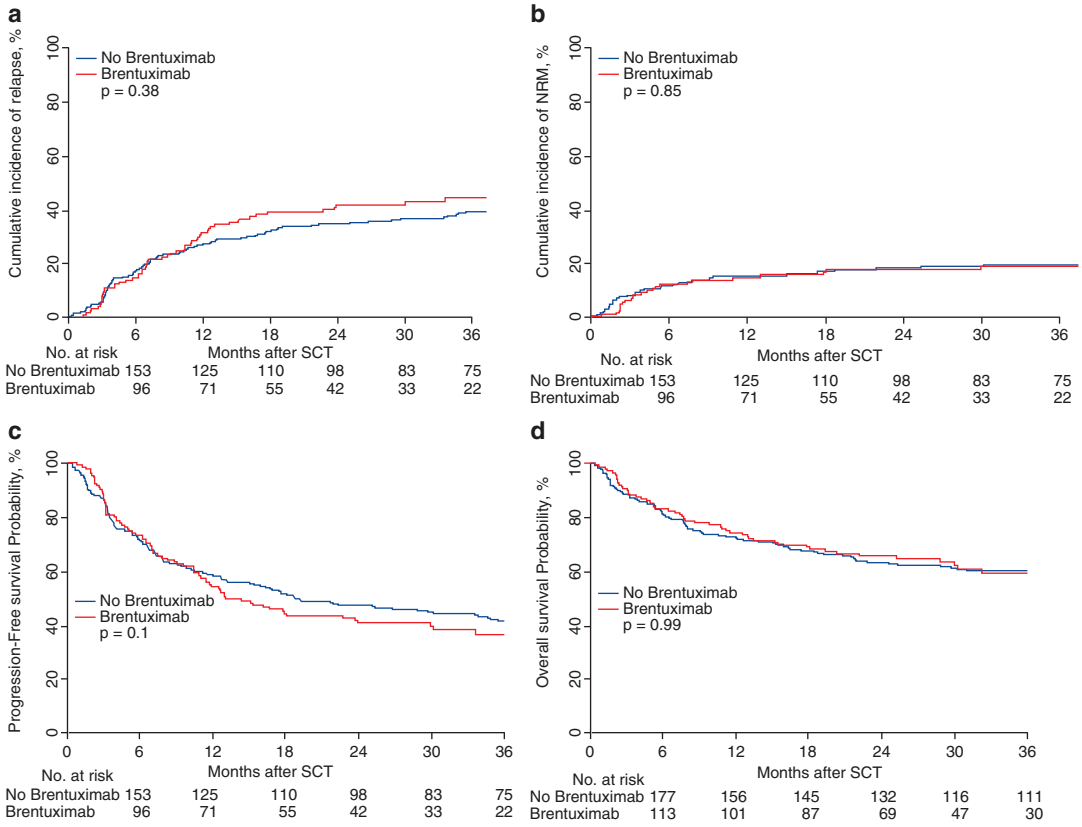

Fig. 21.3 Effect of pretransplant BV as last salvage therapy before allo-SCT on posttransplant outcomes. (**a**) Cumulative incidence of relapse; (**b**) cumulative incidence of non-relapse mortality; (**c**) progression-free survival; (**d**) overall survival. *BV* brentuximab vedotin, *NRM* non-relapse mortality, *SCT* allogeneic stem cell transplant (Bazarbachi A et al. [63], with permission)

pembrolizumab became available. A recent retrospective analysis of 39 patients who underwent allo-SCT after a median of 62 days following anti-PD-1 therapy showed encouraging results with 1-year PFS and OS of 76% and 89%, respectively. However, a high rate of GVHD was reported, especially acute (1-year incidence of grade 2–4 aGVHD, grade 4 aGVHD, and cGVHD were 44%, 13%, and 41%, respectively), with four treatment-related deaths (three acute GVHD and one hepatic VOD) [67]. In the extended follow-up analysis of CheckMate 205 Trial, 44 over 243 patients proceeded to allo-SCT after a median time of 49 days from last nivolumab administration. Six-month PFS and OS estimates were 82% and 87%, respectively, with 13% of transplant-related mortality and four over five deaths from acute GVHD [66] (Fig. 21.4). Interestingly, in both studies no clear correlation has been identified between time from last anti-PD-1 administration to allo-SCT and onset of GVHD or NRM. Although the follow-up is limited, these studies indicate that allo-SCT after PD-1 therapy is feasible, but with an increased risk of toxicity. Nevertheless, since anti-PD-1 inhibitors have a very favorable toxicity profile, some responding patients could not benefit from anti-PD-1 discontinuation to proceed to a highly more toxic procedure as allo-SCT; thus the area of uncertainty is growing, making clinical decisions very difficult, especially for patients in CR [68, 69].

Recently, a retrospective multicenter study was conducted in 31 lymphoma patients undergoing

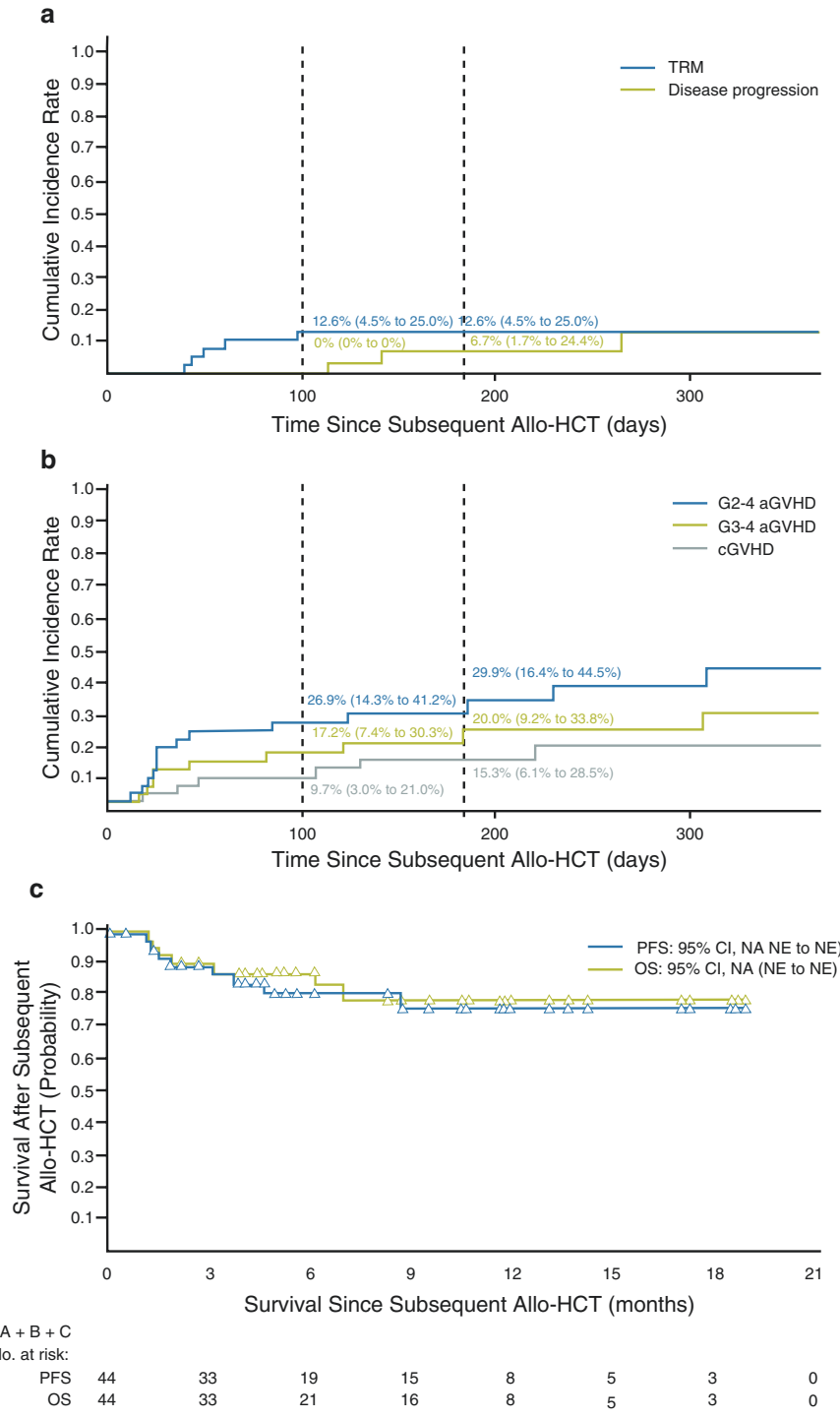

Fig. 21.4 Results of allo-SCT after nivolumab treatment in patients with relapsed/refractory HL. Cumulative incidence of (**a**) transplant-related mortality (TRM) and disease progression, (**b**) acute graft-versus-host disease (aGVHD) and chronic graft-versus-host disease (cGVHD), and (**c**) overall survival (OS) and progression-free survival (PFS) after allogeneic hematopoietic cell transplantation (allo-HCT). Cumulative incidence (95% CI) at 100 days and 6 months for TRM, disease progression, and GVHD and median (95% CI) PFS and OS are shown. Death was considered a competing risk to GVHD, and posttransplant disease progression was considered a competing event to TRM. *G* grade, *NA* not available, *NE* not estimable. (Armand P et al. [66], with permission)

anti-PD-1 treatment for relapse after allo-SCT. The majority of patients in the study (29 over 31) had HL, of which 27 had already received at least one salvage treatment after allo-SCT and before PD-1 blockade. Response rates were very promising, with ORR 77% (15 CRs and 8 PRs). After a median follow-up of 428 days from the first anti-PD-1 administration, 68% of patients were alive, while eight patients died because of GVHD (26%). Overall, 17 patients (55%) developed GVHD (six acute, four overlap, and seven chronic), after a median of 1–2 anti-PD-1 doses. GVHD was acute grade 3–4 or chronic severe in nine patients and was frequently steroid refractory, with the majority of patients requiring two or more systemic therapies and only two patients achieving CR. Interestingly, 12 over 17 patients had already experienced GVHD. Among these, six patients had active chronic GVHD at time of anti-PD-1 administration, three of which developed GVHD worsening after PD-1 blockade [70]. Similarly, in a French series, prior history of GVHD was reported in all GVHD cases occurred after anti-PD-1 administration. Moreover, median time from allo-SCT to PD-1 blockade was significantly shorter in patients who presented PD-1-related GVHD compared to GVHD-free patients (8 vs. 28 months) suggesting a role for anti-PD-1 blockade in triggering of GVHD [71]. These two retrospective studies and other reports infer that PD-1 blockade is feasible and highly effective also in the context of relapse after allo-SCT, although frequently complicated by severe and refractory GVHD [72–77]. Either in "bridge to allo-SCT" or in post-allo-SCT salvage contexts, further and larger studies are needed to clarify the combined role of PD-1 blockade, conditioning chemotherapy and GVHD prophylaxis (ATG, posttransplant cyclophosphamide, etc.) in the development of GVHD, and to optimize the management of these complications.

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22 Targeting CD30 in Patients with Hodgkin Lymphoma

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_22

22.1 Introduction

The introduction of multi-agent chemotherapy for the treatment of Hodgkin lymphoma is one of the major breakthroughs in clinical oncology. Chemotherapy and improved radiation methods have significantly improved the chance of curing these patients from less than 5% in 1963 to about 80% at present [1–3]. However, there is still a substantial need to improve current treatment approaches particularly for elderly patients or those with relapsed and refractory disease [4–6]. Cured patients unfortunately are at high risk for late side effects including second malignancies, cardiac toxicity, infertility, and fatigue [7–9]. Thus, there is a clear need for new and safer drugs that are more selective in targeting the malignant Hodgkin and Reed-Sternberg (HRS) cells in this disease while sparing normal tissues.

CD30 is a cell surface protein that is highly expressed on HRS cells (Figs. 22.1 and 22.2) and is rarely expressed by normal tissue, making it ideal for targeted therapy. In fact, soon after the identification and characterization of CD30, monoclonal antibodies against this protein were evaluated as potential therapeutics. Although several preclinical experiments established the proof of principle for this treatment strategy, early clinical trials with either naked monoclonal antibodies or a variety of immunoconjugates, including immunotoxins and radioimmunoconjugates against CD30, either did not demonstrate sufficient clinical activity or were too toxic [10–15]. The lack of meaningful clinical efficacy of naked anti-CD30 antibodies in patients with Hodgkin

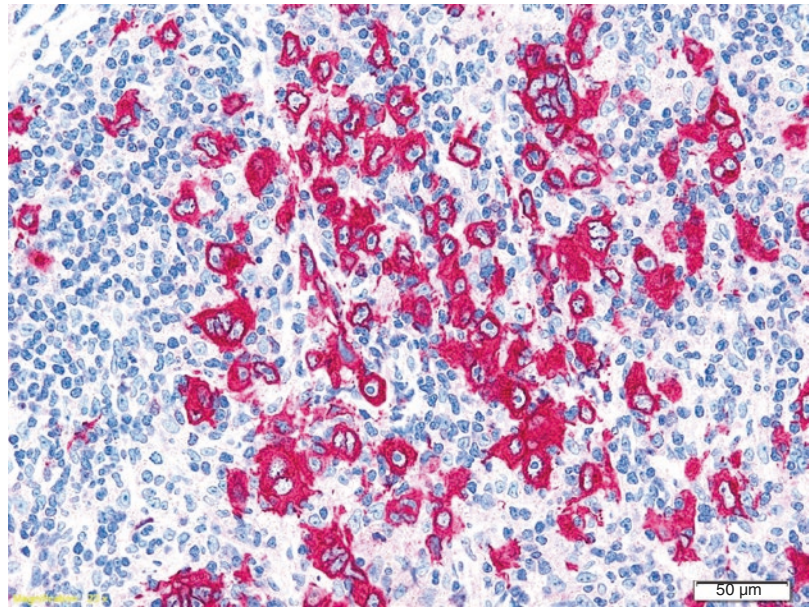

Fig. 22.1 cHL_NS (nodule of CHL, nodular sclerosing (NS) type). Courtesy from Pileri S

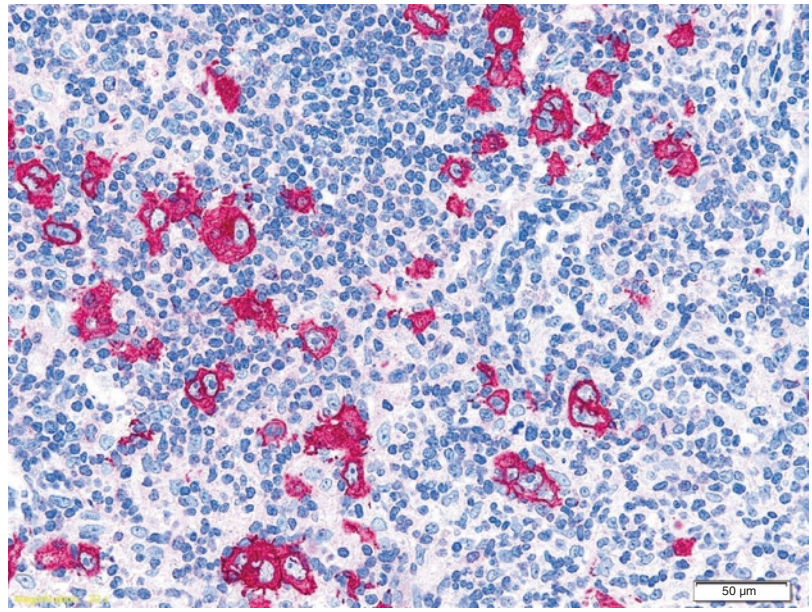

Fig. 22.2 cHL_MC (classical Hodgkin lymphoma (CHL) of the mixed cellularity (MC) type). Courtesy from Pileri S

lymphoma (HL) remains poorly understood, but several hypotheses have been proposed: CD30 is internalized and, thus, does not allow sufficient time for engagement with effector cells. In addition, CD30 is shed in the serum in a soluble form, which may neutralize the efficacy of the antibodies; the early versions of anti-CD30 antibody were not ideal for binding CD30 or effector cells. More recently, advances in linker technology allowed the development of novel and potent antibody-drug conjugates (ADC), such as brentuximab vedotin. This overview will highlight pathophysiology and current clinical experience when targeting CD30 in patients with Hodgkin lymphoma.

22.2 Structure and Function of CD30

In a landmark paper published in 1982, Stein and colleagues identified a new monoclonal antibody called Ki-1 that recognized a new antigen expressed on HRS cell, called CD30 [16]. Originally thought to be specific for HRS cells of Hodgkin lymphoma (HL), it was later found on small subsets of paracortical lymphocytes and a few other malignancies, including anaplastic large cell lymphoma (ALCL) [17–19]. The major limitation of the Ki-1 antibody was the need for fresh or frozen material, which allowed its application only in a limited number of reference centers. This was overcome by the generation of the Ber-H2 monoclonal antibody detecting an epitope of the molecule different from Ki-1 and applicable in routine formalin-fixed paraffin-embedded tissue samples.

Ten years after the identification of the CD30 antigen, the same group cloned the cDNAs coding for CD30 from expression libraries of the human HUT-102 cell line using the monoclonal antibodies Ki-1 and Ber-H2. The open reading frame of the cDNA predicted a 595-amino acid transmembrane protein. The extracellular domain contained six cysteine-rich motifs and shared sequence homology with members of the tumor necrosis factor (TNF) superfamily [20, 21]. The cytoplasmic tail contains several TNF receptor-associated factor (TRAF)-binding sequences that mediate activation of pleiotropic signals, including activation of nuclear factor kappa-B (NK-κB) [22, 23]. CD30 has a broad range of biologic effects depending on the cellular context, including regulation of cytokine secretion and inflammation, induction of apoptosis, and promotion of cell survival and proliferation [24]. The ligand

for CD30 (CD30L, CD153) is a 26-kDa type II transmembrane protein that belongs to the TNF superfamily and maps to chromosome 9q33 [25]. CD30L is expressed in both resting and activated B cells, activated T lymphocytes, monocytes, granulocytes, and natural killer cells [26, 27].

The exact physiologic function of CD30/CD30L in healthy individuals remains poorly understood, as no human diseases have been associated with alterations in CD30 or CD30L genes. Furthermore, CD30 knockout mice experiments gave conflicting results regarding a possible role of CD30 in thymocyte negative selection [28, 29]. Other studies suggested that CD30-CD30L signaling may be involved in immunoregulation, such as class-switch DNA recombination and antibody production in B cells [30]. CD30 may also play a role in self-tolerance and pathogenesis of autoimmune disorders [31, 32], in addition to regulating Th1 and Th2 cell responses [33–35], CD4+ T-cell-mediated graft-versus-host disease [36], and CD30+ Treg cells [37].

22.3 Therapeutic Targeting of CD30

CD30 is an excellent target for monoclonal antibody therapy due to its restricted expression. A few years after the initial description of the first monoclonal antibody against CD30, Ki-1 [16], monoclonal antibodies such as Ki-4 and Ber-H2 were generated that had higher affinity for the CD30 antigen [30]. Subsequently, these antibodies were conjugated to ricin A chain to form specific immunoreagents. These so-called immunotoxins were extremely effective and specific in vitro and in different animal models [10, 11]. However, a subsequent clinical phase I/II trial using the ricin A-chain immunotoxin Ki-4.dgA targeting CD30 showed little clinical activity in a total of 18 patients with refractory HL. This immunotoxin was associated with vascular leak syndrome as dose-limiting toxicity [14]. In addition, most patients developed anti-ricin antibodies so that further clinical development of this immunotoxin in HL was abandoned. An alternate strategy used the murine anti-CD30 monoclonal antibody (Ber-H2) as carrier for a cytotoxic agent by covalently linking Ber-H2 to saporin (SO6), a type 1 ribosome-inactivating protein [12]. Four patients with advanced refractory HL were treated, and three patients had transient tumor reduction [13]. Human antibodies, however, developed against the murine antibody and the toxin in all patients preventing repeat dosing; thus, further development of this immunotoxin was also stopped.

22.4 Monoclonal Antibodies

Clinical results from first-generation naked monoclonal antibodies targeting CD30 were disappointing, possibly due to their poor antigen-binding properties, ineffective activation of effector cells, and neutralization by soluble CD30 [14, 38, 39]. MDX-060, a fully human anti-CD30 monoclonal antibody, was tested in a phase I/II study in patients with HL, ALCL, and CD30+ PTCL. This antibody had minimal toxicity, and the maximum tolerated dose (MTD) was not reached [15]. However, MDX-060 had minimal clinical activity with six responses in 72 patients and was subsequently abandoned. SGN-30, a CD30-specific chimeric antibody constructed from the variable regions of the anti-CD30 murine monoclonal AC10 and human gamma 1 heavy chain and kappa light chain constant regions, was also tested in phase I/II studies. A phase I study of SGN-30 in 24 HL or CD30+ non-Hodgkin lymphoma (NHL) patients demonstrated that SGN-30 was well tolerated, but only one patient with cutaneous ALCL achieved a complete response (CR) [38]. The phase II results of SGN-30 also showed only modest clinical activity with 9% overall response (2 CRs and 5 partial responses (PR) of 79 patients treated); all responses were limited to patients with ALCL [40]. Given preliminary evidence of selective efficacy of SGN-30 in cutaneous ALCL, SGN-30 was further tested in a phase II study of cutaneous diseases including cutaneous ALCL, lymphomatoid papulosis, and transformed mycosis fungoides; the response rate in this trial was 70% [41]. SGN-30 was subsequently combined with

chemotherapy because preclinical data showed that SGN-30 sensitizes tumor cells to cytotoxic agents and single-agent phase I/II data demonstrated only modest efficacy [42]. In a Cancer and Leukemia Group B randomized phase II trial of SGN-30 with gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD) in relapsed HL patients, 30 patients were treated; however, five patients developed grade 3–5 pneumonitis, leading to premature closure of the trial [43]. The combination of SGN-30 and GVD was not only associated with significant toxicity but also was not associated with better outcomes compared to GVD alone. Given the disappointing results with first-generation naked monoclonal antibodies, a second-generation anti-CD30 humanized antibody, XmAb2513, with improved antigen-binding and enhanced Fcγ receptor IIIA affinity was developed demonstrating increased efficacy in vitro when compared to MDX-060 or SGN-30 [44]. Preliminary results of the phase 1 study of XmAb2513 found the drug to be well tolerated, but not associated with superior efficacy compared to first-generation monoclonal antibodies. Of 13 HL patients treated, tumor reduction was observed in three patients [45].

22.5 Bispecific Monoclonal Antibodies

A different approach to targeting CD30 was the development of bispecific monoclonal antibodies, engaging NK cells or neutrophils as effector cells [10, 46]. A construct based on the anti-CD30 monoclonal antibody Ki-4 and the human anti-CD64 monoclonal H22 showed very promising preclinical activity. In the phase I clinical trial, H22xKi-4 was very well tolerated; responses included one CR, four PRs, and four SDs in a total of ten patients treated [10]. More recently, a bispecific TandAb antibody, AFM13, was reported [47]. AFM13 targets both CD30 on HL tumor cells and CD16A on NK cells. Preclinical data demonstrated antitumor activity with engagement of NK immune effector cells. A phase 1 study of AFM13 in 28 HL patients found the drug safe and well tolerated, but with a modest activity. Overall, 3 of 28 patients achieved partial remissions [47].

22.6 Radiolabeled Antibodies

Schnell et al. developed a radioimmunoconjugate consisting of the murine anti-CD30 monoclonal antibody Ki-4 labeled with iodine-131 (^{131}I). Twenty-two HL patients were treated with ^{131}I-Ki-4 to total body doses ranging from 0.035 to 0.99 Gy. Although there were six responses (one CR and five PRs), a significant rate of severe hematologic toxicity was observed with seven patients having grade four hematologic toxicity 4–8 weeks posttreatment, leading to the cessation of its further development [48].

22.7 Chimeric Antigen Receptor (CAR) T-Cell Therapy

First-generation anti-CD30 CAR T cells were developed in the 1990s, and preclinical studies demonstrated the ability of these cells to lyse CD30-expressing HL cell lines in vitro [49, 50]. Indeed, Epstein-Barr virus-specific cytotoxic T cells transduced with an anti-CD30 CAR have been shown to have activity against CD30$^+$ cancer cell lines in vitro, as well as in vivo, in a mouse xenograft model [51, 52]. In a phase I clinical trial of anti-CD30 CAR T cells with a CD28 co-stimulatory domain including seven cHL and two ALCL patients, four patients had stable disease, one had a complete response, and one had a partial response, while three had disease progression [53, 54]. In another phase I trial, 18 patients (17 with HL and one with cutaneous ALCL) were treated with anti-CD30 CAR containing a 4-1BB co-stimulatory domain and seven patients had a PR, with a median PFS of 6 months [55]. A number of other clinical trials of anti-CD30 CAR-T-cell therapy are ongoing and will provide more information on the efficacy of this approach [56].

22.8 Antibody-Drug Conjugates

22.8.1 Single-Agent Experience with Brentuximab Vedotin

Brentuximab vedotin (BV) is an antibody-drug conjugate (ADC) consisting of the chimeric monoclonal antibody, cAC10, that was conjugated to monomethyl auristatin E (MMAE) [57, 58]. MMAE is a synthetic analog of the natural product dolastatin 10 and functions as a tubulin inhibitor. MMAE is covalently linked to cAC10 via a maleimidocaproyl-valyl-citrullinyl-*p*-aminobenzylcarbamate linker [59]. On average, four molecules of MMAE are conjugated to one cAC10. The mechanism of action of brentuximab vedotin is shown in Fig. 22.3 and involves the following steps: (1) binding of the anti-CD30 ADC via the antibody moiety to CD30 expressed on tumor cells in high density, (2) receptor-mediated endocytosis of brentuximab vedotin and intracellular internalization occurring via clathrin-mediated uptake, (3) uptake of the drug into lysosomal vesicles, (4) MMAE which is released from the antibody by reduction or acid hydrolysis within lysosomes, and (5) MMAE which is released into cytoplasm and inhibits microtubule polymerization leading to arrest of the G2/M phase of the cell cycle, thereby inducing cellular apoptosis [58]. In addition, there is also a small amount of MMAE released into the tumor microenvironment that may alter survival signaling to the HRS cell. Preclinical studies with cAC10-vcMMAE demonstrated stable linkage of the ADC in circulation and efficient release upon internalization into target cells. In addition,

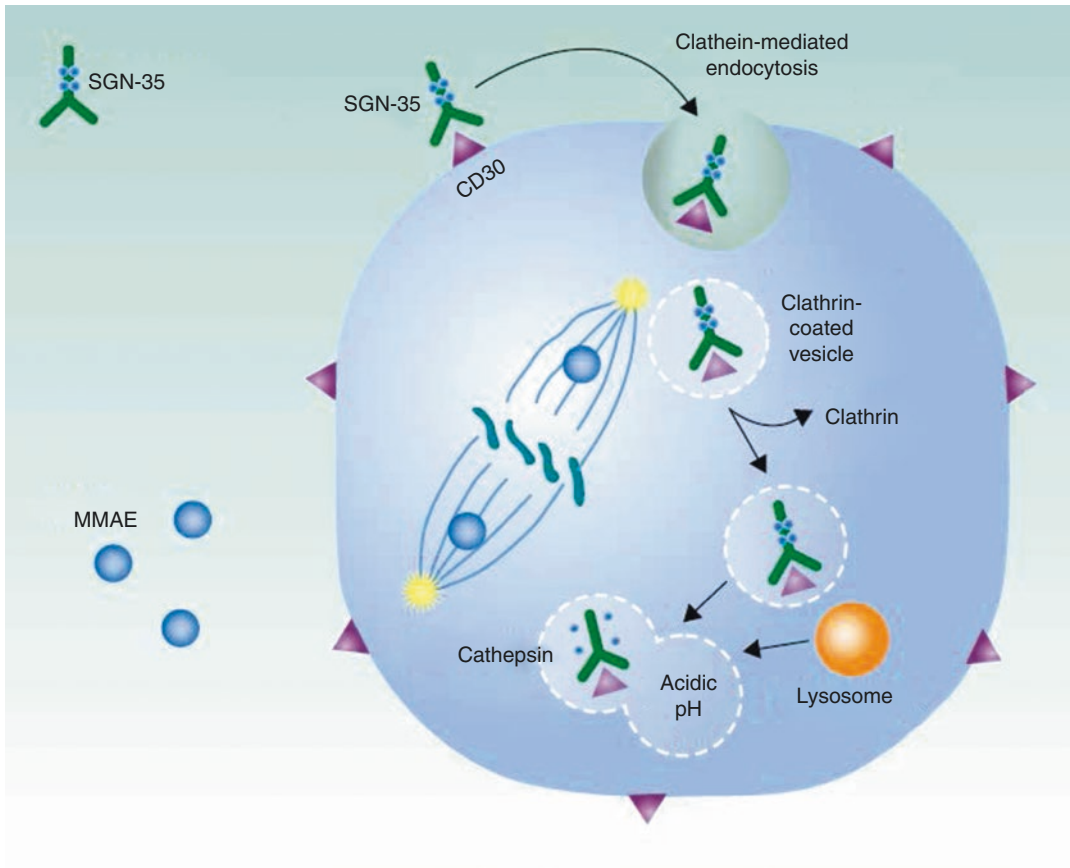

Fig. 22.3 Mechanism of action of brentuximab vedotin (SGN-35) (Figure was adapted from: Katz et al. [58])

cAC10-vcMMAE was found to have significant antitumor activity in HL and ALCL cell lines with an IC_{50} of 10 ng/mL and antitumor activity in subcutaneous disease xenograft models [59].

The initial first-in-man, multicenter, dose-escalation phase I study enrolled 45 patients with relapsed or refractory CD30-positive hematologic cancers, including 42 HL and 3 ALCL patients. BV was administered intravenously every 3 weeks at doses ranging from 0.1 to 3.6 mg/kg. Dose-limiting toxicities were grade 4 thrombocytopenia, grade 3 hyperglycemia, and febrile neutropenia. Remarkably, tumor regression was seen in 86% of evaluable patients, and the MTD was defined at 1.8 mg/kg every 3 weeks. Eleven patients achieved complete responses and six achieved partial remissions. The median duration of response was at least 9.7 months. When the analysis was restricted to patients receiving the dose of 1.8 mg/kg or greater, six of twelve patients responded (50%), including four complete remissions [60].

A second phase I study evaluated the safety and efficacy of BV given on days 1, 8, and 15 in a 28-day cycle (3 weeks on, followed by 1 week of rest). This study demonstrated similar efficacy (ORR 59% and tumor regression in 85% of patients). Given the ease of administration of every 3-week dosing and similar response rates across the two dosing schedules, the 1.8 mg/kg every 3 weeks was selected for further development in phase II studies [61].

The pivotal phase 2 study that led to the FDA approval of BV was conducted in 102 patients with relapsed and refractory HL after receiving autologous stem cell transplantation (ASCT), to determine the efficacy and safety of brentuximab vedotin [62]. Patients received 1.8 mg/kg brentuximab vedotin every 3 weeks as a 30-min outpatient infusion (capped dose at 180 mg) for up to 16 cycles. There was no limit on the number of prior treatment regimens (median of 3.5, range 1–13 regimens). All patients had failed ASCT with a median time to relapse after ASCT of 6.7 months (range 0–131 months). Patients received a median of nine cycles of brentuximab vedotin, and the overall response rate was 75% (33% CRs). In a waterfall plot analysis (Fig. 22.4), 94% of patients had tumor regression. Responses were rapid, with a median time to treatment

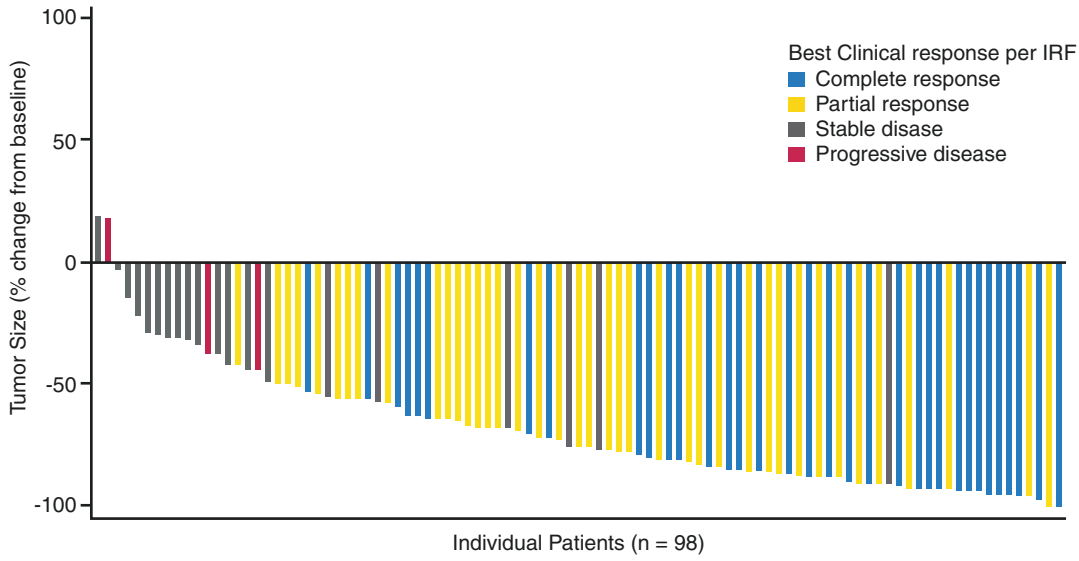

Fig. 22.4 Maximum percent reduction in sum of the product of diameters in individual patients ($n = 98$) in the pivotal phase II trial of brentuximab vedotin for relapsed and refractory Hodgkin lymphoma (Figure was adapted from Younes et al. with permission [62])

response of 5.7 weeks and the median time to achieving complete remission of 12 weeks. The median progression-free survival for all patients was 5.6 months. This study led to the FDA approval of brentuximab vedotin for the following indications: (1) Hodgkin lymphoma after failure of ASCT and (2) HL patients who are not ASCT candidates after failure of at least two prior therapies. The 5-year end-of-study results were reported and in 34 patients who achieved a CR the median PFS and OS were not reached and 13 patients remained in remission at time of study closure. This suggests that a proportion of patients who achieve a CR with single-agent brentuximab vedotin will have long-term disease control and may potentially be cured [63].

22.9 Safety and Tolerability of Brentuximab Vedotin

In the two phase I studies of brentuximab vedotin, the dose-limiting toxicities included cytopenias, diarrhea, vomiting, and hyperglycemia [60, 61]. Data from phase I and II studies of brentuximab vedotin have characterized the adverse effects of the drug, including peripheral sensory neuropathy, nausea, fatigue, neutropenia, diarrhea, pyrexia, vomiting, arthralgia, pruritus, myalgia, peripheral motor neuropathy, and alopecia [62]. In phase II studies, approximately 55% of patients experienced adverse grade 3 and 4 events including peripheral sensory neuropathy (8–12%), neutropenia (20–21%), anemia (6–7%), and thrombocytopenia (8–14%). The associated peripheral neuropathy is typically cumulative and most commonly grade 1–2 characterized by numbness or tingling in the fingers and toes. In addition, 11–14% of patients had grade 3 peripheral neuropathy; no grade 4 was seen. Approximately 80% of patients with peripheral neuropathy experienced clinical improvement after dose reduction or cessation of drug, and 50% experienced complete resolution. As a result of these data, significant cytopenias or neuropathy should prompt consideration for dose modification, delay, or discontinuation. Overall, brentuximab vedotin is well tolerated with manageable side effects and few serious adverse events. Additional rare, but serious adverse events have been reported including pancreatitis and fatal progressive multifocal leukoencephalopathy associated with John Cunningham (JC) virus infection [64].

22.9.1 Brentuximab Vedotin in Frontline Setting for HL

Brentuximab vedotin was successfully combined with chemotherapy for the up-front treatment HL. BV has been evaluated for the frontline treatment of early-stage disease, advanced-stage disease, and for elderly patients. In a phase I study of brentuximab vedotin combined with ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) chemotherapy, significant pulmonary toxicity (40%) was described in conjunction with bleomycin. Therefore, the combination of BV with AVD chemotherapy (without bleomycin) has been established as a safe combination [65].

22.9.1.1 Early-Stage Disease

The aim of incorporating BV into early-stage treatment protocols has been to eliminate RT, particularly in early-stage patients with unfavorable features, such as disease bulk. In a pilot study in early-stage cHL patients with unfavorable risk disease, BV + AVD for four cycles followed by 30 Gy involved-site radiotherapy was found to be safe and well-tolerated without evidence of significant pulmonary toxicity. Among the 30 patients treated, 77% had disease bulk by Memorial Sloan Kettering Cancer Center criteria (>7 cm in transverse or coronal dimension) and reported outcomes were promising with high rates of PET negativity after chemotherapy and a 1-year progression-free survival of 93% [66, 67]. Subsequent cohorts of the study tested if consolidation after BV + AVD × 4 cycles can be decreased to minimize late toxicities associated with radiotherapy. In cohort 2, a lower dose of ISRT (20Gy) was applied post-chemotherapy. In cohort 3, a smaller radiation field to treat only the residual disease post chemotherapy was used and in cohort 4 had no radiation consolidation [67]. Other clinical trials also incorporate BV into early-stage programs with the aim of eliminating RT or enhancing efficacy of short-course chemotherapy.

22.9.1.2 Advanced-Stage Disease

The ECHELON-1 study was a large, international, multicenter, randomized control trial comparing the efficacy of standard ABVD × 6 cycles vs. BV + AVD × 6 cycles for the treatment of advanced-stage HL [68]. This study found a modest benefit in terms of modified 2-year progression-free survival in favor of BV + AVD vs. ABVD (82.1% vs. 77.2%). In certain subgroups of patients, there was a higher degree of benefit observed, including stage IV disease, males, and in patients with high-risk international prognostic scores. However, the BV + AVD treatment program was found to have increased toxicities including peripheral neuropathy and febrile neutropenia; the latter risk was attenuated when growth factor support was used. Importantly, this study established BV + AVD as an FDA-approved frontline regimen for advanced-stage HL. BV has also been incorporated into other ongoing frontline clinical trials, such as the modified BEACOPP regimen with inclusion of BV, called BrECAPP or BrECADD [69].

22.9.1.3 Elderly Patients

Older patients with cHL have poor outcomes due to more aggressive biologic features and poor tolerance of standard chemotherapy such as ABVD. Incorporating BV into treatment regimens for elderly patients can increase efficacy of therapy and decrease toxicity. A study in cHL aged 60 years or older and stage IIB, III, and IV disease with initial BV × 2 cycles then AVD × 6 cycles followed by BV × 4 cycles demonstrated 2-year PFS and OS of 84% and 93%, respectively [70]. These are promising results compared to historically reported outcomes in this patient population. BV has also been used as a single agent and combined with bendamustine and dacarbazine in the older HL population [71, 72].

22.9.2 Brentuximab Vedotin Pre-ASCT

Brentuximab vedotin has been studied in relapsed/refractory HL as a second-line salvage prior to high-dose therapy and autologous stem cell transplant (HDCT-ASCT). In one study, patients were treated with single-agent brentuximab vedotin for two cycles (1.2 mg/kg IV weekly, 3 weeks on and 1 week off), followed by response assessment using PET imaging. Patients who achieved a complete remission with a negative PET (Deauville 1, 2) were allowed to proceed to stem cell collection followed by ASCT, thus avoiding chemotherapy. Patients with PET-positive scans after two cycles of brentuximab vedotin were treated with augmented ICE chemotherapy, followed by ASCT. Using this PET-adapted strategy, approximately 30% of patients achieved CR after two cycles of brentuximab vedotin, avoiding ICE-based therapy [73]. Other dosing schedules of BV pre-ASCT have also been published (1.8 mg/kg IV every 3 weeks for 2–4 cycles) [74]. In addition, BV has been combined with other chemotherapy regimens including bendamustine, ICE, DHAP, and ESHAP [75–79]. Another promising chemotherapy-free salvage treatment program combines BV and nivolumab, a checkpoint inhibitor, for 2–4 cycles pre-ASCT [80]. The combination was well-tolerated and was associated with a complete response rate of 61% (61/62) with an objective response rate of 82%.

22.9.3 Brentuximab Vedotin Maintenance Post Autologous Stem Cell Transplant

To study the role of adjuvant brentuximab vedotin after autologous stem cell transplant, the randomized phase III ATHERA study includes an investigational arm of brentuximab vedotin 1.8 mg/kg administered every 3 weeks for approximately 1 year (a maximum of 16 doses) vs. placebo after ASCT in high-risk HL patients [81]. High-risk features included presence of extranodal disease, B-symptoms, relapse within 1 year of initial treatment, primary refractory disease, less than CR to salvage therapy, or requiring ≥2 salvage therapies before ASCT. The median PFS in the BV group was superior to placebo (42.9 vs. 24.1 months, $P = 0.0013$) and this led to FDA approval for BV maintenance post-ASCT. All patients who were enrolled in

ATHERA were BV naïve, so the applicability of these findings may be limited in the modern era when most patients will receive BV in the first- or second-line setting.

22.9.4 Brentuximab Vedotin-Based Combinations in Posttransplant Settings

Although brentuximab vedotin produces a high overall response rate in patients with relapsed HL, most responses are partial and of short duration. Therefore, there is a need to combine brentuximab vedotin with other active agents to increase the proportion of complete remissions and to prolong the duration of response. Based on preclinical data to suggest synergy between brentuximab vedotin and other agents, BV is being combined with other agents such as bendamustine, temsirolimus, HDAC inhibitors, and PD1/PDL1 monoclonal antibodies.

22.10 Conclusions

With the identification of the CD30 antigen on Hodgkin and Sternberg-Reed cells, different constructs such as the naked monoclonal antibodies Ki-1 and Ber-H2 as well as the ligand for CD30 were initially assessed for therapeutically targeting of Hodgkin lymphoma cells via CD30. Since these constructs had little clinical efficacy against Hodgkin lymphoma, other immunoreagents include immunotoxins, bispecifics, as well as humanized anti-CD30 antibodies such as MDX-060 or SGN-30. The latter was subsequently linked to MMAE, a potent anti-tubulin agent. This construct, SGN-35, was later termed brentuximab vedotin. The efficacy, tolerability, and broad applicability of brentuximab vedotin have dramatically changed treatment paradigms in cHL, improving outcomes for patients at every phase of the disease. In the future, we anticipate there will be advances in risk stratification of cHL patients, allowing for a more individualized approach to treatment and identification of which patients will benefit the most from novel therapies, including BV.

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Hodgkin Lymphoma and PD-1 Blockade

23

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Contents

23.1 Introduction

Classical Hodgkin lymphoma (cHL) is characterized by a unique tumor architecture composed of rare, malignant Reed-Sternberg (RS) cells surrounded by a much more abundant immune infiltrate that is unable to mount a salutary immune response [1]. Signaling through the programmed death-1 (PD-1) pathway appears critical for maintaining this immunosuppressive microenvi-

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_23

ronment. Nearly all cases of cHL harbor a genetic alteration at 9p24.1, an amplicon containing the genes for both PD-1 ligands, PD-L1 and PD-L2. The 9p24.1 amplicon also contains the gene for JAK2, and upregulated JAK/STAT signaling leads to further expression of both PD-1 ligands, as does EBV infection which occurs in a significant minority of cHL patients [2, 3]. Together, these genetic changes drive constitutive overexpression of PD-1 ligands on RS cells which bind to the PD-1 receptor on surrounding T cells (Fig. 23.1) and promote T-cell exhaustion and immune evasion [4]. In addition, higher magnitude of 9p24.1 alterations may be associated with increased resistance to induction therapy. Among a cohort of 108 patients with newly diagnosed cHL, copy number alterations ranging from polysomy to amplification were seen in 97% of patients with the presence of amplification predicting a higher risk of relapse [5].

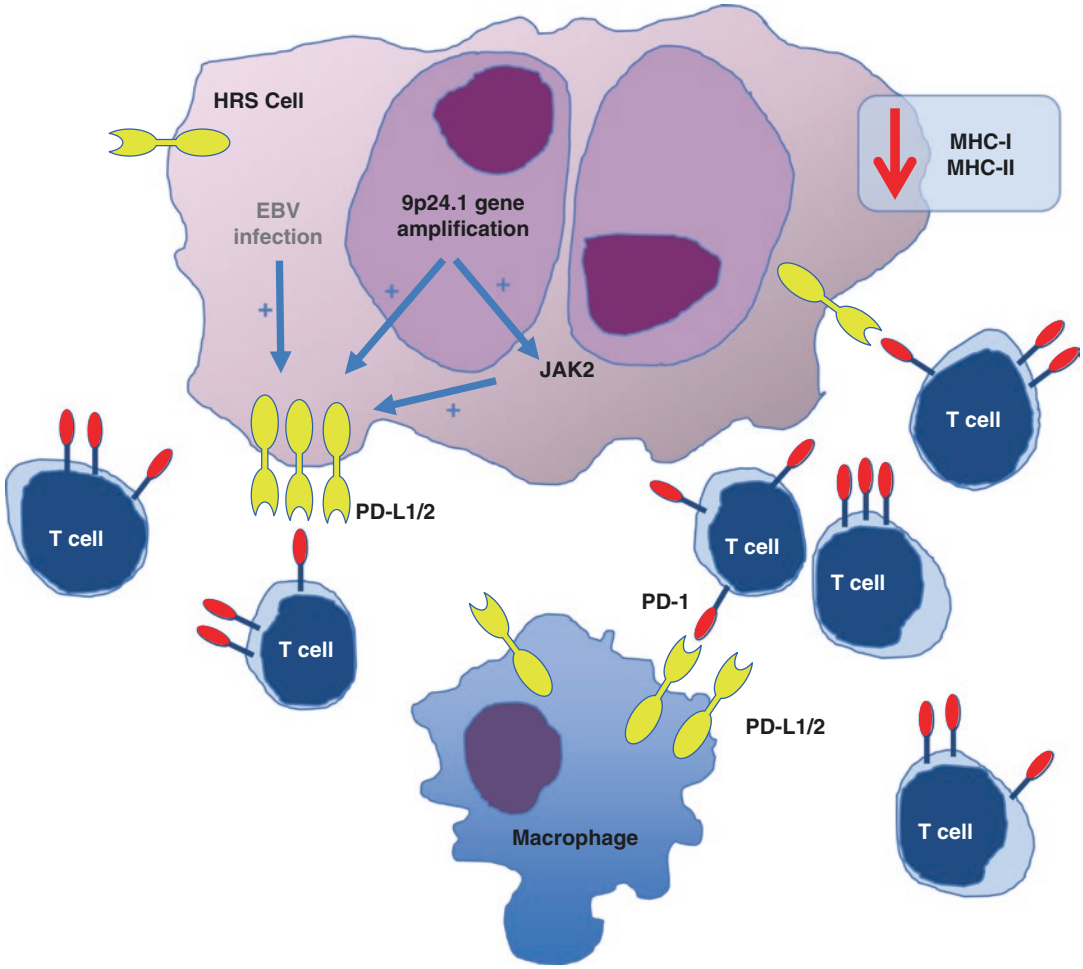

Fig. 23.1 The Hodgkin lymphoma microenvironment is characterized by frequent expression of PD-L1 and PD-L2 on Hodgkin Reed-Sternberg (HRS) and tumor-associated macrophages (TAMs). Frequent genetic alterations involving chromosome 9p24.1 in HRS cells lead to constitutive expression of PD-L1 and PD-L2. The 9p24.1 amplicon also contains the gene for JAK2 and upregulated JAK/STAT signaling further increases PD-L1/2 expression. EBV infection, which occurs in a significant minority of HL patients, also leads to expression of PD-1 ligands through a distinct mechanism. PD-L1 and PD-L2 on HRS cells and TAMs bind to the PD-1 receptor on infiltrating T cells resulting in T-cell exhaustion and immune evasion. In addition, MHC class I and II expression is frequently reduced or absent on HRS cells, further hindering T-cell recognition and immune detection

23.2 Early Clinical Trials

Based on the critical role of the PD-1 pathway in cHL pathogenesis, phase I trials of the PD-1 monoclonal antibodies (mAbs), nivolumab and pembrolizumab, included expansion cohorts of cHL patients. In both trials, patients were heavily pretreated with a median of 4–5 prior lines of therapy including prior autologous stem cell transplantation (ASCT) and brentuximab vedotin (BV) in most patients. CHECKMATE-039, the phase I trial of nivolumab, included 23 patients with cHL. The investigator-assessed overall response rate (ORR) was 87% with a complete response rate (CRR) of 17% [6]. Responses were durable with a median progression-free survival (PFS) not reached after nearly 2 years of follow-up. Similar results were seen in KEYNOTE-013, the phase I trial of pembrolizumab, where among 31 patients with cHL, the investigator-assessed ORR was 65% and CRR was 16% [7]. Remissions were similarly durable with a median duration of response exceeding 24.9 months at the time of last report and a median PFS of 11.4 months [8]. In CHECKMATE-039, all ten patients with available tumor samples had genetic alterations at 9p24.1 detected by fluorescence in situ hybridization (FISH). In both phase I trials, expression of PD-L1 and PD-L2 was detected on RS cells in more than 90% of patients with available samples, confirming the nearly ubiquitous engagement of the PD-1 pathway in this disease [6, 7].

Based on the impressive phase I results, phase II trials for cHL were rapidly planned to test PD-1 blockade in larger cohorts and, in several novel, predefined patient subpopulations. CHECKMATE-205, the phase II trial of nivolumab, enrolled 243 patients with relapsed cHL following ASCT, including a cohort of 63 patients without prior exposure to BV. Among all patients, the centrally assessed ORR and CRR were 69% and 16%, respectively, while BV-naïve patients achieved a similar ORR of 65%. The median PFS was 14.7 months and depth of response was predictive of benefit with patients achieving a complete response (CR) having a longer PFS than patients with either partial response or stable disease (22.2 m vs. 15.1 m vs. 11.2 m) [9]. KEYNOTE-087 tested pembrolizumab in a similar population of 210 patients with relapsed/refractory (R/R) cHL, but also included a cohort of patients who were not eligible for ASCT due to chemoresistance. Among all patients, the ORR and CRR were 72% and 28%, respectively, and the median PFS was 13.7 months [10] (Table 23.1). Notably, in both trials, patients with high-risk disease features had excellent outcomes with PD-1 blockade. Patients with primary refractory disease (ORR 73%) and BV-refractory disease (ORR 68%) had similar response rates with nivolumab compared to the entire trial population. Similarly, patients who were transplant ineligible due to chemoresistance (ORR 67%, CRR 26%) and patients with primary refractory disease (ORR 80%) had similar response rates with pembrolizumab compared to the entire trial population; however their median PFS and duration of response appear to be shorter than other trial cohorts [10].

With more than 500 patients included on these four trials, the safety profile of PD-1 blockade in cHL appears to be very similar to that observed in other diseases. There were no reported fatal adverse events (AEs) and grade 3–4 AEs were infrequent; in the phase II trials, only 4–6% of patients discontinued study treatment because of drug toxicity [6, 7, 9, 11]. Importantly, pneumonitis appears to occur no more commonly than in other diseases despite the frequent use of several potentially pneumotoxic drugs earlier in the treatment of cHL, including bleomycin, carmustine, and mediastinal radiation therapy. Based on the favorable efficacy and safety of these agents, both nivolumab and pembrolizumab received accelerated approval by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treatment of R/R cHL. The ongoing phase III confirmatory trials for each drug are testing different clinical strategies. In KEYNOTE-204 (NCT02684292), patients with R/R cHL are randomized to either BV or pembrolizumab, while CHECKMATE-812 (NCT03138499) is comparing the combination of nivolumab + BV to BV alone. Those studies could facilitate decisions about sequencing and combining the two treatment modalities. However, as both BV and PD-1 mAbs are being increasingly tested and used in earlier clinical settings, the potential clinical impact of these studies may ultimately be limited.

Table 23.1 Results of phase 1 and 2 trials of nivolumab and pembrolizumab

	CHECKMATE-039 nivolumab [6]	KEYNOTE-013 pembrolizumab [7]	Nivolumab CHECKMATE-205 [9] Cohort A (BV-naïve)	Nivolumab CHECKMATE-205 [9] Cohort B (BV after ASCT)	Nivolumab CHECKMATE-205 [9] Cohort C (BV before and/or after ASCT)	KEYNOTE-087 pembrolizumab [10] Cohort 1 (ASCT followed by BV)	KEYNOTE-087 pembrolizumab [10] Cohort 2 (ASCT-ineligible due to chemoresistance	KEYNOTE-087 pembrolizumab [10] Cohort 3 (ASCT without subsequent BV)
Phase	1b	1b	2	2	2	2	2	2
Patients	23	31	63	80	100	69	81	60
Prior ASCT	78%	71%	100%	100%	29%	100%	0%	100%
Prior BV	78%	100%	0%	100%	100%	100%	100%	42%
Rate of drug discontinuation due to toxicity	9%	6%	6%			4%		
ORR	87%	65%	65%	68%	73%	77%	67%	73%
CR	17%	16%	29%	13%	12%	26%	26%	32%
PR	70%	48%	37%	55%	61%	51%	41%	41%
Median PFS	Not reached	11.4 months	18.3 months	14.7 months	11.9 months	13.7 months		
OS	Not reported	87% (at 12 months)	93% (at 1 year)	95% (at 1 year)	90% (at 1 year)	90.9% (at 2 years)		

BV brentuximab vedotin, *ASCT* autologous stem cell transplantation, *ORR* overall response rate, *CR* complete response, *PR* partial response, *PFS* progression-free survival, *OS* overall survival

Other drugs targeting the PD-1 synapse at both the receptor and ligand level are in earlier stages of clinical development. Three anti-PD-1 mAbs (SH1210, sintilimab, and tislelizumab) are being developed in China with encouraging preliminary efficacy and safety results. In phase II trials, these drugs achieved ORRs ranging from 74% to 86% among less heavily pretreated patients with R/R cHL (12–18% prior rate of ASCT) [12–14]. Complete response rates for SH1210 (27%) and sintilimab (24%) were similar to those for approved PD-1 inhibitors; however, the CRR for tislelizumab was higher (61%) than observed in other trials. In contrast to other PD-1 mAbs, tislelizumab was engineered to minimize binding to FcγR on macrophages to block a potential mechanism of resistance to PD-1 directed therapies. Additional studies are necessary for all of these agents to assess durability of responses and to determine if response rates are similar among more heavily pretreated patients and in other patient populations. Monoclonal Abs targeting PD-L1 are also being tested in cHL and could facilitate enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) by binding directly to PD-L1 on the surface of RS cells. However, this approach leaves intact PD-1 <–> PD-L2 interactions which may also be important for fostering the immunosuppressive tumor microenvironment in cHL. Early results from a phase I trial of avelumab, an anti-PD-L1 mAb, showed activity across all tested dose levels with a composite ORR of 55% and a favorable safety profile [15]. Additional trials testing other PD-L1 mAbs, including durvalumab (NCT02733042) and atezolizumab (NCT03120676), may provide further answers about the relative utility of this approach.

23.3 Measuring Response to PD-1 Blockade: Pseudoprogression and Treatment Beyond Progression

In solid tumors, 5–10% of patients treated with PD-1 blockade experience "pseudoprogression"—for purposes of this review defined radiographically and not biologically as transient growth of existing lesions and/or development of new lesions followed by later clinical response [16]. Similar rates of pseudoprogression have been observed in early clinical trials in cHL and in a series of off-trial patients [17]. Current response criteria in lymphoma were designed largely based on experience with chemotherapy and chemoimmunotherapy and could result in early discontinuation of clinically beneficial immune therapies. To address this, investigators proposed the Lymphoma Response to Immunomodulatory Criteria (LYRIC), a set of provisional modifications to existing response criteria for lymphoma patients receiving immune-based treatments [18]. LYRIC created a novel response category, indeterminate response, which includes patients who have any of the following:

1. Early progression without clinical deterioration.
2. Overall stable or improved disease burden with the appearance of new lesions or isolated growth of existing lesions.
3. An increase in FDG uptake without a corresponding increase in lesion size or number.

These patients would have previously been categorized as having progressive disease, but using LYRIC, it is recommended that such patients who are clinically stable could continue treatment with restaging imaging within 12 weeks to re-evaluate their tumor response. To account for potential pseudoprogression, the newest version of RECIL (Response Evaluation Criteria in Lymphoma) also recommended a similar approach with confirmation of progressive disease on subsequent imaging scans for patients receiving immune-modulating agents and checkpoint inhibitors [19].

To account for the possibility of pseudoprogression, the phase II nivolumab trial was amended to allow patients to continue treatment beyond conventionally defined progression if certain criteria were met including stable performance status (PS) and perceived clinical benefit. Among 105 patients who had progressed at last follow-up, 70 underwent treatment beyond progression (TBP), receiving a median of eight

additional doses over 5.2 months. While objective responses with TBP were rare (only seen in seven of fifty-one evaluable patients), 61% of patients experienced stable or reduced target tumor burdens. Patients who received TBP achieved a longer time-to-next-treatment (TTNT) and a trend toward improved OS compared to progressers who did not receive additional nivolumab. Although this may reflect selection bias in this nonrandomized comparison, it suggests that TBP in carefully selected patients may be a useful clinical strategy that warrants additional prospective study. Ideally, radiographic or clinical features could predict which patients are most likely to benefit from TBP. Based on this initial dataset, it appears that patients with a good PS and those whose progression is due to a new tumor lesion (rather than growth of preexisting tumors) might be more likely to benefit [9]. Additional study is needed to validate provisional response criteria for lymphoma patients receiving immune-based treatments and to determine if clinical features can be used to select patients for TBP.

23.4 Minimal Residual Disease in cHL

Novel biomarkers that more directly reflect biologic response to PD-1 therapy may also be helpful to adjudicate clinical response in patients with possible pseudoprogression. Circulating tumor DNA (ctDNA) is emerging as a powerful biomarker in lymphoma. Using panel-based next-generation sequencing, an initial report showed that delayed clearance of ctDNA following induction chemotherapy could predict patients at a higher risk of relapse. Among cHL patients receiving PD-1 mAbs, the same technique was able to identify changes in dominant clonal patterns with suppression of ancestral clones and replacement by new clones harboring novel mutations [20]. This technique and others measuring ctDNA are currently being tested and may soon provide another tool to guide treatment in patients with cHL.

23.5 Mechanisms of Response and Resistance

While 65–70% of patients with R/R cHL achieve a response with PD-1 blockade, the majority of responders will relapse, most within the first 2 years of treatment [8, 9, 11]. A better understanding of mechanisms of primary and acquired resistance will be important to better select patients for treatment and to rationally design trials of PD-1-based drug combinations.

While more severe alterations in 9p24.1 had previously been linked with inferior outcomes to induction therapy [5], the opposite has been observed for patients treated with PD-1 blockade. In the phase II trial of nivolumab, the magnitude of 9p24.1 copy number alteration was predictive of depth of response with 9p24.1 amplified patients having the highest rates of CRs [21]. The magnitude of 9p24.1 alterations has also been positively correlated with PD-L1 expression on RS cells. To analyze the predictive value of PD-L1 expression, patients were divided into quartiles based on PD-L1 H score (the product of the frequency and intensity of PD-L1 staining on RS cells). PD-L1 H score was also positively associated with response quality; as an example, all patients who achieved a CR had PD-L1 expression in the third or fourth quartile, while all patients with progressive disease had PD-L1 expression in the first quartile [21]. While these markers provide useful predictive information, they are not yet sufficient to guide clinical decision-making as patients across all levels of 9p24.1 alterations and PD-L1 expression can derive clinical benefit from PD-1 blockade [11, 21].

Effective antigen presentation is critical for T-cell responses and alterations in this process have also been linked with response to PD-1 blockade. In most murine models and human solid tumors, CD8+ T cells are thought to be the critical immune effector cells for PD-1 blockade [22–24]. However, CD8+ T cells require antigen presentation via major histocompatibility complex (MHC) class I receptors which are frequently absent on RS cells. Unlike solid tumors,

HRS cells, because of their lineage as germinal center B cells, may express MHC class II, although this too is often absent [25]. In a cohort of 72 cHL patients treated with nivolumab for relapse after ASCT, there was no association between MHC class I expression and clinical outcomes. In contrast, intact RS cell expression of MHC class II predicted a higher likelihood of CR to nivolumab therapy. In addition, among patients who received nivolumab more than 12 months after ASCT, intact MHC class II was predictive of improved PFS; however, this association was not seen for patients who started nivolumab earlier after ASCT [26]. The frequent absence of MHC class I on RS cells and the potential importance of MHC II expression for clinical efficacy of PD-1 blockade raise important questions about the role of alternative effector cells, like CD4+ T cells and natural killer (NK) cells. A topographic analysis of cHL tumors demonstrated that RS cells are enriched for contacts with CD4+ T cells, many of which are PD-1 positive, while interactions with CD8+ T cells are less frequent [27]. NK cells, which are capable of detecting and killing cells that are missing MHC class I receptors, may also be important for the efficacy of PD-1 blockade. Patients with cHL have higher levels of circulating PD-1 positive NK cells compared to healthy controls. These NK cells are suppressed by circulating PD-L1 expressing monocytes; however, ex vivo studies suggest that this inhibition can be overcome in the presence of PD-1 mAbs [28]. These alternative mechanisms of action have important implications for potential PD-1 combination partners. For example, lymphocyte-activation gene 3 (LAG-3) negatively regulates CD4+ T-cell responses by binding MHC II with higher affinity than CD4 [29, 30], and antibodies blocking LAG3 are currently being tested in clinical trials (NCT03598608, NCT02061761). NK cell-directed therapies, like AFM13 (a bispecific antibody targeting CD30 on cHL cells and CD16A on NK cells), could also provide additive benefit to PD-1 blockade by increasing antitumor NK-mediated activity.

Finally, additional efforts are underway to understand baseline features and dynamic changes in the cHL tumor microenvironment following PD-1 blockade, which could reveal potential mechanisms of immune evasion. In solid tumors, upregulation of alternative checkpoints has been observed at the time of progression on a checkpoint inhibitor. In a murine model, resistance to CTLA-4-directed therapy occurred when tumor cells upregulated PD-L1 [31]. Similarly, increased expression of T-cell immunoglobulin domain and mucin domain 3 (TIM-3) on lung cancer cells was observed following PD-1 blockade and the addition of an anti-TIM3 antibody following failure of PD-1 blockade was associated with a survival advantage in mouse models [32]. Less is known about changes induced in the cHL microenvironment in response to anticancer therapies. A recent analysis of 30 cHL patients undergoing frontline chemotherapy found a significant increase in PD-1+ leukocytes, PD-L1+ leukocytes, and PD-L1+ RS cells on progression biopsies compared to initial diagnostic biopsies [33]. These findings could inform strategies for sequencing PD-1 blockade with other therapies since increased PD-L1 expression on RS cell has been associated with deeper responses in prior studies. However, many questions remain. A smaller study examining biopsies prior to PD-1 blockade and at the time of progression showed similar patterns with increased PD-1+ T cells in nearly all patients and increased PD-L1 expression on RS cells in some patients [34]. Additional studies that examine serial biopsies in cHL patients are needed to confirm these observations and to determine if changes in alternative checkpoint pathways or infiltration of immunosuppressive immune cells also might provide targets for future therapies.

23.6 PD-1 Blockade-Based Combination Treatments and Use in Earlier Lines of Therapy

The success of initial studies of PD-1 mAbs in cHL, combined with the realization that most patients will eventually relapse [9, 11], has spurred dozens of ongoing clinical trials that are increasingly guided by an improved understand-

ing of the PD-1 pathway and potential mechanisms of resistance. These trials are generally taking one of two approaches: (1) incorporating PD-1 mAbs earlier in the treatment paradigm with potentially curative therapies or (2) combining PD-1 blockade with rationally selected agents in the R/R setting to increase the rate of CRs and maximize remission duration. Initial results suggest that success with either approach is possible.

23.6.1 Frontline Therapy

Outcomes of frontline therapy with either ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) or BV-AVD are excellent, with generally tolerable side effect profiles and cure rates exceeding 75% among advanced stage patients [35, 36]. As such, there is very high bar for novel regimens for frontline treatment of cHL. Based on encouraging data from the relapsed/refractory setting, there are at least 11 planned or ongoing clinical trials (Table 23.2) that are testing PD-1 blockade as part of frontline treatment and seeking to answer a number of important clinical questions. Can PD-1 blockade-based treatment replace polychemotherapy for elderly or unfit patients? Can PD-1 blockade be added to induction regimens to improve outcomes for selected high-risk patient populations based on baseline features or interim response assessments? And can PD-1 mAbs be added to chemotherapy with the goal of avoiding radiation therapy in patients with unfavorable disease? Initial data from frontline trials offers some preliminary answers and lessons for future studies in this setting. Cohort D of CHECKMATE-205 enrolled a cohort of 51 patients with advanced stage, untreated cHL who received four initial doses of nivolumab followed by nivolumab-AVD for six cycles [37]. There was one treatment-related death (acute respiratory failure), but otherwise the treatment was well-tolerated with low rates of grade 3–4 immune-related events (4%) or discontinuation due to toxicity (8%). At the end of treatment, the centrally assessed CRR and ORR were 67% and 84%, respectively; however, response assessments were notably different between investigators and the independent review committee (IRC). Among the 12 patients who did not achieve a CR based on IRC review, seven were deemed to have achieved a CR by investigators and ten patients had not received subsequent treatment at the time of last data update. Accordingly, the modified PFS (defined as death, progression, or receipt of subsequent systemic treatment) was encouraging 92% at 9 months. Longer follow-up is necessary to determine if CRs achieved with PD-1-based induction will be durable and if patients with indeterminate responses will relapse. It may be that PET-based response assessments are more prone to false positives following PD-1 blockade in cHL patients who have not received prior lymphodepleting chemotherapy. Ongoing studies will help to address the efficacy of this approach and best practices for assessing response. A North American Intergroup randomized phase III study comparing nivolumab-AVD to BV-AVD for frontline treatment is currently in planning stages and may ultimately guide the potential use of nivolumab as part of initial therapy in cHL.

23.6.2 First Relapse: Salvage Therapy

The standard of care treatment for fit patients with relapsed or refractory cHL after induction therapy is multiagent salvage chemotherapy followed by ASCT, which can cure approximately half of patients [38, 39]. Investigators are incorporating PD-1 mAbs into salvage regimens with the hope that an immune-based strategy may help overcome chemoresistance in a population that has already recurred after multiagent chemotherapy. The combination of nivolumab and BV was tested as second-line therapy in 62 ASCT-eligible cHL patients in a phase II trial. Infusion-related reactions were frequently observed (44% of patients) and immune-related AEs requiring systemic steroids occurred in 8% of patients, but grade 3–4 AEs were rare. The ORR and CRR were 82% and 61%, respectively,

Table 23.2 Selected cHL frontline trials incorporating PD-1 blockade

PD-(L)1 agent	Treatment	Patient population	Phase	Number of patients	NCT Number
Nivolumab	Four cycles of nivolumab and four cycles of AVD with 30 Gy RT	Patients >60, not fit for polychemotherapy. Early stage unfavorable	II	110	NCT03004833
Nivolumab	Nivolumab alone or in combination with vinblastine	Patients >60 years old, not fit for polychemotherapy	II	64	NCT03580408
Nivolumab	Nivolumab + BV	Patients >60 years old or unable to receive ABVD	II	75	NCT02758717
Nivolumab	Nivolumab + BV	Patients 60 and above	II	25	NCT01716806
Nivolumab	Nivolumab and either ABVD or AVD	High-risk patients: – Patients less than 60 with IPS 3–7 or positive interim PET scan – Patients over the age of 60	I/II	26	NCT03033914
Nivolumab	All patients receive two cycles of ABVD. PET2- patients are randomized to either three cycles of BV/nivolumab or two cycles of ABVD followed by six doses of nivolumab. PET2+ patients receive four cycles of BV-AVD followed by six doses of nivolumab	Early stage patients aged 16 and older	II	264	NCT03712202
Nivolumab	BV-AVD induction followed by BV + nivolumab in patients with an interim-positive PET scan	Early stage, non-bulky	II	82	NCT03233347
Pembrolizumab	Group 1: Patients will receive two cycles of ABVD. Slow early responders will transition to pembrolizumab-AVD for two cycles followed by radiation therapy Group 2: Patients will receive two cycles of OEPA. Slow early responders will received pembrolizumab-COPDAC28 for four cycles	Group 1: Non-bulky stage IA, IB, or IIA Group 2: Stage IIEB, IIIEA, IIIEB, IIIB, IVA, or IVB All patients must be 3–25 years in age	II	440	NCT03407144
Pembrolizumab	Pembrolizumab-AVD	Chemotherapy-fit patients, all stages	II	30	NCT03331341
Pembrolizumab	Pembrolizumab alone followed by pembrolizumab-AVD	Chemotherapy-fit patients, all stages	II	30	NCT03226249
Avelumab	Four doses of avelumab followed by ABVD-based induction therapy (based on the RATHL trial)	High-risk stage II or advanced stage	II	47	NCT03617666

AVD adriamycin, vinblastine, dacarbazine, *BV* brentuximab vedotin, *ABVD* adriamycin, bleomycin, vinblastine, dacarbazine, *IPS* international prognostic score, *PET* positron emission tomography, *OEPA* vincristine, etoposide/etophopos, prednisone/prednisolone, doxorubicin, *COPDAC* cyclophosphamide, vincristine, prednisone/prednisolone, dacarbazine

which is similar to current standard-of-care multiagent chemotherapy regimens [40]. Among the entire cohort, the 21-month PFS was 82%. Outcomes were better for patients who underwent subsequent ASCT, particularly for the 42 patients who proceeded to ASCT directly after BV + nivolumab (21-month PFS 97%), the majority of whom had achieved a CR (37/42), [41]. These results are encouraging and suggest that achieving a CR following nivolumab-based salvage therapy may predict excellent outcomes. Longer-term follow-up and larger cohorts of patients are necessary to determine if this approach might be superior to traditional salvage regimens. Additional phase 2 trials incorporating PD-1 blockade with either ICE (ifosfamide, carboplatin, etoposide) (NCT03016871, NCT03077828) or GVD (gemcitabine, vinorelbine, doxil) (NCT03618550) are ongoing and could provide further support for the inclusion of PD-1 mAbs in salvage regimens.

23.6.3 Maintenance Following ASCT

The remodeling immune landscape after ASCT may also be an excellent setting to deploy PD-1 blockade based on increased antigen presentation, innate immune system activation, and a relative preponderance of effector immune cells seen immediately after ASCT [42, 43]. In addition, the AETHERA trial [39], which randomized patients to either BV or placebo after ASCT, established the feasibility and efficacy of post-ASCT maintenance strategies among high-risk cHL patients. Based on this, multiple trials are currently testing different PD-1-based maintenance therapies after ASCT. For example, a phase II trial tested eight doses of pembrolizumab maintenance after ACST for 30 patients with R/R cHL [44]. Maintenance pembrolizumab was generally well-tolerated with only three patients experiencing grade 3–4 AEs and four patients stopping maintenance therapy early due to toxicity. The 18-month PFS and OS were 78% and 100%, respectively. These results compare favorably to those observed with BV maintenance in the AETHERA trial (67% PFS and 91% OS at 18 months in the BV arm); however the patient populations in the two trials are different. Twenty-six of thiry patients (86%) in the pembrolizumab study met the AETHERA inclusion criteria for high-risk disease (primary refractory disease, remission duration <12 months, and/or extranodal sites of relapse), but the rate of pre-ASCT PET positivity was higher in AETHERA compared to the pembrolizumab trial (39% vs. 10%). Additional trials of PD-1-based maintenance therapies are ongoing including trials of nivolumab maintenance and nivolumab + BV maintenance (NCT03436862, NCT03057795). These trials will hopefully provide additional insight that can guide additional testing of PD-1 blockade in this setting.

23.6.4 Combination Approaches in Multiply Relapsed/Refractory Patients

Trials are also testing PD-1 blockade in multiply relapsed patients including in combination with other immune-based agents. Dual immune checkpoint blockade may preclude immune evasion and has been a successful strategy in other malignancies, like metastatic melanoma [45]. A phase II trial tested the combination of nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) in PD-1 mAb-naïve patients with R/R hematologic malignancies, including 31 patients with cHL. Dual checkpoint therapy was more toxic than PD-1 monotherapy with 29% of patients experience grade 3 or higher AEs. Among cHL patients, response rates (ORR 74%, CRR 19%) were similar to those observed with PD-1 mAb monotherapy [46]. Longer follow-up is needed to determine if more durable remissions might warrant the added toxicity of this combination. Multiple other combination immune checkpoint trials are underway which are testing PD-1 blockade with inhibitors of LAG3 (NCT03598608, NCT02061761) and killer immunoglobulin-like receptor (KIR) (NCT01592370). In addition, PD-1 blockade is being tested with other immune-based strategies, like bispecific antibodies. The NK cell targeting bispecific antibody AFM13 achieved a single-agent ORR of 23% and a dis-

ease stability rate of 77% when tested at higher dosing levels in a phase I trial [47]. Based on emerging evidence that NK cells may be an important mediator of PD-1 blockade activity in cHL, AFM13 was combined with pembrolizumab in a phase Ib trial. The combination resulted in high rates of infusion-related reactions (80%), including grade 3–4 reactions (13%), but only led to treatment discontinuation in one patient. Among 29 evaluable patients, the independently assessed ORR and CRR were encouraging at 87% and 39%, respectively [48].

PD-1 mAbs are also being tested in combination with several targeted therapies based on encouraging preclinical data. Like PD-L1 and PD-L2, JAK2 is constitutively overexpressed as a result of 9p24.1 genetic alterations and promotes increased cellular proliferation in cHL. Treatment of cHL cell lines with selective JAK2 inhibition rapidly reduces JAK/STAT signaling and cell proliferation in a copy number-dependent manner. Selective JAK2 inhibition also inhibits cHL tumor growth and prolongs overall survival in murine xenograft models [49]. To date, clinical experience with JAK inhibition in cHL has been disappointing, but the JAK inhibitors tested (ruxolitinib and SB1518), [50, 51] have not been specific for JAK2 and off-target inhibition of JAK1 and JAK3 may diminish T-cell function. A phase I/II trial of pembrolizumab and ruxolitinib is currently accruing patients (NCT03681561) and will be the first study to simultaneously target both pathways affected by 9p24.1 alterations. Understanding the importance of JAK2 selectivity may require additional clinical investigation.

Another broad group of other therapies could enhance responses to PD-1 blockade by inducing favorable changes in specific immune cell populations or enhancing recognition of tumor cells. Tenalisib is a PI3 kinase δ/γ inhibitor that has single agent activity in patients with cHL [52] and can induce a switch in tumor-associated macrophages from an immunosuppressive M2 phenotype to a pro-inflammatory M1 phenotype in preclinical models [53]. A phase I/II trial of tenalisib in combination with pembrolizumab is ongoing (NCT03471351). Through off-target inhibition of interleukin-2-inducible T-cell kinase (ITK), ibrutinib and other Bruton tyrosine kinase (BTK) inhibitors may shift the balance from Th2 to Th1 T cells potentially enhancing antitumor responses. Based on a lymphoma mouse model showing synergy between ibrutinib and an anti-PD-L1 mAb [54], multiple clinical trials are testing the combination of a BTK inhibitor and a PD-1 mAb (NCT02940301, NCT02362035, NCT02950220). Preclinical work suggests that epigenetic modifiers might enhance responses to immune treatments by upregulating endogenous retroviral genes in tumor cells [55]. In cHL, a small retrospective series reported an unusually high rate of CRs with PD-1 blockade among patients who had previously received 5-azacytidine [56]. Based on these findings, a phase II trial is testing the combination of SHR-1210 and decitabine in multiply relapsed cHL patients. Finally, investigators are combining PD-1 blockade with radiation therapy in multiple clinical trials (NCT03480334, NCT03495713, NCT03179917). Radiation therapy is typically considered a local therapy, but it induces tumor antigen release, which can trigger systemic innate and adaptive immune responses. Indeed, abscopal responses (systemic regression of tumors outside the local radiation field) have been reported across multiple cancers [57]. In cHL, two small case series report that radiation may be capable of inducing systemic responses among previous PD-1 nonresponders [58, 59]. Even if many of these trials are not successful in selectively modulating the immune system to enhance response to PD-1 mAbs, they will likely provide important lessons for future generations of rationally-designed combination trials.

23.6.5 Impact of PD-1 Blockade on Subsequent Therapies

PD-1 mAbs have long-serum half-lives and their impact on the immune system appears to persist long after therapy is stopped, which could affect the outcome of subsequent treatments. Two retrospective series have suggested that immune checkpoint treatments may re-sensitize patients to chemotherapy. In a French series, patients with

an inadequate response to PD-1 blockade were next treated with chemotherapy alone ($n = 18$) or with chemotherapy + continued PD-1 blockade ($n = 10$). 61% of patients treated with chemotherapy alone and 90% of patients treated with PD-1 + chemo achieved an improved response [60]. An American series of 50 cHL patients who received subsequent therapy after PD-1 blockade reported an ORR of 52% (CRR 34%) and found that response to PD-1 blockade predicted response to subsequent therapy (ORR with subsequent therapy among PD-1 responders 70% vs. 37% for PD-1 nonresponders) [61]. Together, these series provide further rationale for trials that combine chemotherapy with PD-1 mAbs. In addition, they provide some reassurance that patients who achieve a response with PD-1 blockade may not need immediate consolidation with allogeneic transplantation, since they appear to have a high response rate with subsequent salvage therapies.

23.7 PD-1 Blockade and Allogeneic Stem Cell Transplantation

The lasting immune effects of PD-1 blockade also have important implications for patients who subsequently undergo allogeneic hematopoietic stem cell transplantation (allo-HSCT). There is a rapidly growing literature on the use of PD-1 blockade before and after allo-HSCT, which has been recently reviewed elsewhere [62, 63] and is outside the scope of this chapter. Briefly, an initial series suggested that allo-HSCT after PD-1 blockade may be associated with higher rates of early immune complications, including severe acute graft-versus-host disease (GVHD) and a noninfectious febrile syndrome [64], which led to an FDA label warning. Despite these concerns, PFS following allo-HSCT for these patients compares favorably with historical controls, promoting the overall feasibility of this approach. In addition, several series have suggested lower rates of relapse following allo-HSCT, perhaps due to enhanced graft-versus-lymphoma effect driven by lingering immune alterations from PD-1 blockade [9, 64, 65]. Longer-term follow-up of larger patient cohorts is ongoing to clarify these observations. In addition, efforts are underway to determine if alternative transplant strategies, like use of posttransplant cyclophosphamide for GVHD prophylaxis, might reduce rates of early immune complications [66].

PD-1 blockade is also being cautiously used for patients who relapse following allo-HSCT, a patient population with very poor outcomes and limited treatment options. Two retrospective series reported excellent ORRs (79–95%) with this approach and CRRs (42–54%) that appear higher than those seen in the pre-allo-HSCT setting [67, 68]. However, PD-1 blockade was also associated with very high rates of GVHD (30–55%), including rapid-onset, steroid-refractory, and occasionally fatal GVHD. Across both studies, 25% of patients died from complications of treatment-emergent GVHD. A prospective trial is testing dose-escalation strategies with nivolumab to try to mitigate the risk of GVHD, but preliminary results suggest a considerable risk of GVHD even at reduced dose levels [69]. Balancing the risk and benefits of PD-1 blockade in this setting is challenging, and PD-1 mAb should be used cautiously, particularly for patients with a history of GVHD or early relapse after allo-HSCT.

23.8 Conclusion

Genetic alterations at 9p24.1 are nearly universal in cHL and promote immune evasion. Disrupting PD-1 signaling using PD-1 mAbs is a highly effective treatment strategy and has improved outcomes for patients with R/R cHL disease. Based on this clinical success, PD-1 blockade is currently being tested in thousands of cHL patients and has changed the cHL clinical trial landscape at every stage of treatment. Yet, numerous scientific and clinical questions remain, including basic questions about the mechanisms of action and resistance to PD-1 mAbs in cHL, which may prove more complicated than initially believed. Continued improvements in our scientific understanding and carefully designed, collaborative clinical trials should drive additional

breakthroughs leading to novel effective treatment combinations and potential incorporation of PD-1 blockade earlier in the cHL treatment paradigm.

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Other New Agents for Hodgkin Lymphoma

24

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Contents

24.1 PI3K/Akt/mTOR Pathway

Constitutive activation of the PI3K/Akt/mTOR pathway is present in both HL cell lines and primary tissue [1, 2]. The significance of this pathway in HL was demonstrated by the efficacy of everolimus, an mTOR inhibitor, in patients with relapsed or refractory (rel/ref) HL. In the phase II study evaluating everolimus in rel/ref HL, patients received 10 mg/day until progression of disease [3]. Among the 57 patients enrolled, the overall response rate (ORR) and complete response (CR) rate were 45.6% and 8.8%, respectively. Seven (12%) patients were long-term responders (lasting >12 months). Treatment was well tolerated with grade 3 or 4 thrombocytopenia and anemia occurring in 21% and 14%, respectively. Furthermore, only 3.5% of patients experienced grade 3 stomatitis, and pneumonitis occurred in 10.5% (all grade 1 or 2).

The value of targeting this pathway in HL was further tested through a phase II study evaluating idelalisib, a delta-specific PI3 kinase (PI3Kδ) inhibitor. PI3Kδ is preferentially expressed in cells of hematopoietic origin, particularly B cells, and is highly expressed in HL cell lines compared to other PI3K isoforms [4]. Twenty-five patients with rel/ref HL enrolled on this study and were treated with idelalisib 150 mg BID until progression, with the option to increase to 300 mg BID. The ORR was 20% with one complete response and four partial responses [5]. As was seen with everolimus, a few prolonged responses were observed and median duration of response was 8.4 months. Adverse events typically seen with this drug class were observed and included grade ≥ 3 elevations in ala-

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_24

nine aminotransferase and/or aspartate aminotransferase in five patients, colitis (grade 1 or 2) in three patients, and grade 2 pneumonitis in one patient.

Preclinical studies have led to several clinical trials evaluating novel regimens involving drugs affecting the PI3K pathway. For example, the demonstration of synergy between everolimus and panobinostat in HL cell lines led to a phase I/II study evaluating this combination [6, 7]. This combination, however, did not appear to be more efficacious than observed with either drug alone. There is also rationale for combining PI3K pathway inhibitors and immunotherapeutic agents. PI3K blockade inhibits regulatory T cells and reduces anti-inflammatory cytokines; therefore PI3K inhibitors likely function in part through promotion of antitumor immunity and have potential to synergize with PD-1 blockade [8, 9]. Pembrolizumab plus idelalisib is being evaluated in a study for chronic lymphocytic leukemia and indolent B-cell non-Hodgkin lymphomas (NCT02332980). In addition, a study evaluating PD-1 blockade plus everolimus for solid tumors is underway (NCT02890069). If these combinations are found to be safe, it would be reasonable to evaluate them in HL as well.

24.2 HDAC Inhibitors

The histone deacetylase (HDAC) inhibitors target both HL Reed-Sternberg (RS) cells and their tumor microenvironment and therefore are particularly attractive agents for HL. Their epigenetic effects on gene expression support apoptosis of RS cells and cause disruption of the cytokine- and chemokine-mediated interactions between the RS cells and their microenvironment [10, 11]. The available HDAC inhibitors differ by their specificity for particular HDAC isotypes, and the more selective HDAC inhibitors may have the advantage of causing less hematologic toxicity.

Both pan-HDAC inhibitors (vorinostat and panobinostat) and more selective inhibitors (mocetinostat and entinostat) have been evaluated in HL. Vorinostat demonstrated only modest activity in rel/ref HL in a phase II study by the Southwest Oncology Group (SWOG), with only 1 out of 25 patients achieving PR [12]. Panobinostat demonstrated more promising activity in an international phase II study in rel/ref HL [13]. Of 129 patients, there were 35 (27%) responses, which included 5 (4%) CRs and 30 (23%) PRs. Furthermore, tumor reductions were observed in 74% of patients. Responses were durable with median duration of response of 6.9 months. Common toxicities seen with this agent were thrombocytopenia (79% grade 3/4), diarrhea, nausea, and fatigue.

Mocetinostat, which selectively inhibits class I and IV HDACs, was evaluated in 51 patients with HL and demonstrated an ORR of 33% [14]. In contrast to panobinostat, hematologic toxicity was rarely seen with mocetinostat; however, 6% of patients developed nonfatal pericardial effusions. Entinostat, a selective class I HDAC inhibitor, demonstrated an ORR of 12% (6 PRs among 49 patients) and tumor reductions in 58% of patients [15].

Overall, the HDAC inhibitors consistently demonstrate activity in HL and cause only moderate toxicity; therefore, they are good candidates for evaluation in combination with other agents for HL. Their role in enhancing antitumor immunity through activating natural killer cell-mediated cell killing provides rationale for combination with PD-1 blockade [16]. An ongoing phase II study with pembrolizumab plus entinostat in Hodgkin lymphoma and follicular lymphoma is testing this concept (NCT03179930).

24.3 Lenalidomide

The antitumor activity of lenalidomide in HL is potentially mediated through activation of the E3 ubiquitin ligase cereblon, resulting in direct cytotoxicity, alteration of tumor cell microenvironment, and/or antiangiogenesis [17, 18]. Evidence of activity of lenalidomide in HL was initially reported by Böll and colleagues among 12 patients with rel/ref HL treated on a named patient program; all of the patients achieved clinical benefit and 50% achieved objective responses [19]. One patient achieved a complete response which was ongoing after 2 years of therapy. In a larger phase II study of 36 patients with rel/ref HL, lenalidomide induced objective responses in seven (19%) patients. An additional five (14%) patients achieved stable disease for 6 months or more, and prolonged responses were observed yielding a

Table 24.1 Summary of newer agents for Hodgkin lymphoma (other than brentuximab vedotin and PD-1 inhibitors)

Class	Drug	*n*	ORR (%)
HDAC inhibitor	Vorinostat [12]	25	4
	Panobinostat [13]	129	27
	Mocetinostat [14]	51	33
	Entinostat [15]	38	12
mTOR inhibitor	Everolimus [3]	57	45.6
PI3K inhibitor	Idelalisib [5]	25	20
Immunomodulator	Lenalidomide [20]	36	19

median time to treatment failure of 15 months [20]. Although not tremendously active as a single agent in HL, lenalidomide produces durable responses and represents another good candidate for combination. Lenalidomide has been evaluated in combination with everolimus as well as panobinostat; however neither combination appears more active than the individual agents [21, 22]. Ongoing studies are evaluating lenalidomide in combination with nivolumab (NCT03015896) and brentuximab vedotin (NCT03302728).

24.4 Emerging Therapies

Newer methods for targeting CD30 are under investigation and include chimeric antigen receptor (CAR)-T cells and bispecific antibodies. An initial phase I study evaluating anti-CD30 CAR-T cells demonstrated only limited activity in HL, likely due to lack of pre-CAR-T lymphodepleting chemotherapy [23]. Lymphodepleting chemotherapy improves CAR-T cell expansion and is incorporated into two ongoing studies which show promising activity in small numbers of patients so far [24–26].

AFM13 is a bispecific antibody construct that binds CD30 on tumor cells as well as CD16A on NK cells. It works by enhancing NK cell-mediated tumor cell killing. A phase I study of AFM13 showed single-agent activity in relapsed and refractory HL and it is currently being evaluated in combination with pembrolizumab [27, 28]. The combination is well-tolerated and interim results show ORR and CR rates of 87% and 35% among 23 evaluable patients.

CD25 is another promising target for HL, given that it is expressed on both Hodgkin Reed-Sternberg cells and regulatory T cells. ADCT-301 (camidanlumab) is an antibody-drug conjugate comprised of an anti-CD25 monoclonal antibody conjugated to the pyrrolobenzodiazepine dimer (PBD) toxin. In a phase I study, 60 patients with HL were treated and ORR rate among evaluable patients ($n = 55$) was 69% with 43.6% achieving CR [29]. Furthermore, at the recommended dose for expansion (45 μg/kg), the ORR and CR rates among 26 patients were 80.8% and 50%, respectively. Notable toxicities observed with camidanlumab included Guillain Barre (3.3%), grade 3 transaminitis (10%), and grade 3 rash (13.3%). A phase II study further evaluating efficacy and toxicity of this agent in HL is planned (Table 24.1).

24.5 Conclusion

Even with the availability of BV and anti-PD1 antibodies, there is considerable room for improvement in the treatment of HL. In the rel/ref setting, treatment options eventually become exhausted as patients ultimately progress following BV or anti-PD1-based treatment. Furthermore, more individualized and better-tolerated therapies are needed in the frontline and second-line treatment setting for HL. Therapies currently under investigation in HL target activated pathways within the RS cells, the HL microenvironment, or both, and the key challenge will be to identify markers that predict likelihood of response and to determine the optimal way to combine these agents to produce well-tolerated, effective regimens. As we continue to develop new effective agents for HL, emerging biomarkers, such as circulating tumor DNA [30], will undoubtedly aid us in identifying the right patient for the best treatment at the optimal time (Figs. 24.1 and 24.2).

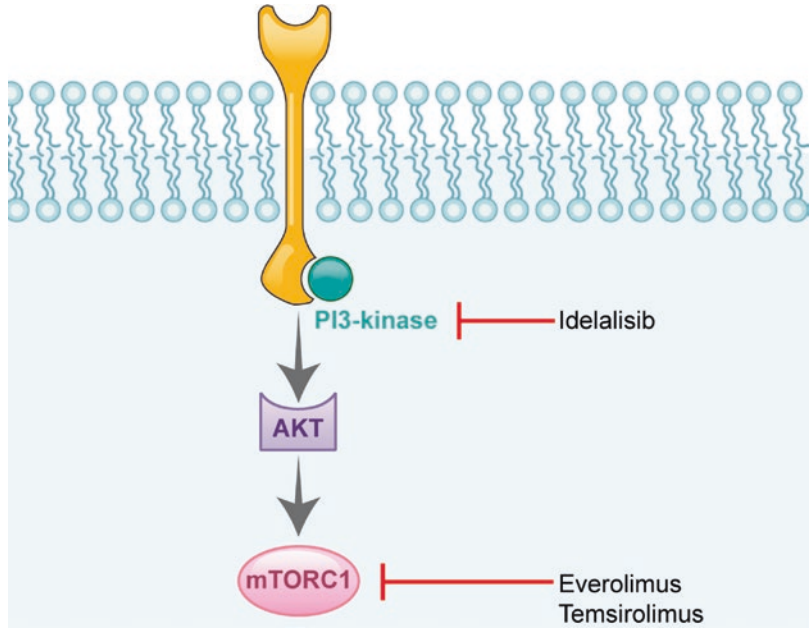

Fig. 24.1 Targeting the PI3K Pathway in Hodgkin lymphoma

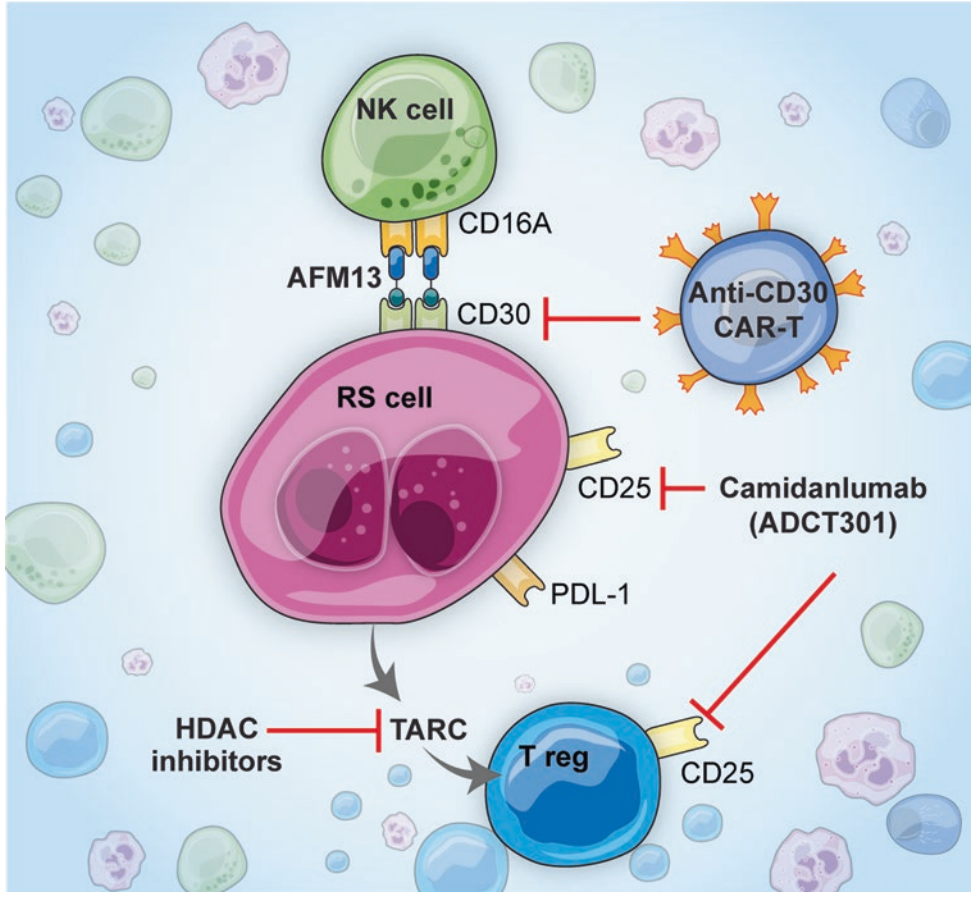

Fig. 24.2 Targeting Reed-Sternberg cells and the microenvironment

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Part V

Survivorship

Quality of Life in Hodgkin Lymphoma

25

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Contents

25.1 Quality of Life in Hodgkin Lymphoma

The excellent cure rates for Hodgkin lymphoma (HL) patients of more than 90% for all stages led to a continuously growing number of typically young long-term survivors. Thus, late sequelae during survivorship and impairments in the survivor's health-related quality of life (HRQoL) recently has gained relevance in clinical research. Many HL survivors experience significant physical and psychological distress, which contributes to a deterioration of their HRQoL [1–4].

HRQoL is a multidimensional construct reflecting the World Health Organization's (WHO) definition of health as incorporating physical, mental, and social health [5].

Impaired HRQoL is a major problem for many HL survivors, which often relates to high levels of fatigue and persisting impairment in cognitive, physical, and social functioning [6]. Various factors might contribute to the complexity of HRQoL including treatment-induced organic dysfunction, psychological distress, as well as social reintegration, e.g. return to work and family life.

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_25

Accordingly, we have experienced an increasing amount of research over the past 10–20 years focusing on HRQoL in HL survivors. However, most HL-related HRQoL research has been limited by the use of cross-sectional approaches and small patient numbers, with inadequate patient and treatment history as well as variable follow-up [7]. For a long time, only two prospectively planned HRQoL studies in HL were available: one from the SWOG (Southwest Oncology Group) and the other from the EORTC (European Organisation for Research and Treatment of Cancer) [4, 8]. Both studies were restricted to early-stage patients, and only in the SWOG study pretreatment baseline values were documented. Thus, reliable and prospective data on the longitudinal course of HRQoL according to disease-, treatment-, and patient-related characteristics were missing.

In this chapter, we describe the methods to determine HRQoL and then summarize the currently available results from cross-sectional and longitudinal studies in HL.

25.2 Health-Related Quality-of-Life Assessment

HRQoL includes many aspects of physical, psychological, and social functioning. It therefore mirrors these aspects of patients after treatment for cancer. The determination of HRQoL relies on patient-reported outcomes (PROs) – a term which is being used for health status measurement that comes directly from the patient. According to the FDA (US Food and Drug Administration), PRO measures include "such extremely complex concepts as HRQoL, which is widely understood to be a multi domain concept with physical, psychological, and social components" [9].

25.2.1 HRQoL Instruments

Most published trials in HL addressing late effects and HRQoL used different, mainly non-HL disease-specific instruments or questionnaires. The most commonly used multidimensional instruments in a recently published systematic review on HRQoL in HL were the European Organisation for Research and Treatment of Cancer Quality of Life Questionaire (EORTC QLQ-C30), the 12- or 36-Item Short Form Survey (SF-12 or SF-36), and the Health Utilities Index (HUI) [7, 10–12]. Other frequently used measures included the Hospital Anxiety and Depression Scale (HADS) and the Functional Assessment of Cancer Therapy (FACT) Questionnaire [13]. The FACT-Lymphoma questionnaire has been developed more than a decade ago to assess QoL in the broad group of all subtypes of lymphoma cancer patients. Following expert relevancy ratings, patient input and item correlations, a lymphoma subscale of 15 items was constructed [14].

Today, the most suitable cancer-specific core instrument for the assessment of HRQoL in large clinical trials is the EORTC QLQ-C30 questionnaire. Data provided by the EORTC QLQ-C30 questionnaire consist of five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, nausea and vomiting), six single-item symptoms (dyspnoea, appetite loss, constipation, diarrhoea, sleeplessness, and financial), and a global health and quality of life scale. Patients respond to the questions in a graded format ranging from 1 = "not at all" to 4 = "very much". All scales range in scores from 0 to 100. High scores for the functional scales represent a better level of functioning; high scores for the symptom scales implicate higher level of symptoms [10]. According to published data, an absolute change of >10 points on a 0–100 scale is usually considered as clinically relevant difference for all domains analysed [15, 16].

Both, the EORTC QLQ-C30 and the FACT are cancer specific, multidimensional in structure, appropriate for self-administration, and available in a range of different languages. However, since no HL-specific modules for the assessment of HRQoL and fatigue were available for many years, the EORTC and the German Hodgkin Study Group (GHSG) developed and validated a combined questionnaire for HRQoL for survivors of HL, the Quality-of-Life questionnaire for Survivors (QLQ-S). This combined questionnaire has been used for systematic and prospective HRQoL assessment in all GHSG first-line trials since 1998. It incorporates the

EORTC QLQ C30, the Multidimensional Fatigue Inventory (MFI)-20, additional scales from a German Testicular Cancer Trial Group addressing sexuality, partnership, strain from treatment and disease, and global retrospective evaluation of treatment. In total, the QLQ-S includes 45 questions on 14 functional, symptom, and fatigue scales, 15 additional single items, and three open questions. A feasibility analysis generally showed good acceptance of the questionnaire by patients and physicians. The QLQ-S was first applied in two large multicentre trials in HL: the EORTC H8 trials and the GHSG HD8 trial [8, 17]. Furthermore, the questionnaire was routinely used in the GHSG trials HD10 to HD18 and enabled several longitudinal studies which are summarized below.

Recently, four disease-specific EORTC QoL questionnaires were developed on an international basis in order to more comprehensively assess QoL in patients with HL, non-HL, and chronic lymphocytic leukaemia (CLL), respectively [18]. Large differences were observed in the mean and prevalence of items for the four tumour groups, where some items were relevant to certain subgroups while at the same time upsetting other subgroups. After completion of phase 4 full psychometric testing in 337 patients from five European countries, this resulted in a questionnaire with 27 items for HL (EORTC QLQ-HL27), 29 items for high-grade NHL (EORTC QLQ-NHL-HG29), 20 items for low-grade NHL (EORTC QLQ-NHL-LG20), and 17 items for CLL (EORTC QLQ-CLL17). These questionnaires are to be used in conjunction with the EORTC QLQ-C30 core questionnaire and are expected to raise standards of outcome measurements in patients with lymphoproliferative disorders in future trials [18].

25.2.2 HRQoL in Special Patient Groups

Different patient groups require individually tailored instruments to measure HRQoL and late effects. Only recently there has been progress in the development of instruments to measure HRQoL and late effects in paediatric oncology [19, 20]. HRQoL assessment in children must address normal developmental issues in areas such as peer relations, school, family, and play, which differ from the topics addressed in adult instruments. Questionnaires must also be suitably administered. In children under the age of 10 or 11, self-reporting by questionnaires is in general neither reliable nor feasible; proxy ratings by the parents or caregivers are necessary. A number of proxy and self-rating tools are already available from paediatric psychology and psychiatry, but no established tested instruments exist specific for HRQoL research in children and adolescents with HL. In a recently published cross-sectional trial looking into the long-term outcome of paediatric HL patients, the HRQoL assessment used a combination of instruments for children and adults [21]. Further analyses will also deal with the comparison of the psychometric properties of these instruments.

As with the HRQoL assessment in paediatric oncology, HRQoL assessment in elderly patients must address the individual aspects of daily living and the adjustment to physical and mental disabilities. Questionnaires must be suitably devised and administered, and the patients may need assistance in filling out forms. Some proxy and self-rating tools are meanwhile available from geriatrics, but no validated instruments exist for HRQoL research in elderly HL patients.

25.3 HRQoL in Clinical Trials for Hodgkin Lymphoma

25.3.1 Lessons from Retrospective and Cross-Sectional Studies

More than 60 primary studies have been identified since 1986 dealing with HRQoL in HL as reviewed recently [7]. In brief, mainly cross-sectional studies in HL survivors have been performed over the last two decades with a medium sample size of 135 included patients (range 15–1834). Studies varied by assessed aspects of HRQoL and specific instruments employed. Most studies were cohort studies; however, some trials used a matched control design or compared patient data with data from general population

surveys. Cross-sectional studies captured patients within a wide range of time periods after diagnoses with a median time range of 10 years after treatment. These analyses demonstrated that a relevant number of patients still carry a substantial burden even many years after the end of therapy.

Among the single domains explored, psychosocial was the most frequently identified with the psychosocial assessments being more common in cross-sectional studies compared to longitudinal analyses. As studies differed in scales and measures, the results within this domain were inconsistent and the presence of psychosocial distress varied among reports. Early studies indicated that HL survivors experience increased psychological distress which was later supported by longitudinal data [6, 22–24]. Several studies used symptom-specific questionnaires of which the majority focussed on fatigue. The three most commonly used fatigue instruments included the Fatigue Questionnaire (FQ), the Multidimensional Fatigue Inventory (MFI), and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue). Results in this domain were more homogenous with multiple studies indicating that HL survivors are at increased risk for fatigue when compared to healthy controls [2, 25–28].

Some relevant findings from case-control studies performed in HL survivors are listed in Table 25.1. All but one study involved healthy

Table 25.1 Selected results from HRQoL studies in long-term survivors of HL

Study	Cases (patients)	Controls	Main results
Joly et al. [29]	93 patients issued from the regional cancer registry	186 matched controls (age and sex) from the regional population registry	More physical, role, and cognitive impairments among cases. Major limitation in borrowing from banks remained the major problem in cases
Loge et al. [1]	459 patients (1971–1991) treated at the Norwegian radium hospital	General Norwegian population	Higher levels and longer lasting of fatigue among cases. Disease stage predicted fatigue. No association with treatment characteristics
Wettergren et al. [30, 31, 34]	121 patients treated in Stockholm County (1972–1991)	236 matched controls (age and sex) from the regional population registry	Most important reported life areas were family, personal health, work, relations to other people lower physical health in patients
Rüffer et al. [28]	836 patients from the GHSG trials HL1-6 (1981–1993)	935 matched controls (age, sex, living area) from regional population registries	Higher levels of fatigue in cases. Fatigue associated with systemic symptoms, Karnofsky, occurrence of relapse
			Time since end of treatment had no influence on the reported fatigue levels
Holzner et al. [32]	126 patients treated at a single institution (1969–1994)	926 controls from the general Austrian population	Higher functional, social Well-being, and total scores in cases compared to controls
Hjermstad et al. [33]	475 patients (1971–1997) treated at the Norwegian radium hospital	General Norwegian population	Higher levels of total fatigue (TF) in cases. Persisting chronic fatigue (CF) was associated with B-symptoms at diagnosis and treatment period 50% of patients reporting CF in 1994 did not report CF 8 years later. No correlation of fatigue levels with treatment variables (e.g. radiation fields)
Calaminus et al. [21]	1202 patients from the paediatric German–Austrian therapy studies HD-78, HD-82, HD-85, HD-87, HD-90, HD-95 (1978–2002)	General German population	"Global" and "physical QoL" scores comparable to general population, "emotional" and "social functioning" more than ten points lower. Higher symptom scores for "fatigue" and "sleep". Gender effects showing lower functioning and higher symptom levels in women, most prominently in the group of young women (21–25 years). No association with the time since treatment, the age of HD survivors at diagnosis, or the extent of therapy burden

controls from regional population registries or from the general population. In summary, results of these studies are related to a variety of areas but consistently report on emotional strain and fatigue even years after the end of treatment. The latest study on survivors of paediatric HL confirms the findings from the previous adult studies. To summarize, these cross-sectional studies have shown persisting impaired HRQoL especially with regard to fatigue for a substantial number (up to 40%) of HL patients, but besides age, no risk factor was consistently reported [1, 21, 28–34]. Although these studies used control groups, their design neither allows firm conclusions on the aetiology of persisting impaired HRQoL nor to develop a model for a persisting defective HRQoL in HL.

25.3.2 Results from Prospective Trials

The first study reporting a longitudinal prospectively designed investigation on HRQoL in HL was conducted by the SWOG [4]. In the early 1990s, there was considerable debate about the necessity for staging laparotomy in early-stage HL (clinical stage IA and IIA), which was driven by the morbidity of the procedure. Thus, there was increasing interest in using short courses of chemotherapy with more limited radiotherapy to maximize cure and minimize toxicity. The SWOG designed a treatment protocol (SWOG 9133) to investigate alternative strategies for the management of early-stage HL, investigating subtotal lymphoid irradiation (STLI) vs. three cycles of doxorubicin and vinblastine followed by STLI (combined-modality therapy (CMT)) in early-stage HL patients. This study was accompanied by a prospective quality-of-life study termed SWOG 9208. The objectives of this study were to evaluate prospectively the health status and HRQoL of early-stage HL patients receiving either STLI or CMT, to describe the short-term effects of the treatments on symptoms and QoL, and to evaluate the intermediate and long-term effects of the two treatments on HRQoL. Short-term and intermediate outcomes during the first 2 years after random assignment were reported. Both treatment groups experienced a short-term increase in symptoms, fatigue, and poorer QoL as a result of the treatment, which was more severe in the CMT group at 6 months after diagnosis due to more prolonged treatment. However, 1 year after random assignment, outcomes in the two treatment groups were indistinguishable. In this study, increased fatigue was identified in favourable HL patients before treatment that persisted after successful curative treatment. Importantly, fatigue levels for both study groups (CMT 45.9 and STLI 49.7) were increased at baseline. These scores were lower than scores for the general population. Before any treatment, these early-stage HL patients reported scores that were about a half SD below normal and were more consistent with scores from older patients with ischaemic heart disease. While fatigue is a known symptom for HL, it was unexpectedly prominent in this patient cohort having a favourable prognosis without B-symptoms. It was expected to improve subsequent to treatment and induction of remission. However, the fatigue level did not improve to normal values. The vitality scale scores at 1 and 2 years were slightly below the baseline score and were substantially lower than comparative data from a breast cancer survivor sample after adjuvant treatment and radiotherapy. Though this is one of the most important studies on HRQoL in HL, no conclusions can be drawn with regard to tumour stage at baseline or aggressiveness of the chemotherapy being a risk factor for HRQoL impairment, since only early-stage low-risk patients were included.

The second study was published in 2009 by Heutte and colleagues [8]. They reported the results of their longitudinal HRQoL study examining short-term and long-term HRQoL among HL survivors from a large phase 3 trial (EORTC-H8). The study included early favourable HL patients and compared chemotherapy plus radiotherapy with radiotherapy alone; in patients with early unfavourable disease, different chemotherapy–radiotherapy combinations were compared. Of 1577 patients recruited to the trial throughout Europe, 2666 assessments from 935 patients were available for the analysis with

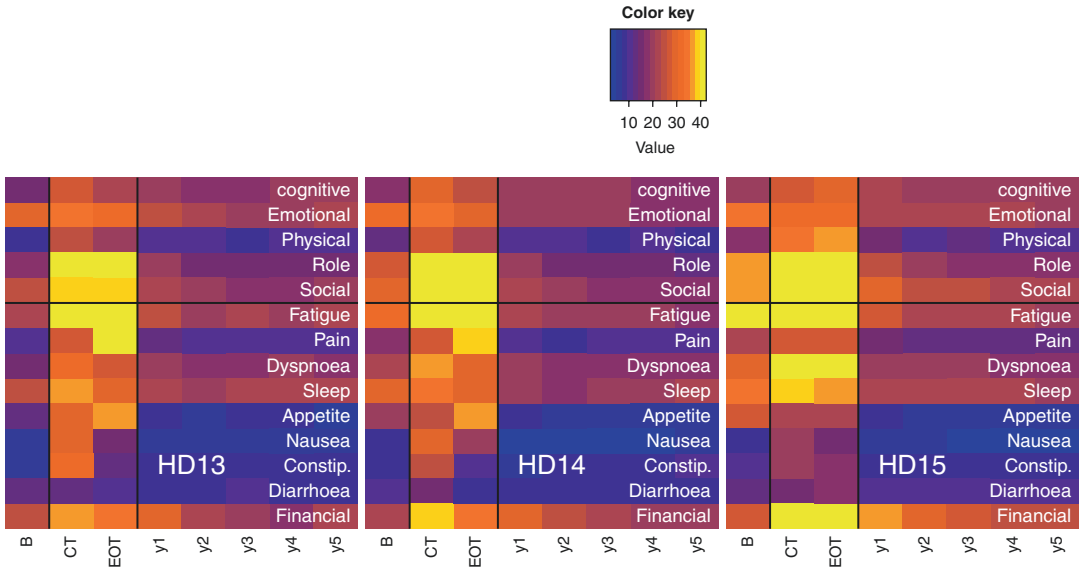

Fig. 25.1 Heatmaps of HRQoL in three GHSG trials over 5 years (negative differences compared with the German reference population). Kreissl S et al., data submitted, not published 2019

median follow-up of 92 months. Interestingly, therapeutic modality (radiotherapy vs. chemotherapy) did not have significant effects on HRQoL, and many patients experienced recovery within 18 months of completing treatment. However, high-level fatigue more than 2 years after therapy was common (Fig. 25.1).

The only factor that predicted long-term fatigue was fatigue at the end of treatment. Factors associated with significantly impaired HRQoL were older age and female sex. Furthermore, age affected all functioning and symptom scores. Also, of note, emotional domains did not show the same magnitude of improvement after treatment as physical domains. Strengths of this report were the longitudinal design, large cohort size, homogeneous patient population, and long-term follow-up. These aspects allowed a sufficient analysis of clinically relevant patient-based and disease-based subgroups. A major limitation was the fact that the authors did not capture HRQoL data before treatment, which would have shed light on the potential role of pretreatment fatigue in predicting long-term outcomes. In addition, the number of patients at a given time point within defined treatment arms is rather small, and advanced stage patients were not included. Thus, again only a subgroup of patients was evaluated in this study, and, without baseline (i.e. pretreatment) values for HRQoL, the findings cannot be used to develop a model of HRQoL outcome in HL.

To close this gap of knowledge the GHSG aimed to complement the clinical results of the GHSG's fifth generation HD13, HD14, and HD15 trials for early-stage favourable, early-stage unfavourable, and advanced stage HL, respectively, with a comprehensive analysis of HRQoL (Kreissl et al., data submitted). A total of 4215 patients were evaluable for the analysis, and patients in all stages of HL were enrolled. To analyse HRQoL, all functional and symptom scores of the EORTC QLQ-C30 questionnaire were used and deviations from reference values were described. Patients and survivors completed the questionnaires at the following timepoints: immediately after diagnosis (baseline), after two to four cycles of chemotherapy, immediately after the end of treatment, and at predefined follow-up examinations up to 5 years after end of treatment.

The authors reported that clinically relevant deviations in HRQoL were prevalent in HL patients even before the onset of chemotherapy, with substantial differences between disease

stages. In all trials, HRQoL was worst during chemotherapy and continually improved over time. During survivorship "cognitive functioning", "emotional functioning", "role functioning", and "social functioning" as well as "fatigue", "dyspnoea", "sleep", and "financial problems" were severely and persistently affected. In these domains, HRQoL in the second and fifth year after therapy was significantly influenced by baseline scores and age, but not by randomized treatments. Survivors ≥50 years reported lower HRQoL than younger survivors, most pronounced in advanced stages. Of all HRQoL domains, fatigue presented as the strongest correlating factor. This longitudinal analysis of HRQoL in HL adds new and relevant information to the field as it includes all stages of HL and it provides HRQoL data already at the time of diagnosis before patients entered the treatment process. The analysis revealed a high and persistent amount of different HRQoL problems in HL survivors, which are largely independent of the applied chemotherapies. Treating the psychosocial side effects of the cancer experience in these rather young survivors thus appears to be the most promising option to improve their HRQoL.

Besides these important general findings, Behringer et al. reported further results of the GHSG fourth generation of trials (G4) with special emphasis on sexual quality of life (SX) [35]. Here also an impaired SX was found at baseline which was more pronounced in advanced stages and in patients over the age of 50 years. Interestingly a benefit from therapy was found in advanced stages with more patients that improved after therapy than suffering from therapy-induced impaired SX. However, a normalization of SX was only reached in early stages. Furthermore as well as in the other domains of HRQoL, a clear impact of therapy could not be detected in early or advanced stages. Only in early unfavourable stages, the comparison of ABVD versus BEACOPP showed a small but significant advantage in favour of ABVD. As for fatigue, the authors developed a model to predict long-term SX. The model showed that SX from 12 to 18 months after therapy is highly predictive for further SX scores up to 27 months.

25.4 Conclusions

In recent years, late sequelae during survivorship and impairments in HRQoL gained relevance in HL due to a continuously growing number of young long-term survivors. Impaired HRQoL is a major problem for many HL survivors, often related to high levels of fatigue and persisting impairments in cognitive, physical, and social functioning as well as severe financial problems. Several studies have highlighted these difficulties of survivors even years after the end of treatment. Since most of these studies were using a cross-sectional, retrospective design, details on the longitudinal impairments in HRQoL and disease-, treatment-, and patient-related risk factors were missing. To provide a complete picture on the longitudinal course of HRQoL, large prospective clinical trials are urgently needed. A comprehensive analysis of the GHSG HD13-HD15 trials showed a high and persistent amount of different HRQoL problems in HL survivors, which were largely independent from the applied treatment regimens. In all stages, each of the investigated HRQoL domains 2 and 5 years after therapy were significantly influenced by baseline scores and age. Longitudinal data contribute to a better understanding and acceptance of patients and survivors suffering from impaired HRQoL. Quality-of-life assessment should benefit patients by defining relevant issues, by developing prevention strategies, and by providing support for their social reintegration after being cured.

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Second Malignancy Risk After Treatment of Hodgkin Lymphoma

26

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Contents

26.1 Introduction

In view of the excellent cure rates that are currently achieved in the relatively young population of patients with Hodgkin lymphoma (HL) [1], it has become increasingly important to evaluate and limit the long-term complications of treatment. Research conducted over the last three decades has clearly demonstrated that, paradoxically, some treatments used to treat cancer have the potential to induce new (second) primary malignancies. Of all late complications of treat-

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_26

ment, second malignant neoplasms (SMNs) are considered to be among the most serious because they cause not only substantial morbidity but also considerable mortality. Among long-term survivors of HL, second cancer deaths have been reported to be the largest contributor to the substantial excess mortality that these patients experience [2–4].

Increased risk of SMNs has been observed both after radiotherapy (RT) and chemotherapy (CT). In 1972, Arseneau and colleagues [5] were the first to report an increased risk of second cancer after HL treatment. Based on 12 second malignancies in 425 patients treated at the US National Institutes of Health from 1953 to 1971, they estimated a 3.5-fold risk increase compared to the general population. MOPP combination chemotherapy (mechlorethamine, vincristine, procarbazine, and prednisone) for HL was introduced in 1967; the leukemogenic potential of this regimen and similar ones became evident in reports published in 1973 [6], 1975 [7], and 1977 [8]. In the 1980s several studies showed that, after an induction period of 5–10 years, radiotherapy for HL increased the risk of solid malignancies, especially lung cancer [9–12].

It is important to recognize that not all SMNs are caused by treatment. The occurrence of two primary malignancies in the same individual may have several causes. It may represent a chance occurrence (in which case the two cancers developed as a result of unrelated factors); it may result from host susceptibility factors (e.g., genetic predisposition or immunodeficiency); it may be linked to carcinogenic influences in common, or a clustering of different risk factors in the same individual; or it may represent an effect of treatment for the first tumor [13, 14]. In view of the high prevalence of cancer in the general population and the increasing incidence of most cancers with age, background etiological factors other than treatment are likely to be responsible for a substantial proportion of second cancer, especially in older populations. Therefore, whenever a clinical impression arises that a specific combination of two distinct primary malignancies occurs more frequently than expected, comparison with cancer risk in the general population is imperative. If a SMN has been demonstrated to occur in excess, the contributions of other risk factors and the role of host susceptibility factors should be ruled out convincingly before the risk increase can be attributed to treatment. Even then, host factors may modify treatment effects, so that the risk associated with a given treatment will vary among individuals. The evaluation of the carcinogenic effects of therapy is further complicated by the fact that therapeutic agents are frequently given in combination. Appropriate epidemiologic and statistical methods are required to quantify the excess risk and to unravel treatment factors responsible for it.

In this chapter we address major aspects of SMN risk following treatment for HL. After an overview of the methods used for assessing second cancer risk, we discuss major contributors to second risk, i.e., radiation therapy and chemotherapy. Subsequently, a review is given of the risks of leukemia, non-Hodgkin lymphoma (NHL), and selected solid tumors in patients treated for HL. Emphasis is on large studies that were published recently. Finally, clinical implications of the most important findings are discussed.

26.2 Methods of Assessing Second Cancer Risk

Estimates of second cancer risk after treatment for HL derive from several sources, including population-based cancer registries, hospital-based cancer registries, or clinical trial series. The cohort study and the nested case-control study are the most common epidemiologic study designs used in second cancer research [15, 16]. Case reports have an important role in the early recognition of potential associations between different malignancies. However, because of lack of information on the underlying population at risk, they are not useful in quantifying risks.

In a *cohort study*, a large group of patients (the cohort) with a specified first malignancy is fol-

lowed for a number of years to determine the incidence of second (and subsequent) malignancies. Because most patient cohorts in which second cancer risk has been assessed were identified retrospectively, follow-up of all patients in such studies is completed up to some point in the recent past. To evaluate whether second cancer risk in the cohort is increased compared with cancer risk in the general population, the observed number of SMNs in the cohort is compared with the number expected on the basis of age-, gender-, and calendar year-specific cancer incidence rates in the general population. This can be done in a so-called "person-years" type of analysis. In this approach, adjustment is made for the distribution of the cohort according to age, sex, and calendar period, while the observation period of individual patients (person-years at risk) is also taken into account. The *relative risk* (RR) of developing a SMN is estimated by the ratio of the observed number of SMNs in the cohort to the number expected. In epidemiologic terminology, the *observed-to-expected ratio* is often called the *standardized incidence ratio* (SIR). For cancer deaths, the equivalent measure is the *standardized mortality ratio* (SMR), in which observed second malignancy deaths are compared with expected numbers of deaths.

A disadvantage of the person-years method as applied in its simplest form is that it assumes the risk of SMN development to be constant over time; that is, it assumes the second cancer experience of 1000 patients followed for 1 year to be comparable to that of 100 patients followed for 10 years. When this assumption is inappropriate (as with treatment-related cancers developing after an induction period), it is more informative to calculate SIRs within specified posttreatment intervals (usually 5-year periods) [17, 18]. A temporal trend of excess SMN risk may in itself provide an important initial clue to treatment-related causes; for example, the SIR of solid malignancy following RT for HL generally increases with time since exposure.

When the observed-to-expected ratio is increased, the question arises whether the risk increase is caused by the treatment. This can be evaluated by comparing SIRs between treatment groups, preferably with a reference group of patients not treated with RT or CT. Such a comparison group is unfortunately not available for patients with HL. When the observation period (or survival rate) differs between treatments, their overall observed-to-expected ratios cannot be validly compared without accounting for the difference in length of follow-up. This adjustment for treatment-associated differences in follow-up time (or age) is often done using Poisson regression (see below).

Second cancer risk in the cohort (and in different treatment groups) can also be expressed by the *cumulative* (actuarial estimated) *risk* [19], which gives the proportion of patients expected to develop a SMN by time t (e.g., 5 years from diagnosis) if they do not die before then. When the cohort's death rate from causes other than SMNs is high, the assumption of "non-informative censoring" underlying the actuarial method is often not valid. In particular, the assumption that patients who died due to other causes would have the same temporal pattern of SMN risk as those who survived is incorrect. In such cases actuarial risk tends to overestimate the true risk and *competing-risk techniques* should be used to estimate cumulative risk [15, 20–23]. In comparing estimates of cumulative risk across studies, it is important to keep in mind that this measure of risk depends strongly on the age distribution of a specific cohort; because of the low background incidence of cancer at young ages, cohorts of HL patients including childhood HL will report much lower cumulative risks than cohorts including adults only.

Most studies reporting cumulative risks make no comparison with cancer risk in the general population, yet population-expected cumulative risks over time can be easily calculated on the basis of cancer incidence rates from a population-based registry [24]. Because certain treatment-related cancers are rare in the general population (e.g., leukemia, sarcoma), a high SIR (compared to the population) may still translate into a rather low cumulative risk. *Absolute excess risk* (AER),

which estimates the excess number of SMNs occurring per 10,000 patients per year (beyond those expected to occur based on cancer rates in the general population), best reflects the clinical burden of SMN in a cohort. Consequently, this risk measure is also the most appropriate one to judge which second malignancies contribute most to the excess morbidity or mortality.

The calculation of observed-to-expected ratios on the basis of person-years analysis, and the calculation of cumulative risks using life table analysis, involves rather simple statistical methods, which have a strong intuitive appeal. Besides these elementary methods, statistical modeling with Cox proportional hazards model and Poisson regression techniques is increasingly being used to refine the quantification of second cancer RRs (e.g., by estimating dose- and time-response relationships) and to examine the interplay between treatment variables and other factors [25–27].

Each of the data sources that are commonly used to constitute cohorts has specific advantages and disadvantages. *Population-based cancer registries* have large numbers of patients available, which allows the detection of even small excess risks of second cancers [27–30]. An additional advantage is that the observed and expected numbers of cancers come from the same reference population. Disadvantages include limited availability of treatment data and underreporting of SMNs [13, 30, 31] (in particular hematologic malignancies). Population-based registries differ greatly in these aspects and hence in their usefulness for second cancer studies. If treatment data are not available, it is impossible to know whether excess risk for a SMN is related to treatment or to shared etiology with the first cancer. Underreporting of SMNs clearly leads to an underestimation of second cancer risk. Far higher risks of second leukemia following HL have been found in hospital series [11, 32] than in population-based studies [29]. Part of this difference, however, may be attributable to the more intensive treatments administered in large treatment centers [33]. Despite their disadvantages, population-based registries are well suited to evaluate broadly which SMNs occur in excess following a wide spectrum of different first primary malignancies. They are also a valuable starting point for case-control studies that evaluate treatment effects in detail (see below).

A major advantage of *clinical trial databases* is that detailed treatment data on all patients are available. Comparison of SMN risk between the treatment arms of the trial controls for any intrinsic risk of SMNs associated with the first cancer. However, a limitation of most trials is the small number of patients involved. Although this problem can be overcome by combining data from a number of trials [34], multicenter trial series pose other problems. For example, the main end points of interest in most clinical trials are treatment response and survival, and many trials neither collect information on treatment for recurrences nor on long-term occurrence of SMNs, so that follow-up data to a fixed end date may be very incomplete (and biased). Ideally, routine reporting and assessment of SMN risk should become an integral part of clinical trial research [15, 35, 36].

Most *hospital-based tumor* registries have been in existence for decades and collect extensive data on treatment and follow-up. They share the advantages of clinical trial databases and sometimes have better opportunities to obtain long-term follow-up data. Investigators using hospital tumor registries have ready access to the medical records; often a review of the histologic slides of the first and the second malignancy can also be arranged easily. An additional advantage is that, compared with trial data, hospital registries provide a wider range of treatments and dose levels, which may yield important information on drug and radiation carcinogenesis. Most studies of second cancer risk following HL have been based on hospital registries [8, 32, 37, 38]. As with trial data, however, loss to follow-up and surveillance bias compared to population-based studies can be problematic.

The cohort study is not an efficient study design for detailed examination of the association of treatment factors (e.g., cumulative dose of alkylating agents) with second cancer risk.

Large cohorts are required to yield reliable estimates of second cancer risk, rendering the collection of detailed treatment data for all patients prohibitively expensive and time consuming. In such instances, the so-called nested case-control study within an existing cohort is the preferred approach [15]. The case group consists of all patients identified with the SMN of interest, and the controls are a random sample of all patients in the cohort who did not develop the cancer concerned, although they experienced the same amount of follow-up time. To achieve maximum statistical power, most case-control studies of second cancer risk use a design in which more than one control is individually matched to each second cancer "case." Matching factors employed in most studies include sex, year of birth, and year at diagnosis of the first primary cancer. The most important criterion for control selection is that each control must have survived, without developing the SMN of interest, for at least as long as the interval between the diagnosis of the first and the second malignancy of the corresponding case. Even if the control group is three times as large as the case group, detailed treatment data need to be collected for only a small proportion of the total cohort. It is critical to the validity of the study results that the controls are truly representative of all patients who did not develop the second cancer of interest. In the analysis of a case-control study of second cancer risk, treatment factors are compared between cases and controls. Treatments that have been administered more often, for a longer duration, or with a higher dose to the case group than to the controls are associated with increased risk of developing the SMN of interest. It is important to understand that in a nested case-control study, the risk associated with specific treatments is estimated relative to the risk in patients receiving other treatment and *not* relative to the risk in the general population. The cumulative risk of developing a SMN cannot be derived using data from a case-control study alone. Estimates of the AERs associated with specific treatments can be derived, however, if the case-control study follows a cohort analysis in which observed-to-expected ratios were calculated for broad treatment groups. Although case-control methodology has only come into widespread use for the investigation of SMN risk in recent decades, several landmark studies have already demonstrated its strengths [33, 39–42].

26.3 Magnitude of the Risk Increase of Second Malignancy, Temporal Patterns, and Age Effects

The largest overall SIR (10- to 15-fold increase) compared to the general population is observed for leukemia (with the greatest risk seen for AML (22-fold), followed by a 6- to 14-fold increased risk for non-Hodgkin lymphoma (NHL), and 4- to 12-fold excesses for connective tissue, bone, and thyroid cancer) (Table 26.1). Moderately increased risks (two- to ninefold) are observed for a number of solid tumors, such as cancer of the lung, stomach, esophagus, colon, rectum, breast, cervix, and mouth and pharynx and melanoma (Table 26.1) [27, 43–48]. Because leukemia and NHL are diseases with a low incidence in the population, even a high relative risk compared to the population translates into a relatively low cumulative risk.

Many studies show that, over the long term, the cumulative risk of solid tumors far exceeds that of leukemia and NHL (e.g., 30-year cumulative risks of 28.5% for solid tumors compared to a 25-year cumulative risk of 3% for leukemia, respectively) (Tables 26.2 and 26.3) [32, 45]. Several studies [32, 44–47] show that, compared with the general population, HL patients experience an excess of about 45–80 malignancies per 10,000 person-years of observation (Tables 26.2 and 26.3). Solid tumors account for the majority of excess cancers (approximately 30–60 per 10,000 patients per year), with lung cancer contributing 10–12 excess cases per 10,000 person-years. Leukemia and NHL each account for about 8–9 cases per 10,000 person-years.

Table 26.1 Relative risks of second malignancy after HL for selected sites in large[a] cohort studies published since 2003

	Bhatia et al. [43]	Hodgson et al. [27]	Swerdlow et al. [44]		Schaapveld et al. [45]	Sud et al [46]
	USA	International	Britain		Netherlands	Sweden
	$N = 1380$[b]	$N = 18862$[b]	$N = 5798$[b]		$N = 3905$[b]	$N = 9522$
	Ages ≤ 16 years	All ages	All ages		Ages <51 years	All ages
	Med. fup 17 years	Med. fup 12.2 years			Med. fup 19.1 years	Mean fup 12.6 years
	Years of dx 1955–1986	Years of dx 1970–1997	Years of dx 1963–2001		Years of dx 1965–2000	Years of dx 1965–2012
		RR[c] (*n* observed)	SIR (*n* observed)			SIR (*n* observed)
Site	SIR (*n* observed)		Chemo[d]	Ch + RT[d]	SIR (*n* observed)	
All sites	18.5[e] (143)	–[f]	2.0[e] (157)	3.9[e] (302)	4.6[e] (884)	2.4[e] (1121)
All solid	18.5[e] (109)	–[f] (1490)	–[f]	–[f]	4.2[e] (757)	–
Leukemia	174.8[e] (27)	– (–)[f]	18.4[e] (33)	22.7[e] (42)	9.5[e] (41)	6.5[e] (79)
NHL	11.7[e] (7)	– (–)[f]	11.5[e] (31)	17.1[e] (51)	13.4[e] (104)	8.0[e] (125)
Female breast	55.5[e] (39)	6.1[g] (–)	0.5 (5)	2.4[e] (30)	4.7[e] (183)	2.5[e] (146)
Lung	27.3[e] (4)	6.7[c] (–)	2.9[e] (40)	5.1[e] (60)	6.4[e] (176)	3.6[e] (138)
Stomach	63.9[e] (3)	9.5[c] (–)	1.1 (4)	2.7[e] (8)	7.4[e] (39)	1.8[e] (31)
Colon	36.4[e] (8)	4.3[c] (–)	1.1 (10)	2.0[e] (17)	2.9[e] (42)	2.2[e] (83)
Pancreas	–[f]	4.7[c] (–)	1.0 (2)	2.9 (5)	5.7[e] (23)	2.1[e] (28)
Bone	37.1[e] (8)	– (–)[f]	0	9.0[e] (2)	–[f]	–[f]
Soft tissue	–[f]	– (–)[f]	0	8.9[e] (5)	12.0[e] (22)	5.7[e] (20)
Bone and soft tissue	–[f]	11.7[c] (–)	–[f]	–[f]	–[f]	
Melanoma	–[f]	1.6[c] (–)	0.5 (1)	2.7[e] (7)	2.8[e] (34)	2.1[e] (42)
Cervix	–[f]	2.2[h] (–)	1.4 (2)	2.7 (6)	–[f]	–[f]
Thyroid	36.4[e] (19)	3.1[i] (–)	2.3 (1)	5.7[e] (3)	14.0[e] (23)	5.1[e] (20)

NHL non-Hodgkin lymphoma, *Med. Fup* median follow-up, *Years of dx*, years of diagnosis; *RR*, relative risk; *n*, number of second malignancies

[a]Only includes studies with ≥100 second malignancies; for cohorts included in several reports, only the paper with the longest follow-up is included

[b]Number of Hodgkin disease patients included in the study

[c]RRs are for males and females combined and for individuals diagnosed with HL at age 30 years and attained age range 40–60 years

[d]Chemo refers to patients treated with chemotherapy only; Ch + RT refers to patients treated with chemotherapy plus radiotherapy

[e]Significantly raised ($P < 0.05$)

[f]Data not published

[g]RR is for women diagnosed with HL at age 30 years and attained age 40 years

[h]RR is for all female genital second cancers

[i]RR is for individuals diagnosed with HL at age 30 years and all attained ages

Although SMN risks are often summarized as a single relative risk (SIR) or AER value for the sake of simplicity, it is important to recognize that variation over time is one of the fundamental features of second cancer risk. Further, the nature of this variation is different for different second malignancy sites, and ages at treatment, and additionally relative risks vary over time differently than AERs (Figs. 26.1 and 26.2). Consequently, no single risk value fully describes the SMN risk that patients experience at different times after treatment. Leukemia risk increases approximately 2–4 years following alkylator-based chemotherapy, with the SIR peaking 5–9 years after treatment and decreasing thereafter [32, 33, 44, 45, 47, 52–54]. The SIR of NHL is increased in the first 5 years after treatment, and study findings disagree regarding whether NHL risk

Table 26.2 SIR, AER, and cumulative incidence of second malignancy among HL survivors in selected studies

	Hodgson et al. [27]	Swerdlow et al. [44]		Schaapveld et al. [45]	Sud et al [46]
	International	Britain		Netherlands	Sweden
	N = 18,862[b]	*N* = 5798[b]		*N* = 3905	N=9522
	All ages	All ages		15–50 years	All Ages
	Med. fup 12.2 years	Dx yrs 1963–2001		Med. fup 19.1 years	Mean fup 12.6 years
	Dx yrs 1970–1997			Dx yrs 1965–2000	Dx yrs 1965–2012
		Chemo	Ch+RT		
All cancers					
SIR	(–)	2.0	4.6	3.9	2.4
AER	(–)	32.9	121.8	65.3	71.2
CI	(–)	20 year = 13%	30 years = 32.5%	20 year = 18%	
All solid					
SIR	4.6[b], 3.7[c]	(–)	4.2	2.0	(–)
AER	(–)	(–)	100.5	33.1	(–)
CI	30 years = 18.3% (M)[d] and 26.1% (F)[d]	(–)	30 years = 28.5%	25 years = 21.9%	(–)
Breast cancer					
SIR	6.1	0.5	4.7	2.4	2.5
AER	61[f]	−1.8	54.3	5.1	9.2
CI	(–)		30 years = 16.6%		
(Acute) leukemia					
SIR	(–)	18.4	(–)	22.7	6.5
AER	(–)	12.8	(–)	11.7	6.9
CI	(–)		(–)		

SIR standardized incidence ratio, *AER* absolute excess risk, *CI* cumulative incidence
[b]Supradiaphragmatic sites
[c]Infradiaphragmatic sites
[d]Diagnosed at age 30
[f]AER predicted for a 30-year-old female attained age 50

increases [11, 54] or remains constant over time [37, 44, 47, 53].

Most studies report that the overall SIR of solid tumors is minimally elevated in the 1–4-year follow-up period and increases thereafter [11, 32, 37, 45, 47, 53–55]. In studies that include data on HL patients who survived 20 years or more, the RR of solid tumors continued to increase through the 15- to 20-year follow-up period and stabilized thereafter [32, 37, 38, 43–45, 47, 49–56]. A recent Dutch study of patients diagnosed with HL before age 50 reported that the SIRs of solid tumors remained very stable up to 35 years after HL, without much evidence of a decrease in very long-term survivors [45]. Reports from the Late Effects Study Group on survivors of pediatric HL and the US Childhood Cancer Survivor Study reported a stable 20- to 24-fold increased relative risk from 15 to over 30 years after diagnosis [43, 49]. An international registry-based study of 5-year HL survivors employed Poisson

Table 26.3 SIR, AER, and cumulative incidence of second malignancy among pediatric HL survivors

	Castellino et al. [49]	Bhatia et al. [43]	Basu et al. and Constine et al. [50, 51]
	USA	USA	USA
	1675	*N* = 1380	*N* = 930
	Ages <21 years	Ages ≤16 years	Ages <19 years
	Med. fup 23.8 years	Med. fup 17 years	Med. fup 16.8 years
	Years of dx 1970–1986	Dx years 1955–1986	Dx years 1960–1990
All cancers			
SIR	8.7	18.5	14.2
AER	69.2	65[a]	62.6
CI	30 years = 10.9% (M) and 26.1% (F)	30 years = 26.3%	20 year = 8% (M) and 23% (F)
All solid			
SIR	(–)	18.5	(–)
AER	(–)	51[a]	(–)
CI	(–)	30 years = 23.5%	(–)
Breast (females)			
SIR	17.0	55.5	37.3
AER	29.0	53[a]	18.6
CI	30 years = 18.3%	30 years = 16.9%	30 years = 24%
Acute leukemia			
SIR	12.7	174.8	21.5
AER	3.4	1.3	5.7
CI	(–)	20 years = 2.1%	(–)

SIR standardized incidence ratio, *EAR* excess absolute risk, *CI* cumulative incidence
[a]Results were published per 1000 person-years. For consistency these have been multiplied by 10 (i.e., 10,000 P-Y)

regression methods comparable to those used to evaluate the temporal trends of cancer risk among atomic bomb survivors [27]. Variation in the risk of solid cancer was found to depend strongly on age at exposure, and attained age, with distinctly different patterns for female breast cancer, thyroid cancer, and other solid tumors (Fig. 26.3). With increasing attained age, the relative risk of breast cancer declined among females diagnosed at a young age (modeled age 20 years), whereas this decline was much less pronounced among women treated at older ages (30 or 40 years at HL diagnosis) (Fig. 26.2). In contrast, the relative risk of other solid cancers remained stable with advancing attained age, with a small decline after attained age of 60 years (Fig. 26.1). The AER of breast cancer and non-breast solid cancers increased with increasing attained age for all age groups [27] (Figs. 26.1 and 26.2). These findings demonstrate the importance of considering both age at exposure and attained age in the evaluation of SMN risk, as well as the potential importance of considering different solid cancers separately. Combining different age-at-treatment groups or all solid tumor types together may obscure significant variation in risks over time that can occur among different age groups or different SMN types. Also, the AER of SMNs changes over time differently than the SIR (Figs. 26.1 and 26.2). With increasing time since treatment, the major influence on the AER is the increasing background (i.e., "expected") rate of cancer, which rises rapidly with increasing age. As these baseline risks increase with advancing age, even stable elevations in SIRs translate into rising AER over time (Fig. 26.1).

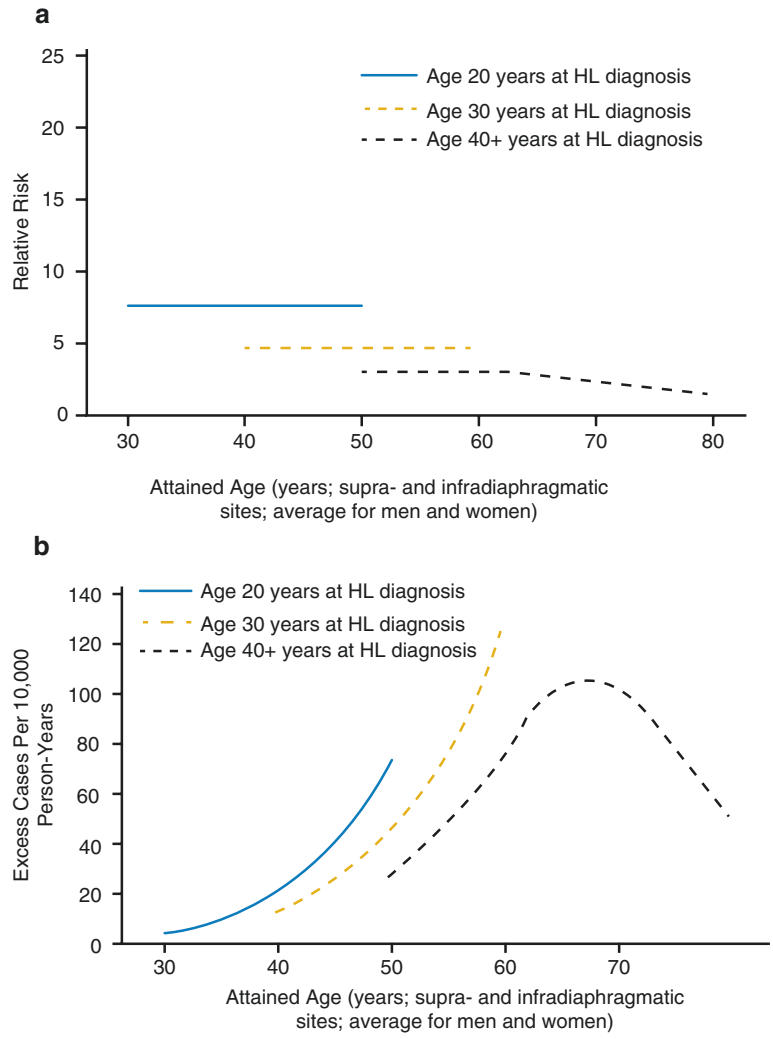


Fig. 26.1 Relative risk (*RR*) and absolute excess risk of supra- and infradiaphragmatic solid cancers according to age at HL diagnosis and attained age. (**a**) RR of supra- and infradiaphragmatic solid cancers. (**b**) AER of supra- and infradiaphragmatic solid cancers (From: Hodgson et al. [27])

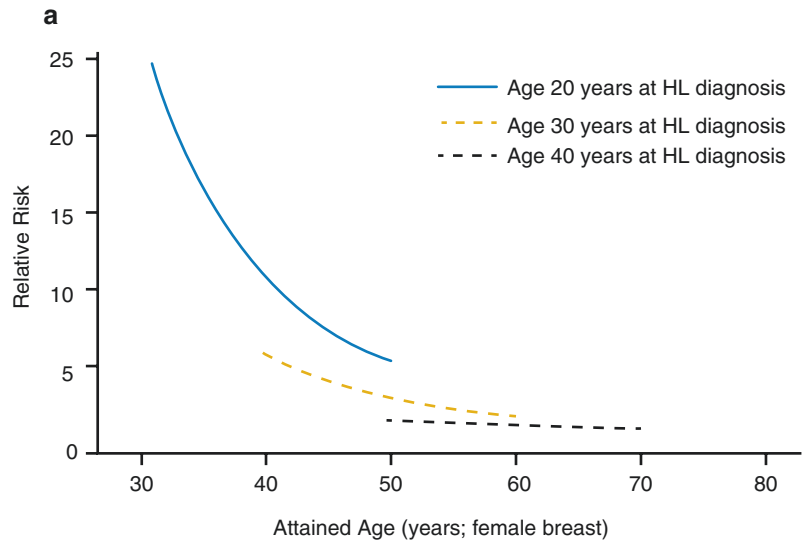


Fig. 26.2 Relative risk (*RR*) and absolute excess of female breast cancer according to age at HL diagnosis and attained age. (**a**) RR of female breast cancer. (**b**) AER of female breast cancer (From: Hodgson et al. [27])

Fig. 26.2 (continued)

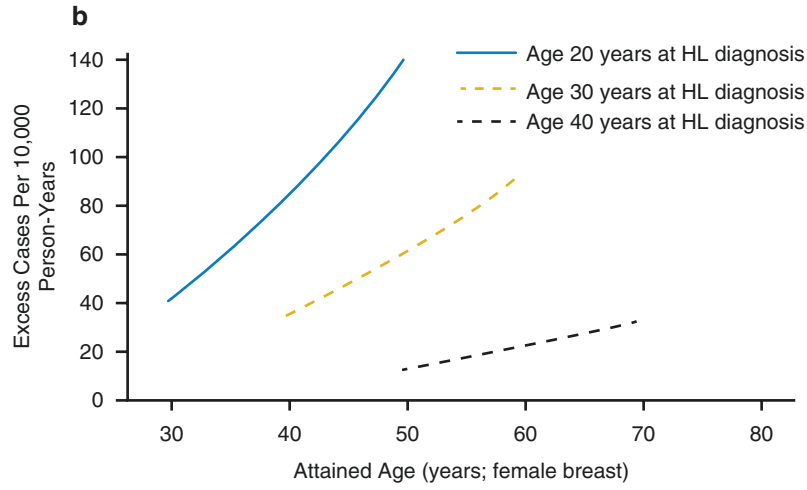
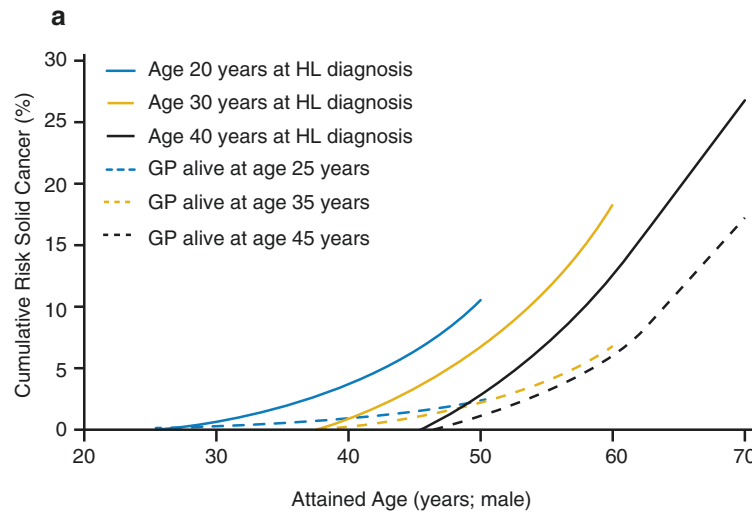
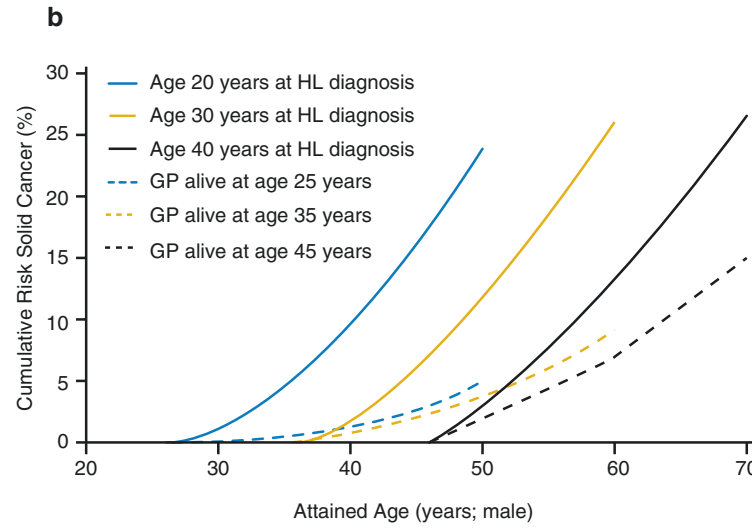


Fig. 26.3 (**a**) Cumulative incidence of all solid cancers among 10,619 male 5-year survivors of Hodgkin lymphoma (HL) compared with men of the same age in the general population (GP). (**b**) Cumulative incidence for 8243 female 5-year survivors compared with women of the same age in the GP (From: Hodgson et al. [27])





26.4 Contributors to Second Cancer Risk

26.4.1 Radiation Therapy

Increased risks of second cancers following RT for HL have been reported for over two decades [29]. These reports add to a substantial body of evidence demonstrating that radiation is carcinogenic over a broad range of doses and can increase the risk of a variety of different tumor types [57–61]. Certain tissues, such as the female breast, and thyroid appear to be particularly susceptible to radiation-induced malignancy.

Among HL patients, treatment with mantle RT (involving the axillary, mediastinal, and neck nodes) to doses of 35–45 Gy is associated with a 2- to 20-fold increased relative risk of breast cancer, with a strong influence of age at exposure, as discussed in detail below [24, 27, 32, 37, 43, 45, 60, 62]. Mantle RT is also associated with an increased relative risk of lung cancer, although the absolute excess risk is in fact small in the first 10–20 years after exposure, particularly among those treated at young ages (e.g., ≤0.2 per 10,000 person-years among those treated before age 20 years) [43, 52]. The risks of other solid cancers, especially stomach cancer, have also been shown to be elevated after RT [40].

Much of our current understanding of the relationship between radiation dose and cancer risk has been derived from cohort studies of individuals exposed to low levels of radiation, such as atomic bomb survivors [60, 63–65]. However, extrapolation of the dose-risk relationships seen at low total body doses into the 15–40 Gy ranges used for HL RT cannot be done with certainty, due to differences relating to dose rate, neutron exposure, and the possibility of cell killing at high doses. More recently, studies of SMN risk have evaluated the dose-risk relationship in the radiation dose range commonly used in the treatment of HL.

There appears to be an approximately linear increase in the risk of leukemia with increasing radiation dose to the bone marrow, up to approximately 2–4 Gy [66–68]. At doses above this, the risk of leukemia per unit radiation dose to the bone marrow appears to decline [66–68], a finding generally attributed to killing or inactivation of preleukemic cells at the higher radiation doses [66, 69]. One study of leukemia risk in survivors of uterine cancer, however, showed little evidence for such a clear downturn in risk [67].

The "bell-shaped" dose-risk curve for leukemia, with a peak at 2–4 Gy, does not seem to apply to the risk of most solid tumors. Most studies examining the dose-risk relationship for solid tumors suggest a continued increase in risk with doses up to approximately 40 Gy [41, 42, 70, 71]. Three studies have evaluated the relationship between radiation dose and breast cancer risk among adult females treated for HL with mantle RT [41, 42, 72]. The RT dose to the area of the breast where the case's tumor had developed was estimated for each case-control set based on simulation films of the original HL radiotherapy and mammograms indicating the position of the breast tumor. All studies showed increasing risk of breast cancer over the dose range commonly used in the treatment of HL. For example, in a large international collaborative case-control study of women treated for HL at age 30 years or less [42] (105 patients with breast cancer after HL and 266 controls without breast cancer), the risk was eightfold increased (95% CI, 2.6–26.4) for the highest dose category (median dose of 42 Gy) compared to the lowest one (<4 Gy) (P trend <0.001, Table 26.4) [42]. Similarly, a recent Dutch case-control study estimated radiation dose to the site of breast cancer for 174 breast cancer cases and 466 controls [72]. The investigators reported a linear increase in breast cancer risk with increasing dose, with an excess odds ratio (EOR) of 6.1%/Gy (adjusted for duration of post-RT ovarian function). Compared to those with <3 Gy to the breast, the odds ratio of breast cancer was 4.7-fold higher among those with breast exposures of ≥36 Gy (Fig. 26.4).

The risk of lung cancer also rises with increasing radiation dose up to 40 Gy and with an increasing volume of lung irradiated (Table 26.4) [73, 74]. Similarly, an international case-control study (32 cases and 71 matched controls) showed that risk of esophageal cancer in HL survivors increased with higher radiation doses with a radi-

Table 26.4 Relative risks of breast, lung, and stomach cancers after Hodgkin lymphoma, according to radiation dose to affected site in breast/lung/stomach and number of cycles of alkylating chemotherapy[a,b]

Breast cancer[a]			Lung cancer[b]			Stomach cancer[c]		
Radiation dose to affected site in breast	Relative risk	95% CI	Radiation dose to affected site in lung	Relative risk	95% CI	Radiation dose to affected site in stomach	Relative risk	95% CI
0–3.9 Gy	1.0	(Referent)	0	1.0	(Referent)	0	1.0	(Referent)
4.0–6.9 Gy	1.8	0.7–4.5	>0–4.9 Gy	1.6	0.5–5.2	>0.1–0.9 Gy	1.3	0.4–4.1
7.0–23.1 Gy	4.1	1.4–12.3	5–14.9 Gy	4.2	0.7–21	1.0–4.9 Gy	1.0	0.3–3.5
23.2–27.9 Gy	2.0	0.7–5.9	15.0–29.9 Gy	2.7	0.2–15	5.0–24.9 Gy	0.5	0.1–2.7
28.0–37.1 Gy	6.8	2.3–22.3	30.0–39.9 Gy	8.5	3.3–24	25.0–34.9 Gy	4.6	1.2–20.5
37.2–40.4 Gy	4.0	1.3–13.4	≥40.0 Gy	6.3	2.2–19	35.0–39.9 Gy	8.2	2.6–29.7
40.5–61.3 Gy	8.0	2.6–26.4				≥40.0 Gy	4.2	1.2–15.6
No. of cycles of alkylating agents								
0	1.0	(Referent)	0	1.0	(Referent)	0	1.0	(Referent)
1–4	0.7	0.3–1.7	1–4	4.0	1.3–12.5	1–5	1.0	0.5–2.4
5–8	0.6	0.3–1.1	5–8	6.2	2.6–17.1	6	1.7	0.7–4.4
≥9	0.2	0.1–0.7	≥9	13.0	4.3–45	7–10	1.9	0.7–4.9
						≥11	3.0	1.2–7.7

[a]Adapted from results by Travis et al. [42]
[b]Adapted from results by Gilbert et al. [72]
[c]Adapted from results by Morton et al. [40]

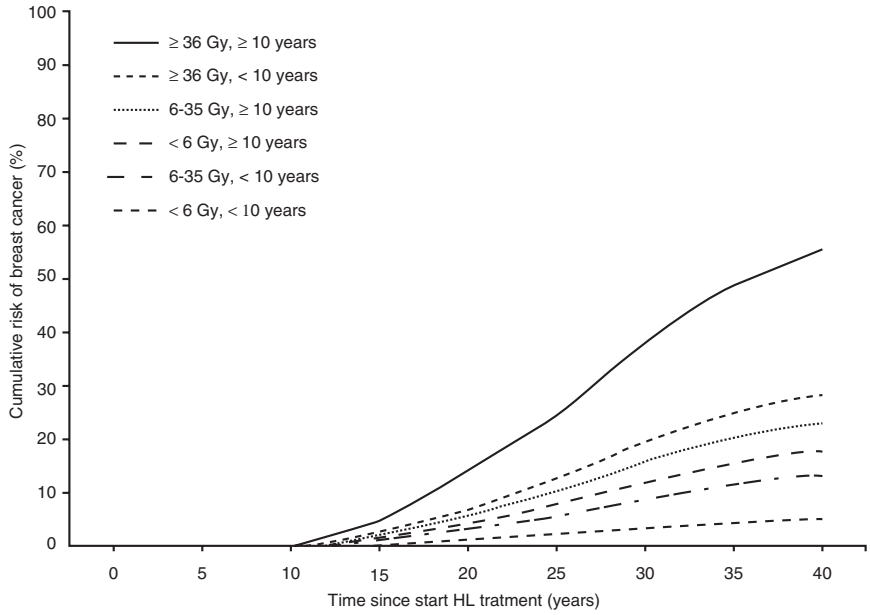


Fig. 26.4 Estimated cumulative incidence of breast cancer in female Hodgkin lymphoma survivors for tertiles of radiation dose to breast tumor location and duration of post-RT intact ovarian function (greater or less than 10 years intact). Cumulative risks among 10-year survivors treated with death as competing risk, estimated form ORs derived from case-control data relative to the cumulative breast cancer risk for the entire cohort, assuming that the distribution of all individuals in the cohort across dose categories was equal to that for the controls (From: Krul et al. [72])

ation dose response compatible with a linear increase in risk (EOR/Gy = 0.38) [75]. Furthermore, two studies in survivors of childhood cancer [76, 77] suggest that the risk of bone sarcoma increases rapidly with increasing dose above 10 Gy [78]. An international case-control study of stomach cancer nested in a cohort of 19,882 HL survivors found that stomach doses ≥25 Gy were associated with a significantly elevated risk of gastric cancer particularly when also given procarbazine-containing chemotherapy [40]. Risk increased with larger radiation doses to stomach up to 40–44 Gy (Table 26.4). Similarly, van den Belt et al. reported that the risk of stomach cancer increases linearly with radiation dose to the stomach, with tenfold increased risk for mean stomach doses of >20 Gy compared to less than 11 Gy [79]. A case-control study, evaluating risk of pancreatic cancer after HL treatment, again found an increased risk with higher radiation dose to the pancreas, with an odds ratio of 9.1 at doses ≥40 Gy compared to patients who received a pancreatic dose <0.5 Gy (adjusted for number of alkylating agent containing cycles of chemotherapy) [80]. Radiation-induced thyroid cancer may be an exception to these general findings for other solid cancers: dose-risk studies have suggested a leveling or decrease in thyroid cancer risk with doses above 10–30 Gy [61, 81, 82] although one study reported increasing risk of thyroid cancer with increasing dose up to 60 Gy [83].

Although no studies have evaluated the association of radiation dose to the colon and subsequent colon cancer risk, several studies observed increased cancer risk after subdiaphragmatic irradiation. In the study by van Eggermond et al. the risk of rectal cancer was 6.3-fold increased and the risk of colon cancer 6.0-fold and the risk among patients treated with inverted-Y irradiation compared to general population rates, with highest risk observed for transverse colon cancer (SIR 15.0; 95% CI, 4.3–40.8) [52]. Compared to patients not treated with infradiaphragmatic radiation therapy and a procarbazine dose ≤4200 mg/m^2, CRC risk was 6.8-fold higher for patients who had infradiaphragmatic radiation therapy and had received a procarbazine dose >4200 mg/m^2.

The treatment of large volumes of normal tissues in pediatric patients, even with lower prescribed doses of 15–36 Gy, was still associated with substantially increased risks of second malignancy in one study [84], illustrating the importance of not only limiting the prescribed dose but also reducing the volume of normal tissue irradiated (and hence the normal tissue dose) compared to historic mantle or extended-field RT.

These dose-risk studies provide a critical component to understanding the potential risk of second cancers associated with contemporary involved field RT (IFRT) or involved node/site RT (INRT/ISRT for HL). Specifically, they suggest that reduction in normal tissue dose associated with reducing the prescribed dose from 36–40 to 20–30 Gy and reducing the volume of irradiated normal tissue by omitting uninvolved nodal regions from the RT volume should produce a lower risk of most solid SMN, perhaps with the exception of thyroid cancer. Data are emerging that this is the case. One study found that for patients with mediastinal disease, the transition from mantle fields to mediastinal IFRT resulted in an approximately 65% reduction in breast tissue exposure, largely due to the exclusion of the axillae [85], and clinical studies provide evidence that this volume-related reduction in breast exposure appears to translate into a reduced risk of subsequent breast cancer. A large Dutch study, including 1122 female 5-year survivors of HL, examined the effect of radiation fields (volume) on the risk of breast cancer up to more than 30 years after treatment of HL [24]. Mantle field irradiation was associated with a 2.7-fold (95% CI, 1.1–6.9) increased risk of breast cancer compared to similarly dosed (36–44 Gy) radiation to the mediastinum alone (Fig. 26.5) [24]. This finding, which was recently confirmed in a much larger Dutch cohort, with updated follow-up, is reassuring since present-day radiotherapy for HL employs smaller radiation volumes which have been shown to reduce normal tissue doses [24, 45, 86, 87].

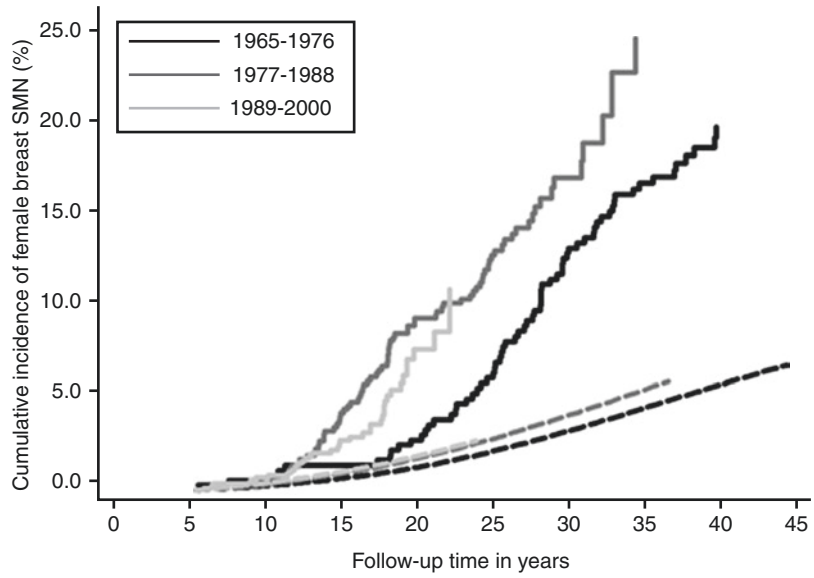


Fig. 26.5 The cumulative incidence of breast cancer after HL according to period treatment among 1698 female 5-year survivors of Hodgkin lymphoma age 15–50 years at first Hodgkin lymphoma treatment. Solid lines represent the observed incidence, dashed lines the expected incidence (From: Schaapveld et al. [45])

26.4.2 Chemotherapy

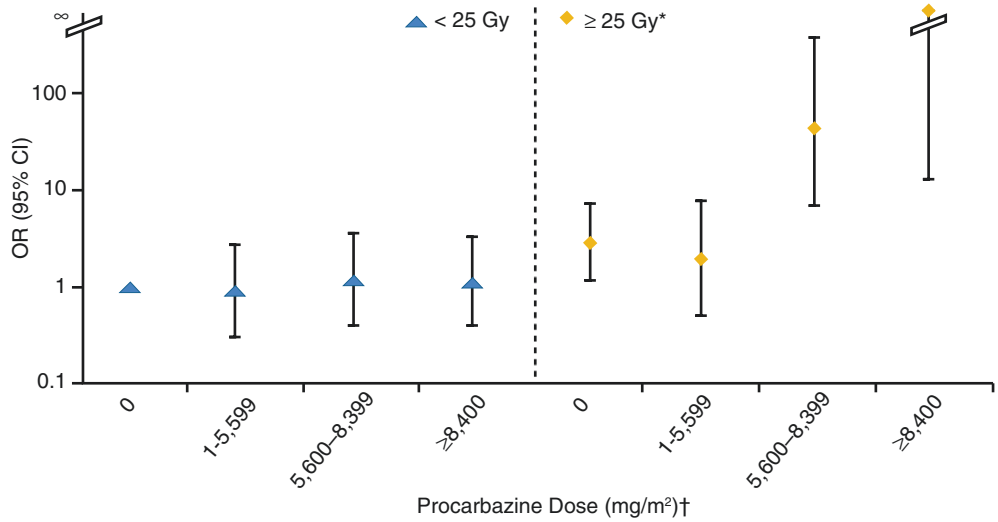
There is a well-established association between exposure to alkylating chemotherapy agents and an increased risk of acute myeloid leukemia (AML) in HL survivors. The MOPP chemotherapy regimen (mechlorethamine, vincristine, procarbazine, and prednisone) was widely employed in the 1970s, as it became evident that it was superior to RT alone in curing high-risk HL. However, it was associated with an increased relative risk of AML of 20- to 50-fold [11, 54, 88–92]. The cumulative dose of alkylating agents appears to be the strongest determinant of risk [14, 88, 93, 94]. Most cases of alkylating agent-induced AML are preceded by myelodysplasia (MDS), which generally progresses to AML within a year [54, 94–96]. Cytogenetic studies of alkylator-induced AML/MDS have shown unbalanced chromosome aberrations, primarily with loss of whole chromosomes 5 and/or 7 or various parts of the long arms of these chromosomes [94, 96, 97].

Several more recent studies suggest that topoisomerase II inhibitors, such as doxorubicin and 4-epidoxorubicin (epirubicin), may also be associated with increased risks of AML [33, 97, 98], but this association is not nearly as well established as it is for alkylating agents and requires further study. Certainly, ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine) is associated with a much lower risk of AML than MOPP chemotherapy, although it is not clear that this risk is eliminated altogether [44, 54, 99]. Etoposide, used in HL chemotherapy regimens such as BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) and OEPA (vincristine, etoposide, prednisolone, doxorubicin), is also leukemogenic [100, 101]. As compared with "classical" alkylating agent-induced AML, etoposide-related AML typically occurs sooner after exposure, generally lacks a preceding myelodysplastic phase, and is characterized by balanced translocations involving chromosome bands 11q23 and 21q22 [14, 94, 102–104].

Evidence increasingly suggests that chemotherapy also may play a role in the development of non-hematologic SMNs, which typically occur >10 years after exposure [14, 105]. Alkylating agents have been reported to increase risks for lung, thyroid, gastrointestinal, and bladder cancers as well as sarcoma. For example, lung cancer risk after HL is increased 2- to 4-fold with increasing number of cycles of alkylating agent-containing chemotherapy, particularly MOPP [39, 43, 44, 74, 106, 107]. Among childhood cancer survivors, receipt of any alkylating agent has been associated with 2.4-fold increased risk for

thyroid cancer; receipt of procarbazine and platinum has been associated with 3.2- and 8.6-fold increased risk, respectively, of gastrointestinal cancer, and both alkylating agents and anthracyclines have been associated with sarcoma risk [52, 75, 108–110].

The causal link between cyclophosphamide and bladder cancer represents one of the few established relationships between a specific alkylating agent and carcinogenesis at a specific site, likely as a result of direct genotoxic exposure of bladder epithelium from cyclophosphamide metabolites [111, 112]. Procarbazine-related risks for the gastrointestinal tract also may be related to direct exposure [40, 52, 80, 109, 113]. For procarbazine and risks of cancers of the stomach and pancreas, dose-dependent effects have recently been found in survivors of HL [40, 79]. Furthermore, patients who received both radiation to the stomach ≥25 Gy and high-dose procarbazine (≥5600 mg/m^2) had strikingly elevated stomach cancer risk (RR, 77.5; 95% CI, 14.7–1452) compared with those who received radiation <25 Gy and procarbazine <5600 mg/m^2. Risk was also elevated (RR, 2.8; 95% CI, 1.3–6.4) among patients who received radiation to the stomach ≥25 Gy but procarbazine <5600 mg/m^2; however, no procarbazine-related risk was evident with radiation <25 Gy (Fig. 26.6). Treatment with dacarbazine also increased stomach cancer risk (RR, 8.8; 95% CI, 2.1–46.6), after adjustment for radiation and procarbazine doses [40]. In a recent study, risk of colorectal cancer was 3.8-fold (95% CI, 2.2–6.1) after >4200 mg/m^2 procarbazine, adjusted for infradiaphragmatic radiation field. Patients who received both >4200 mg/m^2 procarbazine and infradiaphragmatic radiation therapy had a very high colorectal cancer risk (RR, 6.8; 95% CI, 3.0–15.6), compared to patients receiving none of these treatments [52]. Similarly, pancreatic cancer risk increased with an increase in number of alkylating agent-containing chemotherapy



Patients	n	18	7	6	8	18	5	15	10
	%	21	8	7	9	21	6	17	11
Patients	n	70	24	25	19	28	13	2	0
	%	39	13	14	10	15	7	1	0
	OR‡	1.0	0.9	1.2	1.1	1.9	2.0	43.8	∞
	95% CI	reterent	0.3 to 2.7	0.4 to 3.6	0.4 to 3.2	1.2 to 7.6	0.5 to 8.0	7.4 to 861.9	12.9 to ∞

Fig. 26.6 Risk of stomach cancer after Hodgkin lymphoma in relation to radiation dose to stomach and procarbazine dose (From: Morton et al. [40])

cycles. The odds ratio was 17.9 (95% confidence interval 3.5–158) increased for patients treated with both subdiaphragmatic radiation (≥10 Gy) and ≥6 alkylating agent-containing chemotherapy cycles compared with patients receiving neither of these treatments, with a significantly greater than additive joint effect for these two treatments combined (subdiaphragmatic radiation ≥10 Gy and <6 alkylating agents, OR 3.0 (95% CI, 0.7–17), and subdiaphragmatic radiation <10 Gy and ≥6 alkylating agents, OR 1.8 (95% CI, 0.4–9.7)) [80].

26.4.3 Genetic Factors

There is increasing interest in identifying the molecular and cellular basis underlying the development of SMNs in HL survivors and other cancer survivors. Germline mutations in the RB1 tumor suppressor gene, associated with hereditary retinoblastoma, constitute a well-described example of a rare mutation with high penetrance that confers a large risk of developing radiation-related second cancer [114–116]. Although there is evidence that patients with a family history of cancer are more likely to develop radiation-related SMNs [48, 117–122], it is unlikely that a single candidate gene abnormality will account for a significant component of the SMN risk following HL treatment. Currently, there is no uniform evidence that BRCA1 or BRCA2 gene mutations mediate the development of radiation-related breast cancers. Two studies have reported that mammographic radiation exposure does not significantly contribute to the risk seen in BRCA1/2 mutation carriers [123, 124], though three other studies found that young BRCA1/2 mutation carriers had an increased risk of breast cancer if exposed to a significant number of chest X-rays [125–127]. There have been no studies examining whether carriers of BRCA mutations with HL have an increased risk of RT-associated cancers. Homozygous mutations in the ataxia-telangiectasia (ATM) gene are associated with significant radiation toxicity, although two studies have reported that no ATM mutations were found in women who had developed breast cancer after RT for HL [121, 128]. Moreover, while P53 gene mutations are associated with an increased risk of primary malignancy [129], and increased radiation sensitivity in vitro [130, 131], there is currently no evidence that P53 mutations modify the risk of treatment-related SMN in HL patients.

Outside of the context of cancer predisposition syndromes, most studies have investigated SMN risks in relation to specific genes, selected based on understanding the biologic pathways of drug metabolism and carcinogenesis. These studies have reported associations for variants in oxidative stress, DNA detoxification, and DNA repair genes with treatment-related leukemia [132–138] and *FGFR2* with breast cancer after supradiaphragmatic radiotherapy for HL [139].

Methylating agents (e.g., dacarbazine) produce DNA damage, the repair of which is mediated in part by the MLH1 gene. Worrillow et al. examined the frequency of a common MLH1-93 polymorphism among patients who developed cancer following chemotherapy and/or radiotherapy, or were diagnosed with de novo myeloid leukemia or HL, and healthy controls [134]. Carrier frequency of the MLH1-93 variant was higher in patients who developed therapy-related AML or breast cancer after methylating chemotherapy for HL compared to patients without previous methylating exposure.

More recently, genome-wide association studies (GWAS), which agnostically interrogate hundreds of thousands to millions of variants across the genome [140], have revealed genomic regions associated with treatment-related leukemia [141] and with SMNs occurring among HL survivors initially treated with radiotherapy [142–144], supporting the idea of genetic susceptibility to treatment-related SMNs. A recent Dutch study used a GWAS approach to investigate the modifying effects of SNPs on the risk of radiation-induced breast cancer in an international case-case analysis including 327 breast cancer patients after chest RT for HL and 4671 first primary breast cancer patients from the international cohort [143]. Nine SNPs showed statistically significant interaction with RT on breast cancer risk. A polygenic risk score (PRS) composed of these SNPs (RT-interaction-PRS) and a previously

published breast cancer PRS derived in the general population were evaluated in a case-control analysis comprising the 327 HL patients with breast cancer and 491 chest-irradiated HL patients without breast cancer. Patients in the highest tertile of the RT-interaction-PRS had a 1.6-fold higher breast cancer risk than those in the lowest tertile. After external validation this RT-interaction-PRS can be incorporated in risk prediction models for HL patients. Remarkably, the authors observed a 4-fold increased RT-induced risk in the highest compared with the lowest decile of the breast cancer PRS, similar to the effect size found in the general population. Morton et al. also recently reported results of a GWAS study, investigating modification of radiation-induced BC risk by SNPs. Pooling data from the US Childhood Cancer Survivor Study and the St. Jude Lifetime Cohort, comprising 207 survivors (136 with Hodgkin lymphoma) who developed breast cancer and 2774 (246 with Hodgkin lymphoma) without any subsequent neoplasm, this study found a locus on 1q41 (rs4342822) which was associated with a, per allele, 1.9-fold (95% CI, 1.5–2.4) increased subsequent breast cancer risk among survivors who received 10 or higher gray breast radiation exposure [144]. They also reported two suggestive associations for low-frequency variants at 11q23 and 1q32.3 with breast cancer risk after childhood cancer, suggesting a potential role for low-frequency SNPs in RT-induced breast cancer.

Because of the large sample sizes required for such studies, international collaboration will be essential to validate these findings and move this field forward. Lending further support to the importance of this research area, several GWAS have identified genomic regions associated with toxicity after radiotherapy [145, 146].

26.5 Risk of Selected Second Malignancies

26.5.1 Risk Factors for Leukemia

Leukemia following HL is certainly the most studied treatment-induced malignancy, and thus, extensive knowledge of its risk factors has emerged [14, 147, 148]. Leukemia was the first malignancy for which elevated risk after treatment for HL was observed, probably because of the relatively short latency period, the rarity of acute leukemia in the general population, and the high SIR [149].

Overall, in patients treated in the 1960s–1980s, risks compared with the general population have been reported to be 10- to over 80-fold increased (Table 26.1). Nearly all studies show that the SIR of leukemia is higher than that of NHL and much greater than that of solid tumors overall (Table 26.1). Because the background risk of leukemia in the population is low, however, this strongly increased SIR translates into a relatively low cumulative risk, ranging between 1.4% and 4.1% at 15 years [11, 32, 44, 45, 52, 55, 88, 99]. Overall, the AER has varied between 8 and 30 excess cases per 10,000 patients per year (Tables 26.2 and 26.3) [43, 44, 47, 150].

Radiotherapy alone is associated with a small, or no, increased risk of leukemia compared with the risk in the general population [11, 32, 43, 55, 85], while alkylating agent CT, as widely used up to the 1990s, is linked with greatly elevated risk. In cohort analysis of CT-treated patients, the SIRs of leukemia overall tend to be over 20-fold increase compared to the general population, while for AML over 50-fold risk increases are reported [11, 44, 45, 54, 88, 90–92].

Several studies have compared the leukemogenicity of different CT regimens. Where exposure has been quantified, risk appears to be most related to total dose of alkylating agents or nitrosoureas [11, 33, 77, 88, 92, 149]. Risk of AML rises sharply with an increasing number of MOPP (mechlorethamine, vincristine, procarbazine, prednisone) (or MOPP-like) cycles [33, 88]. The risk associated with 10–12 MOPP cycles appears to be approximately 3–5 times higher than the risk following six MOPP cycles [33, 88]. Total dose of alkylators and nitrosoureas is likely the explanation of the higher risk associated with salvage CT or maintenance CT [55, 88, 151], but there is evidence that retreatment may be itself a factor in risk [51, 88, 148, 152]. Among those treated with variations of MOPP that substitute

cyclophosphamide for mechlorethamine, the risks are lower [11, 88, 92, 153, 154]. It has never been clarified whether mechlorethamine or procarbazine has the strongest effect on AML risk.

From the 1980s, MOPP-only CT has been gradually replaced by ABV(D) (doxorubicin, bleomycin, vinblastine, and dacarbazine)-containing regimens in many centers. There are only a few reports on AML occurrence following ABV(D) alone. Patients treated with ABVD in the Milan Cancer Institute, where this regimen was designed, were shown to have a significantly lower risk of AML than MOPP-treated patients (15-year cumulative risks of 0.7% and 9.5%, respectively) [99]. Another study showed that HL patients treated with MOPP/ABV(D)-containing regimens in the 1980s had substantially lower risk of AML/MDS than patients treated in the 1970s with MOPP alone (10-year cumulative risks of 2.1% and 6.4%, respectively, $P = 0.07$) [54]. An international collaborative study showed that the AER of AML declined significantly after 1984, from 7.0 to 4.2 per 10,000 patients per year in those diagnosed before age 35 years and from 16.4 to 9.9 per 10,000 patient-years in the ≥35 age group [155]. Also, AML risk was recently assessed in three generations of Stanford clinical trials for HL patients. The incidence of AML/MDS was significantly lower in patients treated in the period 1989–2003, especially with the Stanford V regimens (0.3% at 10 years) [45, 156].

A large Dutch cohort study also found an almost fourfold lower cumulative incidence of leukemia and myelodysplasia among patients treated in 1989–2000 than among patients treated in 1965–1976 [45].

There is, however, concern about the role of anthracyclines and epipodophyllotoxins (both of which are topoisomerase II inhibitors) in the risk of leukemia. Limited evidence suggests that doxorubicin in combination with higher doses of alkylating agents and/or epipodophyllotoxins may have a synergistic effect on the risk of AML. Analyses of the German Hodgkin Lymphoma Study Group (GHSG) also show low risks of AML after COPP-ABVD (mechlorethamine replaced by cyclophosphamide) and standard BEACOPP (bleomycin, etoposide, doxorubicin combined with COPP), while substantially increased risk of AML was observed for the escalated BEACOPP regimen [34, 150]. A GHSG analysis showed that 6 years after HL treatment patients who received ≥4 cycles of escalated BEACOPP had an increased risk to develop t-AML/MDS compared with patients treated <4 cycles of escalated BEACOPP (1.7% vs. 0.7%, respectively; $P < 0.0001$); for patients not treated with BEACOPP the 6-year risk was only 0.3% [101].

Some studies suggest that RT adds to the leukemia risk associated with CT [147, 157], whereas other large series indicate that the risk of AML after combined treatment is comparable to that after CT alone [33, 43, 44, 88]. The interaction between RT and CT could be evaluated most rigorously in the large case-control study by Kaldor et al. [33] which included 163 cases of leukemia following HL. For each category of radiation dose (<10, 10–20, >20 Gy to the active bone marrow), leukemia risk clearly increased with the number of CT cycles. In contrast, among patients with a given number of CT cycles, risk of leukemia did not consistently increase with higher radiation dose. Taken together, the preponderance of available data does not support the hypothesis that the combination of CT and RT confers a higher risk of leukemia than CT alone.

Therapeutic intensification with autologous stem cell transplantation (ASCT) is commonly used for lymphoma patients who relapse. In some series relatively high actuarial risks (4–15% at 5 years) of AML and myelodysplasia (MDS) have been observed after ASCT for HL [147]. Evidence suggests that much of the risk is related to intensive pretransplant CT. Forrest and colleagues compared the risk of AML/MDS between 202 patients who had undergone ASCT and 1530 patients who underwent conventional therapy for HL [158]. The 15-year cumulative incidence of developing AML/MDS was 1.1% (95% confidence interval (CI), 0.6–1.8) for those treated with conventional therapy alone and 3.6% (95% CI, 0.9–9.6) for those undergoing ASCT ($P = 0.22$). In multivariate analysis, leukemia risk was also not influenced by ASCT [158].

The risk of AML in relation to treatment-associated acute and chronic bone marrow toxicity has been examined in only two studies to date [88, 159]. Significantly increased risks of leukemia were found among patients who developed thrombocytopenia, either in response to initial therapy or during follow-up. After adjustment for type and amount of CT, patients who showed a ≥70% decrease in platelet counts after initial treatment had an approximately fivefold higher risk of developing leukemia than patients who showed a decrease of 50% or less [88]. Severe acute thrombocytopenia may indicate greater bioavailability of cytotoxic drugs, which would likely contribute to the development of leukemia. In support of these findings, a study of leukemia risk after autologous bone marrow transplantation found that low platelet counts at the time of transplant were predictive for MDS/AML development in NHL patients who had received intensive pretransplant CT [159].

The prognosis of AML/MDS after HL treatment is poor, with only 15% of patients surviving more than 1 year without apparent survival benefit from allogenic stem cell transplantation in most studies [147, 156, 160]. However, in a recent GHSG study, treatment-related AML/MDS patients who underwent ASCT did have a significantly better outcome with median OS not reached after a median follow-up of 41 months ($P < 0.001$) [101].

26.5.2 Risk Factors of Non-Hodgkin Lymphoma (NHL)

Krikorian and colleagues were the first to demonstrate a clearly elevated cumulative risk of NHL after HL, which amounted to 4.4% at 10 years in patients given both irradiation and CT [161]. Other investigators have confirmed the increased risk of NHL in HL survivors [11, 32, 37, 43–45, 47, 52, 53, 55, 88]. In most studies the SIR for NHL ranges between 6 and 36 compared to the risk in the general population (Table 26.1). Because the background risk of NHL in the general population is low, this rather high SIR translates into a relatively low cumulative risk, ranging between 2% and 4% at 20 years [32, 45, 52, 162] in the larger studies. AER in these studies has varied between 5 and 13 excess NHL cases per 10,000 patients per year [43, 44, 47]. The majority of cases of second NHL diagnosed after HL are intermediate or aggressive histology B-cell lymphomas [162–164] and more often arise in extranodal sites than primary NHL [163, 165] (79% of cases [164]).

The causes of the excess risk are not well understood. The results of older studies may in part reflect misclassification of the primary lymphoma in the absence of modern lymphoma immunophenotyping protocols (i.e., NHL misdiagnosed as HL) [163]. Rueffer et al. [163] reported that an expert panel of pathologists reviewing the histology of 4104 HL patients (GHSG) rejected 114 cases (2.1%) initially diagnosed as HL and rediagnosed them as primary NHL. Only very few studies included a review of diagnostic pathology slides of the second NHL and original HL in order to avoid such misclassification [53, 88, 163].

Other investigators argued that the clinical, histologic, and immunophenotypic findings of NHL among HL survivors were analogous to those of NHL arising in immunosuppressed patients, suggesting that immunodeficiency plays a role in the pathogenesis of second NHL in these patients [164]. This view is supported by several studies in which risk did not vary appreciably between treatments [11, 52, 90]. However, in other studies, the risk of NHL was found to be lowest among patients treated with RT alone and highest among patients who received intensive combined modality treatment, both initially and for relapse [55, 88, 161, 163, 166]. In the study by Schaapveld et al. HL patients who received a cumulative dose of procarbazine >8400 mg/m^2, as compared with no chemotherapy, had 2.7-fold higher risk of subsequent NHL [45]. Also, patients who had undergone splenectomy had a (1.8-fold) higher risk of NHL than did those who had not undergone splenectomy.

There exists some evidence indicating that transformation to NHL may be part of the natural history of the lymphocyte predominant subtype of HL [165, 167], which might explain the asso-

ciation between lymphocyte predominant HL and NHL risk observed in the International Database on HL [55] and the British National Lymphoma Investigation [168]. It may be that more than one of the above mechanisms operates in the development of NHL following treatment for HL. Although transformation to NHL may be part of the natural history of some types of HL, the role of intensive combined modality treatment and its associated immunosuppression should be explored further. Future studies should incorporate a review of all slides of the second NHL and the original HL diagnosis by an expert pathologist.

26.5.3 Risk Factors for Breast Cancer

For female HL survivors, the strongly elevated risk of breast cancer following radiotherapy is a major concern [24, 32, 45, 47, 169–173]. In several studies breast cancer is the largest contributor to the AER of second malignancy in female survivors [27, 32, 37, 43, 45, 174]. The magnitude of the risk of breast cancer after HL and risk factors for its development have been discussed in several review papers [59, 175–177]. The risk of breast cancer after HL greatly depends on age at treatment, time since treatment, therapies given for HL, and hormonal factors.

The overall SIR of breast cancer in female HL survivors has been only modestly elevated in studies which included all age groups (about 1.5- to 2.5-fold risk increases compared to the general population) (Table 26.1) [27, 29, 43, 47, 54, 55, 154]. Larger SIRs (four- to sevenfold) were observed in studies with predominantly young adults or a large proportion of long-term survivors [24, 32, 37, 38, 45, 178]. AERs for all ages have been around 2–10 per 10,000 HL patients per year (Table 26.3) [47, 52, 54], again with a greater risk (20–60 per 10,000 per year) in studies with predominantly young adults and/or a large proportion of long-term survivors [24, 32, 37, 45, 178]. Several studies covering the whole age range have shown that the SIR of developing breast cancer increases dramatically with younger age at first irradiation (or start of treatment) (Fig. 26.2) [24, 27, 32, 37, 47, 52, 178, 179]. A strong trend of increasing SIR of breast cancer with decreasing age at exposure has also been observed in other radiation-exposed cohorts [65, 180–182]. In a Dutch study, survivors who had radiation treatment before 21 years of age had an 18-fold increased risk of breast cancer compared with the general female population of the same age; women irradiated at ages 21–30 had a sevenfold increased risk, women irradiated at ages 31–40 had a 3.2-fold increased risk, and a small, nonsignificant increase was observed for women irradiated at ages 41 or older (SIR, 1.4) [24]. Similar trends have been reported by others [37, 45, 47, 52, 178, 183]. Most studies confirm that breast cancer risk is not elevated compared with the general population in women treated after age 35–40; a recent analysis however showed a SIR of 1.7 (95% CI, 1.1–2.5) even for women treated at ages 35–50 [45]. In most studies the AER of breast cancer is also highest after treatment before age 20 (Fig. 26.2) [24, 27, 32, 37, 45, 47, 178], but shows little variation between exposure at ages 20–35.

The SIR of breast cancer after HL treatment at ages under 16 has ranged from 17 to 458 [90, 91], with most studies showing SIRs around 50–100 [32, 37, 38, 43, 179, 184–186]. Three studies with long-term follow-up reported that, among women treated before age 20, the SIR compared with age-matched peers from the general population did not consistently vary by age at treatment [43, 70, 184]. This would imply that prepubertal radiation exposure increases the risk to the same extent as exposure during puberty. In the atomic bomb survivors and other radiation-exposed cohorts, the RR also did not vary by exposure age for ages under 20 [187]. However, a recent British study reported greatest SIRs for female HL survivors irradiated around age 14 [178] and a subsequent case-control study observed especially high risk when women were irradiated within 6 months of menarche [188] possibly associated with pubertal breast development. A recent report from the US Childhood Cancer Survivor Study in women treated with chest (60% of whom were treated for Hodgkin lymphoma) corroborated this finding. Women who began chest radiotherapy within 1

year of menarche had a 1.7-fold increased breast cancer compared to women who began chest radiotherapy further from menarche (excluding women who never experienced menarche) [189]. However, in a recent Dutch case-control study, menarche age close to start of radiation therapy did not modify breast cancer risk [72].

The large variation in breast cancer risks across studies, especially in young patients, is not surprising in view of the large differences between series in important variables such as the proportion of patients irradiated, duration of follow-up, and completeness of follow-up. Studies with more complete follow-up have generally found lower risks of breast cancer [32, 43, 47, 91, 178, 186] than those in which follow-up was less complete or not addressed [89, 90, 179].

Incomplete follow-up may lead to overestimation of second malignancy risk if patients who remain well lose contact with clinical follow-up, while those with second cancer come to attention because of this. In a Dutch study, with (nearly) complete follow-up, the 30-year cumulative incidence of breast cancer (accounting for death as a competing risk) amounted to 26% for women first treated before age 21% and 19% for those treated at ages 20–30 [24]. In pediatric HL survivors, Bhatia and colleagues estimated a cumulative incidence of breast cancer of 13.9% at age 40 years, reaching 20.1% at age 45 years [43]. Castellino and colleagues [158] recently reported a cumulative incidence of breast cancer of 18.3% at 30 years after treatment in the US Childhood Cancer Survivor Study. Travis and collaborators estimated treatment-specific cumulative risks of breast cancer: for an HL survivor who was treated at age 25 with a chest radiation dose of at least 40 Gy without alkylating agents, the cumulative absolute risks of breast cancer by age 35, 45, and 55 years were 1.4% (95% CI, 0.9–2.1), 11.1% (95% CI, 7.4–16.3), and 29.0% (95% CI, 20.2–40.1), respectively [190]. Based on 373 breast cancer patients in a very large HL cohort (n = 5002 women), Swerdlow and colleagues [178] recently reported modeled cumulative risks by follow-up time, age at treatment, and treatment modalities. For women who received 40 Gy under age 20, and no alkylating chemotherapy (see below), the cumulative incidence of breast cancer at 40 years was 48%. The case-control study by Krul et al. predicted cumulative incidence of breast cancer based on radiation field and dose and duration of post-RT ovarian function [72]. The predicted 35-year cumulative incidence of breast cancer was highest (27.6%) for women with high-dose mantle field RT (≥35 Gy) and long duration of ovarian function (≥20 years). Women with lower-dose (in)complete mantle field RT (≤35 Gy) and long duration of ovarian function had a lower cumulative incidence (22.4%), followed by women with high-dose (in)complete mantle field RT and medium and short durations of ovarian function (19.6% when 10–19% and 13.8% when <10 years, respectively).

The high risk of breast cancer after HL is largely attributable to chest radiotherapy. Since, in many cohort studies, 80% to over 90% of patients received supradiaphragmatic RT, few studies could estimate RRs associated with such RT compared with no RT [24, 32, 37, 43]. In the British cohort reported by Swerdlow and colleagues, a large proportion of patients had been treated with CT alone, and no increased risk of breast cancer was observed among them [44].

Elevated risk of breast cancer develops late and is typically observed from 15 years after first treatment (Fig. 26.7) [24, 32, 37, 45, 47, 52, 178]. This strong trend in breast cancer risk by time since treatment strongly indicates a radiogenic effect. Furthermore, in several cohort studies, almost all cases of breast cancer after HL have been in or at the margin of the radiation field, for instance, 16 of 16 cases [90], 22 of 26 [38], and all of 42 cases [43] in three publications. In the large, population-based study by Travis and colleagues [42], 49% of 105 breast cancers occurred in the unblocked chest treatment field, 24% under the lung blocks, 15% at the blocked edge, 8% in the field edge, and 3% out of beam, with relative location not known for one patient.

Four case-control studies investigated the effects of RT dose and other treatment factors on breast cancer risk [41, 42, 70, 72]. In all studies, the risk of breast cancer increased significantly with higher RT dose up to the highest dose levels

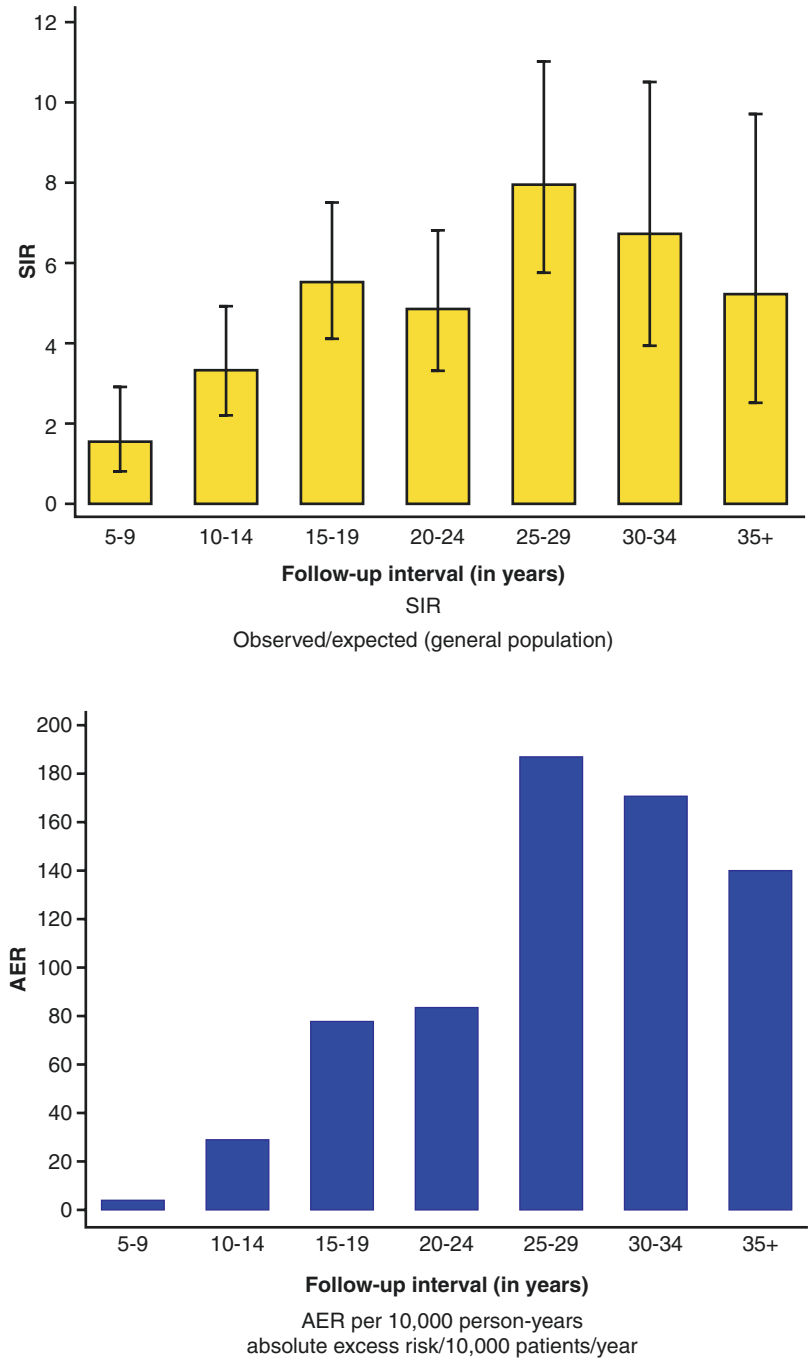


Fig. 26.7 Risk of breast cancer after Hodgkin lymphoma by follow-up time (1698 female Dutch Hodgkin Lymphoma patients; From: Schaapveld et al. [45])

(Table 26.4; see for details: Sect. 26.4.1). A recent large Dutch study examined the effect of radiation fields (volume) on the risk of breast cancer up to more than 30 years after treatment of HL [45]. Among 1698 female 5-year survivors, treated for HL between ages 15 and 50 years (median follow-up time of 19.1 years), 183 cases of breast cancer were identified (overall SIR, 4.7; AER, 54.3 per 10,000 per year). Importantly, a complete mantle field RT (involving the axillary, mediastinal, and neck nodes) was associated with a 2.7-fold (95% CI, 1.4–5.3) increased risk of

breast cancer compared to a similarly dosed (36–44 Gy) supradiaphragmatic field which excluded the axilla.

In six studies, patients who received both CT and RT had significantly decreased risk (about halved) compared to those treated with RT alone, and the RT-related risks were attenuated by treatment with alkylating agents [24, 41, 42, 45, 60, 189]. Risk of breast cancer decreased with increasing number of alkylating agent cycles ($P = 0.003$ for trend); the RR associated with nine or more cycles of alkylating CT compared with no alkylating CT was 0.2 (95% CI, 0.1–0.7) (Table 26.4) [42]. In the large Dutch cohort study, chemotherapy regimens with higher cumulative procarbazine doses seemed to be associated with a greater reduction of breast cancer risk, with 30% and 70% risk reductions for regimens with less than 8.4 g/m^2 procarbazine and more than 8.4 g/m^2 procarbazine, respectively [45]. The substantial risk reduction associated with CT appears to be due to the high frequency of premature menopause in CT-treated patients [24, 41, 72, 188] and the resulting reduction in the exposure to ovarian hormones. De Bruin et al. [24] reported that 30% of all women reached menopause before age 41; such an early menopause was associated with a 60% (95% CI, 20–80%) reduced risk of breast cancer (Table 26.5). A strong decrease in breast cancer risk (about 60%) has also been observed among women who received a castrating dose of 5 Gy or more to the ovaries, compared with those who received lower doses (Fig. 26.4) [24, 41, 42, 70, 72, 189]. These results indicate that ovarian hormones are a crucial factor to promote tumorigenesis once RT has produced an initiating event.

In the Dutch study a long versus short duration of intact ovarian function after radiation was a strong predictor of subsequent breast cancer risk. Women with less than 10 years of intact ovarian function after radiotherapy had a 70% (95% CI, 40–80%) decreased risk of breast cancer compared with women with 10–20 years of ovarian function after irradiation, while those with more than 20 years of intact ovarian function after radiotherapy had 5.3-fold (95% CI, 2.9–9.9) increased risk of breast cancer (Table 26.5). These risk reductions were observed both among women treated before age 21 and among those treated between ages 21 and 30. Among women treated between ages 31 and 40, cumulative exposure to endogenous estrogens was not associated with risk for breast cancer, possibly because these women were closer to natural menopause at time of treatment [24]. These findings were subsequently confirmed in a British case-control study, which reported a 3.6-fold risk increase for women having 25 or more premenopausal years after start of RT [188], and a recent Dutch case-control study which found a 3.8-fold risk increase for women who had an

Table 26.5 Effects of fertile lifespan after irradiation to the breast on breast cancer risk (invasive and DCIS) according to age at first treatment[a]

	All ages <41	Age <21	Age 21–30	Age 31–40
No. of patients	715	201	323	191
No. of events	98	36	40	22
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 3[b]				
Premature menopause[c]				
Menopause at age 41 or later	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Menopause before age 41	0.4 (0.2–0.8)	0.2 (0.0–0.8)	0.1 (0.0–0.5)	1.3 (0.4–3.6)
Model 4[b]				
Years intact ovarian function[c]				
<10 years	0.3 (0.2–0.6)	0.1 (0.0–0.6)	0.1 (0.0–0.3)	1.2 (0.4–3.5)
10–20 years	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
>20 years	5.3 (2.9–9.9)	11.9 (3.7–37.9)	6.0 (2.3–15.4)	3.2 (0.3–30.7)

BC breast cancer, *IBC* invasive breast cancer, *DCIS* ductal carcinoma in situ, *HR* hazard ratio, *Ref* referent, *RT* radiation therapy

[a]Adapted from de Bruin et al. [24]

[b]Adjusted for each other, radiation field size, age at first RT to the breast and time since first RT to the breast, smoking, obesity, nulliparity, oral contraceptive use; calendar time was used as the time scale

[c]Unknown age at menopause was modeled as a separate category

intact ovarian function for 25 years or more post-chest RT [72].

It is not yet known whether current less gonadotoxic CT, such as ABVD, is also associated with reduced risk of RT-associated breast cancer risk. Furthermore, it is important to know whether hormone replacement therapy (HRT) for CT-induced premature menopause affects RT-associated breast cancer risk. HRT is an established risk factor for breast cancer [191, 192] and might counteract the protective effect of CT. The recent Dutch case-control study found that use of HRT ≥2 years did not increase breast cancer risk (OR, 0.9; 95% CI, 0.3–2.3) in women with an early menopause (menopause <45 years) whereas breast cancer risk was nonsignificantly increased among women without early menopause (OR, 3.7; 95% CI, 0.97–14.0; *P* for interaction 0.06) [72]. A limitation of this study was that few women used HRT for long durations. Another recent study of breast cancer risk after chest RT in childhood did not find a clear association of HRT use and breast cancer risk [189].

Individual genetic susceptibility may also modify the risk of treatment-related BC. Recently, a Dutch case-control study showed, using a GWAS approach, that radiation-induced BC risk may indeed be modified by individual genomic variation. Individuals in the highest tertile of a polygenic risk score (RT-interaction-PRS), composed of nine SNPs that showed statistically significant interaction with RT on BC risk, had a 1.6-fold higher BC risk than those in the lowest tertile (see Sect. 26.4.3) [143].

A few recent studies investigated whether the clinicopathological characteristics of radiation-induced breast cancers differ from those of sporadic breast cancers [193–196]. Remarkably, one study found that breast cancers following RT for HL have a molecular profile distinct from idiopathic breast cancers from age-matched women. Another study reported more estrogen-negative breast cancers after RT for HL [195]. However, two other studies did not find much difference in breast cancer-specific survival between women with breast cancer after HL and other age-matched breast cancer patients [194, 196].

In summary, from 10 to 15 years after treatment chest RT at young ages is associated with a very high dose-dependent risk of breast cancer that persists for at least 40 years. This hazard needs to be borne in mind both when selecting treatment for girls and young women with HL and when following up patients treated in this way. Gonadotoxic chemotherapy such as the MOPP regimen reduced the increased risk of breast cancer from RT through the induction of premature menopause. Reductions of radiation dose and field size (replacement of mantle RT by involved field/involved node/site RT) in current treatment protocols are expected to result in lower breast cancer risk. Nonetheless, although in the recently published Dutch cohort study a large proportion of the female survivors treated in 1990–2000 had received less extensive supradiaphragmatic irradiation fields, there was little evidence that these women had a lower risk of breast cancer than those who were treated in earlier periods [45]. One possible explanation for this finding is that the concomitant change towards less gonadotoxic chemotherapy may have partly counterbalanced the effects of lower radiation exposure of the breasts.

26.5.4 Risk Factors for Lung Cancer

Next to breast cancer, lung cancer accounts in many studies for the largest absolute excess of solid malignancy after HL [45, 47, 52]. An excellent review of risk factors for lung cancer after HL has been published [197]. The risk of lung cancer after HL depends on time since treatment, age at treatment, treatments administered for HL, and smoking.

The SIR of lung cancer is hardly increased in the first 5 years after treatment, with larger SIRs (five or greater), thereafter until at least 25 years [32, 37, 39, 45, 47, 52, 198].

A meta-analysis of 21 observational studies reported that the relative risk of lung cancer varied little with age at HL treatment and was highest among those aged 15–24 years (RR = 8.6) and lowest among those aged >55 years at first treat-

ment (RR = 2.9) [190]. Dores et al. [47] reported that the SIR of lung cancer decreased from a 5.5-fold increase (compared with the general population) for patients diagnosed before age 21 to a 1.5-fold excess for patients diagnosed at age 61 or above. In the UK study [52], the SIRs for lung cancer decreased from 20-fold among those diagnosed before age 25 to a 2.2-fold excess for patients diagnosed at age 55 or above.

A large international collaborative case-control study examined lung cancer risk in relation to the radiation dose to the specific location in the lung in which cancer later developed [39]. This study included 222 lung cancer patients and 444 matched controls (patients with HL in whom lung cancer had not been diagnosed) [39, 73]. Case patients developed lung cancer after an average of 10.8 years. The risk increased with increasing radiation dose to the area of the lung in which cancer later developed (*P* for trend <0.001; see also Table 26.4). The risk estimates for the highest dose categories of 30.0–39.9 Gy and ≥40 Gy compared with no RT were 8.5 (95% CI, 3.3–24) and 6.3 (95% CI, 2.2–19), respectively, suggesting that the risk might level off at very high doses [73]. This study also addressed the modifying effects of the patient's smoking habits on RT-associated risks. The increased RRs from smoking appeared to multiply the elevated risks from radiation (Table 26.6). This implies that there are very large AERs for lung cancer among irradiated patients who smoke.

Chemotherapy for HL can also increase the risk of lung cancer [39, 44, 52, 53, 197, 199]. The British National Lymphoma Investigation cohort study of 5519 patients [44, 52] showed a significantly elevated risk of lung cancer following CT alone, with the SIR (3.3; 95% CI, 2.2–4.7) compared with the general population being of similar magnitude to that observed in patients treated with either RT (SIR = 2.9; 95% CI, 1.9–4.1) or mixed modality treatment (SIR = 4.3; 95% CI, 2.9–6.2).

Two large case-control studies have investigated the separate and joint roles of CT, radiation, and smoking in detail [39, 74]. In both reports, there was a clear trend of increasing lung cancer risk with greater number of cycles of alkylating CT (*P* trend <0.001 (Table 26.4) [39]) or MOPP-CT (*P* trend = 0.07 [74]). In the study by Travis and colleagues [39], data were also collected on cumulative dose of individual cytotoxic drugs. Among patients treated with MOPP, increasing total dose of mechlorethamine or procarbazine was strongly associated with increasing lung cancer risk when evaluated separately (*P* trend for dose for each <0.001) [39]. Risk of lung cancer after treatment with alkylating agents and radiation together was as expected if individual excess RRs were summed: RRs of 4.2 (95% CI, 2.1–8.8) were observed for patients given alkylating agents alone, 5.9 (95% CI, 2.7–13.5) for patients treated with RT alone (>5 Gy), and 8.0 (95% CI, 3.6–18.5) for those who received combined modality treatment, compared with the reference group of patients who received no alkylating agents and had less than 5 Gy of radiation [39]. As was observed for the joint effects of smoking and RT, the risks from smoking appeared

Table 26.6 Risk of lung cancer in patients with HL according to type of treatment and smoking category

Treatment for Hodgkin lymphoma		RR (95% CI) by smoking category (no. of case patients; control patients)[a]	
Radiation ≥5 Gy	Alkylating agents	Nonsmoker, light, other[b]	Moderate–heavy[c]
No	No	1.0[d]	6.0 (1.9–20.4)
Yes	No	7.2 (2.9–21.2)	20.2 (6.8–68)
No	Yes	4.3 (1.8–11.7)	16.8 (6.2–53)
Yes	Yes	7.2 (2.8–21.6)	49.1 (15.1–187)

Adapted from Travis et al. and Swerdlow et al. [39, 44]
RR relative risk, *95% CI* 95% confidence interval
[a]Represents estimated tobacco smoking habit 5 years before diagnosis date of lung cancer and corresponding date in control patients, with the use of information recorded up to 1 year before these dates
[b]This group includes nonsmokers, light current cigarette smokers (less than one pack per day), former cigarette smokers, smokers of cigar and pipes only, and patients for whom tobacco smoking habit was not stated
[c]Moderate (one to two packs per day) and heavy (two or more packs per day) current cigarette smokers
[d]Reference group

to at least multiply risks from alkylating CT (Table 26.6) [39].

Smoking remains a major cause of lung cancer in patients treated for HL, as is evident from the observation that only 7 out of 222 cases included in the study by Travis and colleagues [39] occurred in patients who had never smoked. Further, it was estimated that 9.6% of all lung cancers were due to treatment, 24% were due to smoking, but 63% were due to treatment and smoking in combination; the remainder (3%) represented tumors in which neither smoking nor treatment played a role.

In summary, both supradiaphragmatic RT and CT contribute to the elevated risk of lung cancer after HL. In addition, the above data suggest that patients with HL who smoke will have a considerably greater risk of lung cancer after chest RT and/or CT than those who do not smoke, and this is in accord with experience in other radiation-exposed groups [200]. As a consequence, smokers who have received chest RT should be particularly strongly advised to refrain from smoking. The evidence implicating specific chemotherapeutic agents as carcinogenic to the lung is less clear. It is not yet known whether modern CT regimens other than MOPP also increase the risk of lung cancer. The role of lung cancer screening in HL patients has not yet been assessed; international collaboration is needed to study the efficacy of screening with low-dose spiral computer tomography [36, 197]. Of note, a cost-effectiveness simulation study, which also used data from low-dose spiral computer tomography screening in 53 HL survivors showed that screening may be cost-effective for smoking HL survivors treated with mantle field irradiation but likely was not for irradiated nonsmokers although a small life expectancy benefit of computer tomography screening was also noted for nonsmokers [201].

26.6 Clinical Implications

Hodgkin lymphoma survivors who are at high risk of developing second cancers can be identified largely based on their prior treatment exposures, current age, and latency since treatment. Expert opinion-based recommendations have been published advocating the early onset of breast cancer screening starting 8 years following mediastinal RT, for women who are age 25–30 [202]. However, a large proportion of irradiated females do not perceive their risk of breast cancer to be much higher than that of the general population [203–206]. As a consequence, a large proportion of HL survivors do currently not undergo appropriate breast surveillance at young ages, when their risk is already high and comparable to that of carriers of BRCA1/2 mutations. A study among irradiated female childhood cancer survivors in the USA showed that 64% of those aged 25–39 years and 24% of those 40–50 years old had not had a mammography in the past 2 years, despite a guideline recommending annual screening [206]. Although early breast surveillance starting is recommended following mediastinal RT, the optimal screening modalities have yet to be determined. However, because mammography is less sensitive in young women with dense breast tissue, magnetic resonance imaging (MRI) should be considered at younger ages. Ng et al. reported the outcome of 148 women screened with breast MRI ≥8 years after mediastinal RT (given prior to age 35 years) and a median age at enrollment of 43 years [207]. The sensitivity of mammogram alone, MRI alone, or both modalities was 68%, 67%, and 94%. Specificity for each modality alone or in combination was not significantly different. One of 18 cancer cases detected had lymph node involvement. A similar study of MRI breast screening among survivors of pediatric HL in which the median age at first screening was 30 years reported that the sensitivity for mammogram alone, MRI alone, and both modalities was 70%, 80%, and 100%, respectively, with all detected cases being node negative. In both studies, mammography was more likely to miss invasive cancers than MRI [208]. These studies suggest that the addition of MRI to mammography will detect breast cancers at earlier stages than mammography alone. However, the use of MRI will also likely increase the proportion of false-positive test results. In a simulation study Hodgson et al. predicted that using alter-

nating mammography/MRI-based screening 79% of all participating female adolescent Hodgkin lymphoma survivors treated with mediastinal radiotherapy would experience at least one false-positive test over the course of screening [209]. However, this study also showed that early initiation of BC screening could reduce BC mortality among these women with one breast cancer death prevented for every 80 women invited to MRI screening (when treated at age 15 years and starting screening at age 25 years).

Some have recommended that patients who received para-aortic RT and/or procarbazine should undergo colorectal cancer screening starting 10–15 years following treatment [49]. Two recent colonoscopy screening study showed a high prevalence of advanced colorectal neoplasia in patients previously treated with abdominal and/or pelvic RT and/or procarbazine-containing CT. In the study by Daly et al., in 54 survivors (mostly Hodgkin lymphoma patients) who underwent colonoscopy screening at a median age of 45% years, 44.4% had polyps detected, deemed precancerous in 15 patients [210]. Rigter et al. also found a high prevalence of advanced colorectal neoplasia (advanced adenomas 14%, advanced serrated lesions 12%) in 101 Hodgkin lymphoma survivors who underwent colonoscopy (median age at colonoscopy of 51 years) [211]. The prevalence of advanced adenomas was nonsignficantly increased among Hodgkin lymphoma survivors compared to 1426 population controls (9%; $P = 0.08$), but Hodgkin lymphoma survivors significantly more often had advanced serrated lesions (12% vs. 4% in controls) and serrated polyposis syndrome (6% vs. 0% in controls).

Screening for secondary lung cancer is more controversial. As noted above, older HL survivors treated with alkylating agents or mantle RT are at significantly increased risk of developing lung cancer, particularly if they are smokers. One important consideration is that the absolute risk of lung cancer is low among nonsmoking patients treated before age 30 with contemporary chemotherapy (e.g., ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine), and it is unlikely that they would benefit from screening. Risk is highest among those treated with chest RT and alkylator-based chemotherapy at ages >40 years, particularly if they are smokers. The results of studies evaluating the efficacy of screening with spiral computer tomography in other high-risk patients may illuminate the potential benefit to HL survivors, but it currently remains investigational.

Physicians should make a special effort to dissuade HL patients from smoking. While most survivors will be aware that smoking increases their risk of lung cancer, they may not understand that their smoking-related risk may be significantly greater than that of others with whom they share the activity, and they are often not aware of the poor prognosis associated with lung cancer. Advice on smoking cessation during an office visit can improve quit rates, and pharmacotherapy improves the probability of success [212].

While retrospective studies describing the RT-related risk of SMNs have been useful in identifying groups of survivors for whom the early utilization of cancer screening may be worthwhile, and have been instrumental in motivating the development of clinical trials which are now much less reliant on the use of RT, it is important to recognize that they often have limited value in counseling contemporary patients about the risks of modern therapy. For example, most of the widely cited cohort studies of SMN risk among HL survivors include patients treated in the 1960s [43, 45–48, 52, 54]. At that time, RT was often the sole primary treatment for early-stage HL, and the RT fields typically encompassed the whole neck, bilateral axillae, the entire length of the mediastinum, the spleen, and para-aortic nodes. Patients were often prescribed 40–45 Gy and treated without customized lung shielding [213, 214]. Since that time, several important improvements have occurred in the delivery of RT that reduce the normal tissue exposure: prescribed doses are typically 20–30 Gy for adults and 21 Gy for children. With the development of involved-field RT (IFRT), the omission of uninvolved axillary nodes from these historic fields significantly reduced the average breast tissue dose compared to historic mantle RT fields, and follow-up studies of more limited field RT suggest that the associated reduction in

irradiated breast volume translates into a clinically significant reduction in SMN risk [24, 34, 45]. More recently, utilization of modern image guidance and the further reduction in target volumes limited to only the initially involved lymph nodes, referred to as involved node RT (INRT) or involved site RT (ISRT), further reduce the dose to normal tissues, with early results demonstrating excellent disease control [86, 87]. As our understanding of the relationship between radiation dose and SMN risk develops, it should be possible to create predictive models of the SMN risk associated with modern HL treatments based on epidemiologic observations and radiobiologic principles.

Obviously the best means of limiting radiation-related SMN is to avoid using RT when it does not contribute meaningfully to HL cure. Data are emerging that may facilitate the selection of a greater proportion of patients for treatment with chemotherapy alone based on clinical or biologic factors. As an increasing proportion of patients are treated with chemotherapy alone, an emerging issue will be the extent to which contemporary chemotherapy regimens contribute to the risk of solid tumors. Many patients in second cancer studies received MOPP chemotherapy, and the increased SMN risks associated with alkylator-based chemotherapy do not apply to patients receiving, for example, ABVD chemotherapy. Patients treated initially with chemotherapy alone, even in more recent years, have increased risks of solid cancers [27, 44, 52], though it is unknown what regimens or specific agents might account for this risk. A British National Lymphoma Investigation (BNLI) study found that the relative risk of second cancer was raised among 2366 HL survivors treated with chemotherapy alone (RR = 2.0), although the risk was not increased among the 257 patients treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) [44]. As noted above, genetic susceptibility likely plays a role in the development of treatment-related SMNs, but it is unlikely that an abnormal allele in a single candidate gene will account for a significant proportion of SMNs. New cohorts should be assembled to create a resource of biologic samples that would facilitate study of the molecular biology of second cancers.

Finally, when interpreting results of second cancer studies, it must be kept in mind that the problem of treatment-induced malignancies has arisen by virtue of the successes of HL treatment. The SMN risk of treatment must be balanced against the potential benefit in terms of curing patients' HL. For example, 10-year follow-up of patients treated with "dose-escalated" BEACOPP demonstrated that this regimen increased the risk of secondary AML compared to COPP/ABVD (0.4% vs. 3.0%), but produced a significant improvement in overall survival (75% vs. 86%) [215]. These outcomes highlight both the challenges of improving the cure rate for high-risk patients without adding clinically significant toxicity and the importance of considering SMN risk in the context of the beneficial effects that the exposures under study may have on curing the primary HL.

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Cardiovascular and Pulmonary Late Effects

27

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Contents

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_27

27.1 Cardiovascular Toxicity

Radiotherapy and chemotherapy for Hodgkin lymphoma may both cause cardiovascular toxicity. Cardiovascular toxicity following radiotherapy is usually not observed until more than 5 years after therapy, whereas anthracycline-related toxicity is observed at varying intervals after therapy. This chapter mainly focuses on late effects. Tables 27.1 and 27.2 show detailed information on standardized mortality rates and standardized incidence rates of several cardiovascular diseases following treatment for Hodgkin lymphoma including the absolute excess risks, mainly from cohorts treated using historical treatment techniques. A population-based cohort study from Sweden [1] demonstrated that excess mortality from circulatory disease has decreased continuously since the 1980s, and it is expected to decrease further with more modern treatment techniques.

27.1.1 Chemotherapy-Associated Cardiotoxicity

27.1.1.1 General Aspects of Chemotherapy-Associated Cardiotoxicity

The most relevant cardiotoxic chemotherapeutic agents used in treatment of Hodgkin lymphoma patients are anthracyclines, specifically doxorubicin and epirubicin. Anthracycline-associated toxicity may occur at different intervals after therapy. Cardiotoxicity may present as electrocardiographic changes and arrhythmias or as cardiomyopathy leading to congestive heart failure. Anthracycline-associated cardiotoxicity is mainly caused by direct damage to the myocardium, but anthracyclines are also recognized to cause vascular endothelial dysfunction which may increase cardiovascular risk. Several risk factors for anthracycline-associated cardiotoxicity have been identified (see Table 27.3). The occurrence of acute anthracycline-associated cardiotoxicity is dose dependent [13] and increases dramatically with cumulative doses higher than 500 mg/m^2 doxorubicin [14]. The total dose of anthracyclines during first-line therapy for Hodgkin lymphoma does usually not exceed 300 mg/m^2. For example, the cumulative dose of six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is 300 mg/m^2 and of eight cycles of bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (escalated BEACOPP) is 280 mg/m^2. However, it is now recognized that there is no risk-free dose of anthracyclines, and particularly younger patients have experienced cardiac damage at doses of <250 mg/m^2 [13, 15].

Whether toxicity following chemotherapy and radiotherapy is additive or synergistic remains unclear. Clinical studies have shown that anthracycline-containing therapy may further increase the radiation-related risk of congestive heart failure and valvular disorders by two- to threefold compared to radiotherapy alone [20]. This effect may be more than additive [21]. A British study also demonstrated that an increased risk of death from myocardial infarction was related to anthracycline and vincristine treatment as well as supradiaphragmatic radiotherapy; the risk of death from myocardial infarction was increased for patients who did not receive supradiaphragmatic radiotherapy but had received vincristine (standardized mortality ratio (SMR) = 2.2,

Table 27.1 Risk of death from cardiac diseases in large cohorts of patients treated for Hodgkin lymphoma

Authors	Treatment period	No. in cohort	Age range at treatment in years	Follow-up in years (range)	Type of treatment	Endpoint	SMR[a]	(95% CI) SMR[a]	AER[b]
Boivin [2]	1940–1985	4665	All ages[c]	Mean 7 (–)	Mediastinal RT ± CT	MI	4.1	(1.5–10.9)	–
Hancock [3] and Hoppe [4]	1960–1991	2232	1–82 (mean 29)	Mean 9.5 (–)	89% including mediastinal RT	MI	3.2	(2.3–4.0)	17.8
King [5]	1954–1989	326	5–72 (mean 25.6)	Mean 13.3 (3–37)	Mantle RT ± CT	MI	2.8	(0.7–4.9)	10.4[d]
Glanzmann [6]	1964–1992	352	4.0–81 (mean 33.8)	Mean 11.2 (1.0–31.5)	Mediastinal RT ± CT	MI	4.2	(1.8–8.3)	–
Brierley [7]	1973–1984	611	17–90 (median 31)	Median 11.0 (0.7–18.0)	97% RT ± CT	MI	1.5	(0.7–3.0)	5.4
Ng [8]	1969–1997	1080	3–50 (median 25)	Median 12	96% RT ± CT	Cardiac death	3.2	(1.9–5.2)	9.0
Aleman [9]	1965–1987	1261	Median 26	Median 17.8	97% RT ± CT; 84% mediastinal RT	MI	4	(2.3–6.5)	5.6
Swerdlow [10]	1976–2000	7033	All ages	Median 11.1	72% RT ± CT; 34% including mediastinal RT	MI	2.5	(2.1–2.9)	12.6

SMR standardized mortality ratio, *CI* confidence interval, *AER* absolute excess risk, *RT* radiotherapy, *CT* chemotherapy, *MI* myocardial infarction

[a]Standardized mortality ratio (SMR) as the ratio of the observed (O) and expected (E) numbers of cardiovascular events in the cohort. The expected numbers are calculated based on general population rates

[b]Absolute excess risk (AER) per 10,000 person-years as O minus E, divided by the number of person-years at risk, multiplied by 10,000

[c]62% <40 years

[d]Calculated from the data in the paper: (observed [7] – expected (2.5)/person-years at risk (4335)) × 10,000

Table 27.2 Standardized incidence ratio and absolute excess risks of coronary heart disease as first event, congestive heart failure as first event, stroke, and transient ischemic attack by sex, age at start of treatment, follow-up interval, attained age, and treatment in patient treated for Hodgkin lymphoma[a]

	CHD		CHF		Stroke		TIA	
	SIR	AER	SIR	AER	SIR	AER	SIR	AER
Total cohort	3.3	70	5.1	30	2.2	12	3.1	9
Sex								
Male	1.4	25	4.1	28	2.0	10	2.7	8
Female	6.2	114	6.4	33	2.4	14	3.8	11
Age at treatment (years)								
<18 MI and CHF, ≤20 stroke and TIA	7.1	46	26.5	25	3.8	7	7.6	5
18–30 MI and CHF, 21–30 stroke and TIA	3.9	63	11.0	32.5	3.1	14	4.2	7
31–40	2.8	91	4.1	30	2.0	15	3.1	13
41–50	2.0	98	2.0	29	1.4[b]	11	2.1[b]	18
Follow-up period (years)								
5–9	2.9	30	4.9	11	2.1[b]	5	2.3	3
10–14	3.1	51	6.2	22	2.3	10	3.3	8
15–19	3.6	94	6.1	32	2.6	18	4.4	17
20–24	3.1	108	6.4	55	2.1[b]	17	2.5[b]	11
25–29	2.8	132	5.0	58	1.9[b]	26	2.8	23
30–34	2.3	122	2.2	24				
≥ 35	1.8	124	1.9	59				
Attained age (years)								
Age at treatment 25–34 years								
Attained age <45 years	4.2	41	9.3	17				
Attained age 45–59 years	3.8	131	5.5	34				
Attained age ≥60 years	2.7[b]	64	1.1[b]	3				
Age at treatment <51 years								
Attained age <51					2.5	7	3.2	4
Attained age ≥51					2.0	29	3.1	30
Treatment								
No mediastinal RT, no anthracyclines	1.5	17	1.4	4				
Anthracyclines, no mediastinal RT	3.0	54	4.6	20				
Mediastinal RT, no anthracyclines	3.1	82	4.8	30				
Mediastinal RT and anthracyclines	4.7	79	16.0	53				
Treatment								
Radiotherapy alone					2.0	11	3.4	12
Chemotherapy alone					0.4[b]	−6	–	–
Radiotherapy/chemotherapy					2.6	15	3.4	10

CHD coronary heart disease, includes both myocardial infarction and angina pectoris, *CHF* congestive heart failure, *TIA* transient ischemic attack, *SIR* standardized incidence ratio, *AER* absolute excess risk, *RT* radiotherapy

[a]Adapted from Van Nimwegen et al. [11] and De Bruin and Dorresteijn et al. [12]. CHD and CHF data from cohort of 2524 Dutch patients diagnosed as having HL at age younger than 51 years (median age, 27.3 years) who had been treated between 1965 and 1995 and had survived for 5 years since their diagnosis and stroke and TIA data from cohort of 2201 5-year survivors of Hodgkin lymphoma treated before the age of 51 between 1965 and 1995

[b]Not statistically significant

95% CI = 1.6–3.0) and anthracyclines (SMR = 3.2, 95% CI = 1.9–5.2), especially those who were treated with the ABVD regimen (SMR = 7.8, 95% CI = 1.6–22.7) [10].

The potential role of genetic variability in the pathogenesis of chronic cardiotoxicity including congestive heart failure is beginning to be elucidated. A growing number of studies in humans have provided evidence that genetic susceptibility may play a role in the risk of anthracycline-associated cardiotoxicity. Patients with particular genetic profiles, leading to higher levels of

Table 27.3 Risk factors for anthracycline-associated cardiotoxicity

Risk factor	Features
Total cumulative dose	Most significant predictor for abnormal cardiac function
Age	For comparable cumulative doses, younger age predisposes to a greater relative risk of cardiotoxicity
Length of follow-up	Longer follow-up results in higher prevalence of myocardial impairment
Gender	Females more vulnerable than males for comparable doses perhaps due to a greater fat percentage of body mass [16]
Race	Those of black race possibly more susceptible [17]
Mediastinal irradiation	Enhanced toxicity; not clear whether additive or synergistic
Genetic susceptibility	Patients with particular genetic profiles are more prone to develop chemotherapy-related cardiac dysfunction [18]

Adapted from Table 10.4 of Chap. 10, "Cardiovascular Effects of Cancer Therapy," by Adams, Constine, Duffy, and Lipshultz (and from Simbre et al. [19]) in *Survivors of Childhood and Adolescent Cancer* (second edition) published by Springer

reactive oxygen species and topoisomerase 2β, increased accumulation of cardiotoxic anthracycline metabolites, and poorer sarcomere function, are more prone to develop chemotherapy-related cardiac dysfunction [18].

27.1.1.2 Prevention of Chemotherapy-Associated Cardiotoxicity

The obvious measure to prevent cardiotoxicity is to limit both cardiotoxic chemotherapy (especially anthracyclines) and radiation volume and dose as much as possible [22, 23]. The evidence on the effectiveness of other approaches to reduce or prevent anthracycline-associated cardiotoxicity is limited in terms of quantity and quality [24]. Early studies suggested that limiting the peak serum concentration of anthracyclines administered by continuous infusion could limit cardiotoxicity [25], but this has not been confirmed by subsequent studies, mainly in children. Anthracyclines release free radicals that damage cardiac myocytes, which are especially susceptible to such damage because of their highly oxidative metabolism and poor antioxidant defenses. Dexrazoxane, a free-radical-savaging, iron-chelating agent, has been demonstrated to reduce cardiotoxicity [26, 27]. Liposomal doxorubicin, an alternative preparation where the drug is encapsulated in an enclosed lipid sphere, has demonstrated efficacy with a reduced risk of cardiotoxicity [28]. A recent meta-analysis ($n = 633$) of randomised trials carvedilol for the primary prevention of anthracycline-induced cardiotoxicity demonstrated that prophylactic administration may reduce the early onset of left ventricular dysfunction compared with placebo [29]. Furthermore, there are some indications of a possible beneficial effect of angiotensin-converting enzyme (ACE) inhibitors after cardiotoxic chemotherapy [30]. Several other agents including L-carnitine have also been investigated [31] with some promising results. However, these studies have so far not been conclusive.

27.1.1.3 Surveillance for and Management of Chemotherapy-Associated Cardiotoxicity

Guidelines published by the International Late Effects of Childhood Cancer Guideline Harmonization Group [32] recommended regular echocardiographic surveillance for cardiomyopathy in children treated with anthracycline doses of >250 mg/m^2 or lower doses (>100 mg/m^2) in combination with moderate doses of chest radiation (>15 Gy). However, owing to the absence of high-quality evidence in other patient groups, guidelines from different organizations in North America and Europe do not agree on the need for surveillance in survivors of adult cancers with either imaging or other cardiac biomarkers [33]. Whether patients are offered routine surveillance may therefore vary from country to country and by the clinician's assessment of an individual's risk based on the factors outlined in Table 27.3.

Currently, there are no indications that the management of anthracycline-associated congestive heart failure should differ from that due to other causes [34]. Treatment generally focuses on correcting underlying physiological abnormalities such as increased afterload and decreased

contractility frequently including treatment with ACE inhibitors and/or beta-blockers [35]. Several guidelines developed for treating patients with asymptomatic left ventricular dysfunction or heart failure (not specifically after cancer treatment) include beta-blockers, ACE inhibitors, and diuretics [36, 37].

27.1.2 Radiation-Associated Cardiotoxicity

27.1.2.1 General Aspects of Radiation-Associated Cardiotoxicity

Radiation-associated heart disease in cancer survivors includes a wide spectrum of cardiac pathologies, such as coronary artery disease, myocardial dysfunction, valvular heart disease, pericardial disease, and electrical conduction abnormalities [38, 39] (see Fig. 27.1). Pericarditis is sometimes observed early after radiation, although it is rare with modern doses and techniques of Hodgkin lymphoma radiotherapy. Delayed pericarditis may occur months to years after radiation and usually resolves spontaneously although it may develop into chronic and/or constrictive pericarditis [40, 41]. Radiation-associated heart diseases other than pericarditis usually present 10–15 years after exposure, although, recently, a significantly increased risk of ischemic heart disease has been reported within 5 years following radiotherapy for breast cancer. Non-symptomatic abnormalities may develop much earlier on cardiac imaging.

Radiation causes both increased mortality, mainly fatal myocardial infarction (MI), and increased morbidity (see Tables 27.1 and 27.2).

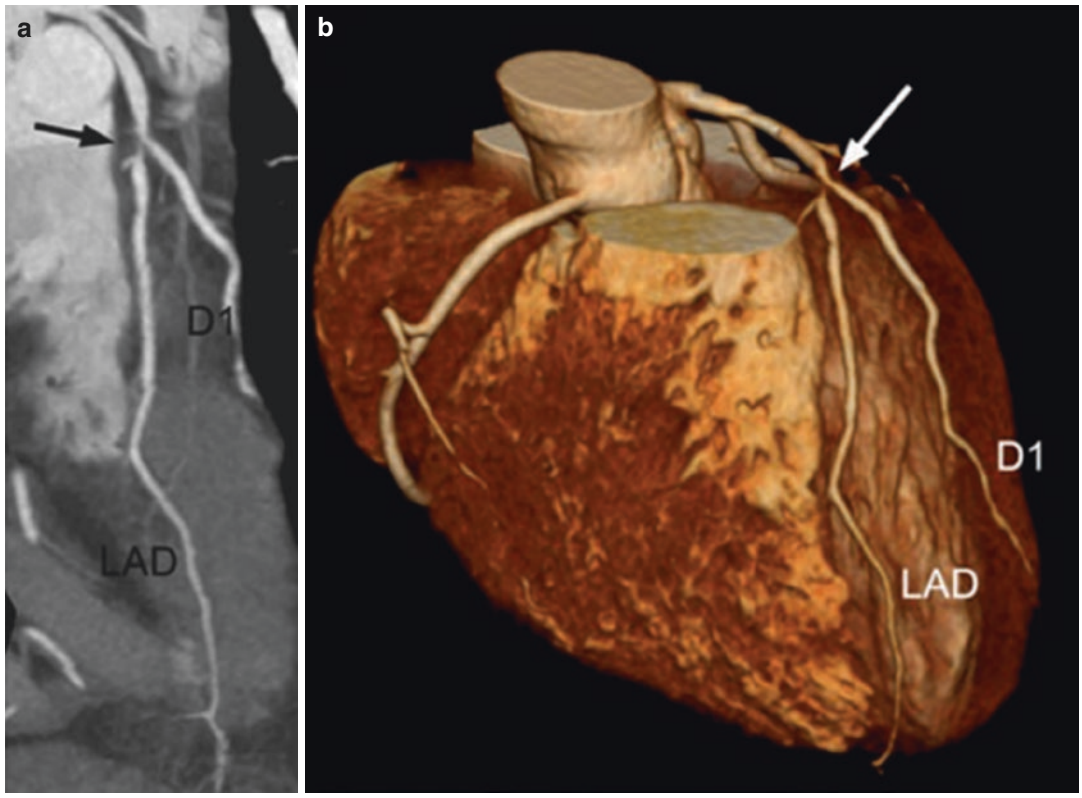

Fig. 27.1 Cardiac CT. Coronary artery disease: a 41-year-old man with severe obstructive coronary disease of the left anterior—diagonal bifurcation (arrow) only a few years after mediastinal radiation therapy because of Hodgkin lymphoma by angiographic (**a**) and cardiac CT (**b**) imaging (from Lancellotti et al. [42])

Table 27.4 Risk factors for the different manifestations of radiation-associated cardiotoxicity

Risk factor	Pericarditis	CM	CAD	Arrhythmia	Valvular disease	All causes of CD	References
Total dose (>30–35 Gy)	✓	✓	✓	✓	✓	✓	[41, 48–51]
Dose per fraction (≥2.0 Gy/day)	✓	✓	✓	✓	✓	✓	[41]
Volume of the heart exposed	✓	✓	✓	✓	✓	✓	[40, 52]
Younger age at exposure	–	✓	✓	✓	✓	✓	[20, 52]
Increased time since exposure	–	✓	✓	✓	✓	✓	[20]
Use of adjuvant cardiotoxic chemotherapy	–	✓	–	✓	✓	✓	[20, 21, 48]
The presence of other known risk factors in each individual such as current age, weight, lipid profile, and habits such as smoking	–	–	✓	–	–	✓	[6, 20]

Adapted from Table 10.5 of Chap. 10, "Cardiovascular Effects of Cancer Therapy," by Adams, Constine, Duffy, and Lipshultz (and from Simbre et al. [19]) in *Survivors of Childhood and Adolescent Cancer* (second edition) published by Springer
CM cardiomyopathy, *CAD* coronary artery disease, *CD* cardiac death

Epidemiological studies on Hodgkin lymphoma survivors show relative risk estimates for MI and cardiac death in the range of two- to fourfold in adults. This risk varies with age at treatment (increased relative risks for irradiation at a young age), the radiation therapy methods used, and the follow-up time [38, 39, 43]. In a Dutch study of Hodgkin lymphoma patients treated before the age of 51 years, even after 35 years or more, four- to sixfold increased standardized incidence ratios (SIR) for coronary heart disease and heart failure were observed, corresponding to 857 excess events per 10,000 person-years [11]. The persistence of increased relative risk over prolonged follow-up is of concern because this implies an increase in absolute excess risks over time, due to the rising incidence of cardiovascular disease with age.

Prospective screening studies demonstrate that clinically significant cardiovascular abnormalities such as coronary artery stenosis [44], reduced left ventricular dimensions, and valvular and conduction defects are very common even in asymptomatic Hodgkin survivors [45]. Hodgkin lymphoma survivors also have a significantly higher risk (SIR 8.4) of requiring valve surgery or revascularization procedures 15–20 years after radiotherapy [46]. Furthermore, an increased risk of restenosis after coronary artery stenting has been reported in patients treated with thoracic radiation for lymphoma [47].

There are several risk factors for radiation-associated cardiotoxicity (see Table 27.4). Cardiotoxicity is evidently related to both total radiation dose and dose per fraction to the heart [41].

27.1.2.2 Dose-Response Relationships for Radiation-Associated Cardiotoxicity

The heart volume included in the radiation field influences the risk of cardiotoxicity [41, 53], although there are still uncertainties regarding dose-effect and volume-effect relationships. A reduction in the increased risk of death from cardiovascular diseases other than myocardial infarction was reported 30 years ago in Hodgkin lymphoma patients treated after partial shielding of the heart and restriction of the total fractionated mediastinal dose to less than 30 Gy [3]. More recently, relationships between different cardiac radiotherapy dose parameters and several radiation-related heart diseases have been demonstrated following treatment for childhood cancer [53], breast cancer [54], and Hodgkin lymphoma [13, 49–51, 55]. These dose-effect relationships can be used to predict CVD risks for patients with newly diagnosed Hodgkin

lymphoma and Hodgkin lymphoma survivors. A linear dose-effect relationship between risk of cardiac disease and mean whole heart dose was found in a large study based on data from randomized trials performed by the EORTC between 1964 and 2004 in Hodgkin lymphoma patients [13]. Furthermore, a series of case-control studies nested in a large cohort of Hodgkin lymphoma patients treated in the Netherlands between 1965 and 1995 showed the following relationships:

- A nonlinear relationship between risk of valvular heart disease and dose to the affected cardiac valve [49] (Fig. 27.2a).
- A linear dose relationship between risk of coronary heart disease and mean dose to the whole heart [50] (Fig. 27.2b).
- A nonlinear dose relationship between risk of heart failure and mean dose to the whole heart (Fig. 27.2c) and a linear relationship between risk of heart failure and mean left ventricular dose [51].

With modern treatment techniques, 20–30 Gy of involved site or involved node radiotherapy can be applied to the mediastinum while keeping the mean heart dose between 5 and 10 Gy. Doses in this range are not expected to cause a significantly increased risk of heart failure or valvular heart disease and only lead to a 1.4–1.7-fold increased risk of coronary heart disease. More data are however needed to validate these dose-effects, to determine dose-volume relationships more precisely for individual cardiac substructures, and to disentangle radiation and chemotherapy effects.

27.1.2.3 Other Risk Factors for Radiation-Associated Cardiotoxicity

The risk for cardiovascular disease may also increase through indirect effects of radiotherapy; irradiation of the left kidney during para-aortic and spleen radiotherapy, for example, may lead to hypertension [56].

General risk factors for cardiovascular diseases such as hypertension, diabetes, hypercholesterolemia, obesity, and smoking [57–59] will also contribute to the risk for cardiovascular disease in patients treated for Hodgkin lymphoma [20, 60]. Whether the cardiovascular risk factor profile in these patients differs from that of the general population is unknown. The joint effects of anthracyclines, radiotherapy, and conventional cardiovascular risk factors (e.g., hypertension, smoking, physical inactivity) appear to be additive [11, 50, 51, 61].

27.1.2.4 Imaging of and Screening for Radiation-Associated Cardiotoxicity

Several studies, mainly in breast cancer, using single-positron emission computed tomography and Doppler echocardiography have revealed subclinical abnormalities [62] less than 2 years after radiotherapy. There is some evidence of a volume effect with such studies demonstrating that the extent of the left ventricle irradiation is predictive of observed imaging abnormalities [63, 64]. Although a relationship between these subclinical abnormalities and subsequent clinical heart disease may be expected, this has not yet been proven [41, 63–65]. However, one study in Hodgkin lymphoma survivors did demonstrate that diastolic dysfunction detected by Doppler echocardiography in asymptomatic patients was associated with stress-induced myocardial ischemia and an increased risk of subsequent cardiac events [66]. Several studies are ongoing looking at the utility of various imaging modalities including cardiovascular magnetic resonance. Conventional and novel blood biomarkers might detect early signs of radiation-associated cardiotoxicity. In the future, we hope to be able to identify survivor groups at high risk of late adverse effects (based on treatment, imaging/blood biomarkers, and/or genotype) for which screening should be recommended and/or intervention trials could be designed. Currently, screening for cardiovascular diseases following thoracic radiotherapy is still a matter of debate [67, 68]. There are uncertainties about the most effective screening modalities. Stress testing may identify asymptomatic individuals at high risk for acute myocardial infarction or sudden cardiac death [69], but this is not yet common practice.

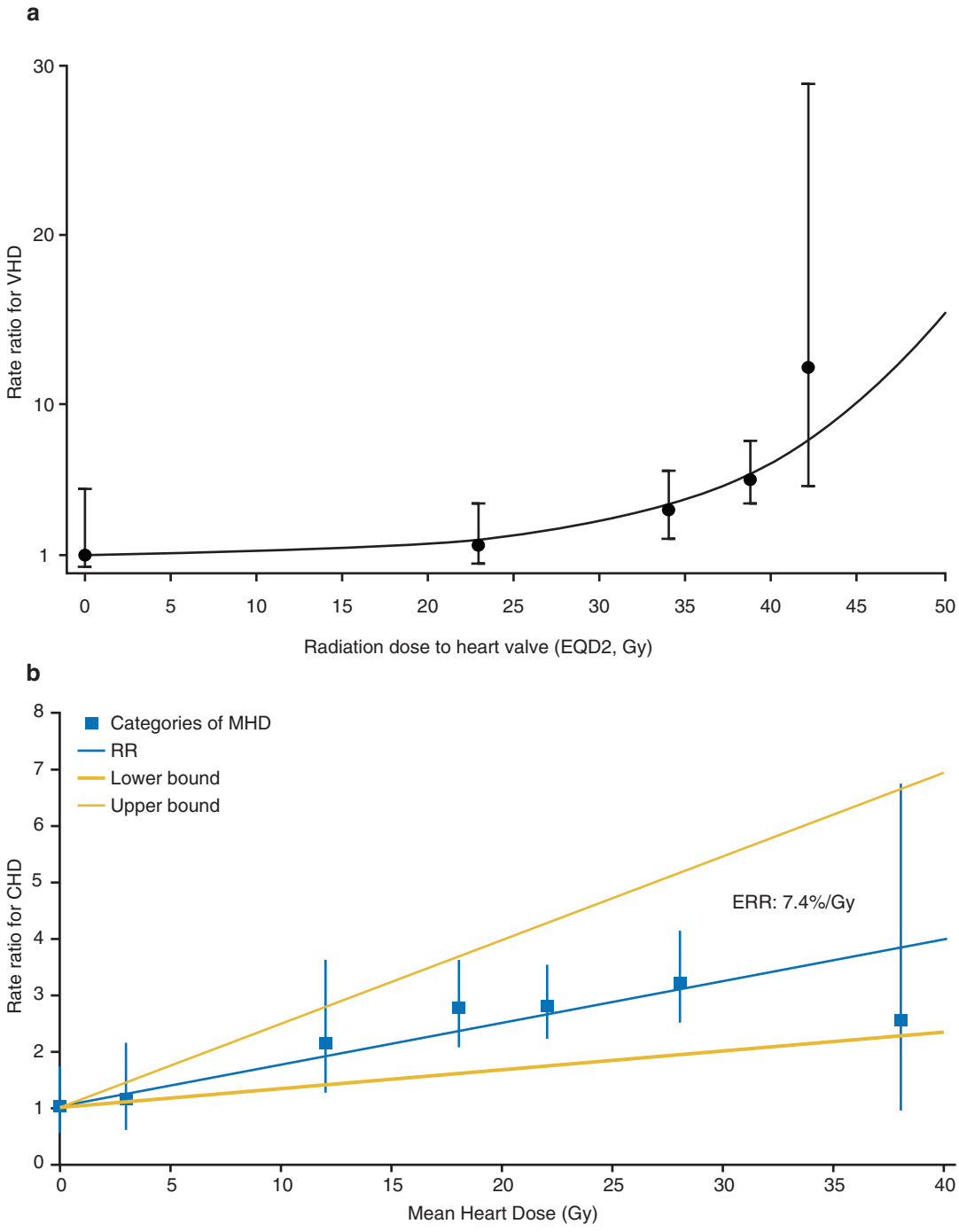

Fig. 27.2 Rate ratios (RR) for valular heart disease (VHD) (**a**) [48], coronary heart disease (CHD) (**b**) [49], and heart failure (HF) (**c**) [50] following radiotherapy for Hodgkin lymphoma by radiation dose to affected heart valve (**a**) and mean heart dose (MHD) (**b**), **c**) measured in Gray (Gy)

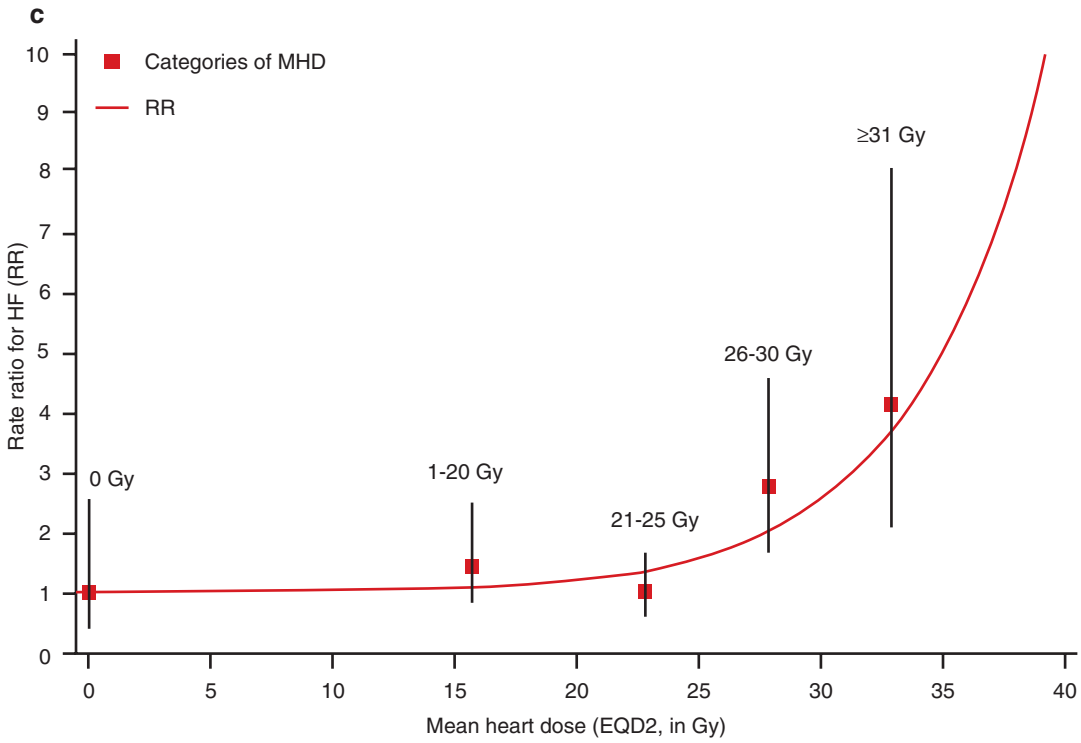

Fig. 27.2 (continued)

27.1.2.5 Prevention and Management of Radiation-Associated Cardiotoxicity

With respect to radiation, it is important to use conventionally fractionated radiation and to limit both radiation dose and volume [22]. Modern radiation techniques such as intensity-modified radiotherapy and radiotherapy during deep inspiration [70] allow radiation with lower exposure of the heart without compromising the radiation dose in the target volume. Proton beam therapy may also allow effective treatment of the mediastinum with reduced radiation doses to the heart and cardiac substructures [71]. Ongoing research is expected to provide more information regarding which structures are most critical and whether it is less harmful to expose a slightly larger volume to a low dose or a smaller volume to a slightly higher dose. Optimization of treatment regimens, including whether to omit radiotherapy entirely in individual cases, is still an important subject of study.

There are currently no indications that radiation-associated ischemic heart disease or other radiation-associated heart diseases need management approaches that are substantially different from the treatment used for heart diseases due to conventional causes. However, if cardiovascular surgery is needed, operating surgeons should be aware of increased risks due to radiation-induced fibrosis [72].

It is recognized that conventional risk factors for cardiovascular disease (e.g., smoking, obesity, hypertension, diabetes, and hypercholesterolemia) can further increase risks in addition to the risks associated with radiation exposure. It is therefore important that these factors are managed appropriately. Lifestyle advice should be offered so that patients should be advised to refrain from smoking from the start of treatment of Hodgkin lymphoma, maintain a healthy body weight, and exercise regularly. Vigorous exercise (i.e., exercise or sports for at least 20 min that made people sweat or breathe hard) has been shown to be associated with substantial reduc-

tions in the risk of major cardiovascular events in a large population of adult survivors of childhood HL even after controlling for important clinical covariates such as cardiovascular risk factors, treatment exposures, and other chronic health conditions [61]. It is quite likely that subgroups of Hodgkin lymphoma survivors can be identified that have risks similar to patients with recognized risk factors like diabetes for whom pharmacological primary prevention should be considered. In many countries, guidelines have been developed for primary and secondary prevention of cardiovascular diseases [73–75].

27.1.3 Radiation-Associated Cerebrovascular Toxicity

27.1.3.1 Radiation-Associated Stroke and Transient Ischemic Attack

As well as coronary artery toxicity, other blood vessels may be damaged by radiation treatment for Hodgkin lymphoma. Damage to the carotid arteries is of particular importance. Significantly increased risks of transient ischemic attack (TIA) and stroke have been described in patients previously treated with radiotherapy for Hodgkin lymphoma [12, 60].

The Childhood Cancer Survivor Study (CCSS) published a self-reported incidence and risk factors for stroke among childhood Hodgkin lymphoma survivors [76]. Twenty-four late-occurring strokes were observed in a cohort of 1926 survivors of childhood Hodgkin lymphoma (RR = 4.32, 95% CI = 2.01–9.29). A Dutch retrospective cohort study among 2201 5-year Hodgkin lymphoma survivors treated before the age of 51 between 1965 and 1995 showed a substantially increased risk for stroke and TIA that was associated with radiation to the neck and mediastinum [12]. The standardized incidence ratio for stroke was 2.2 (95% CI = 1.7–2.8) and 3.1 for TIA (95% CI = 2.2–4.2). Compared with the general population, these risks remained elevated after prolonged follow-up. The cumulative incidence of ischemic stroke or TIA 30 years after Hodgkin lymphoma treatment was 7% (95% CI = 5–8%) in this historical cohort.

27.1.3.2 Prevention and Screening for Radiation Damage to Carotid Arteries

Reduction of the prescribed radiation doses, the use of smaller target volumes, and radiation techniques that allow homogeneous dose distributions now allow the delivery of effective radiotherapy with a lower incidental radiation dose to the carotid arteries. With current concepts used in radiation therapy for patients with Hodgkin lymphoma (involved-node or involved-site radiation rather than involved-field radiation) [22], it is predicted that the risk of radiation-related damage to the carotids in patients treated for Hodgkin lymphoma will diminish [77].

There is no proof for the value of screening for radiation effects on the carotid arteries. Intervention studies are difficult to perform because of the relatively low number of patients treated for Hodgkin lymphoma and the prolonged latency and low absolute numbers of clinical events. Surrogate endpoints including measurement of intima-media thickness of the carotid arteries could be used, but due to lack of evidence for benefit, such screening is not generally recommended.

As for cardiotoxicity, the general risk factors for cardiovascular disease should be monitored and treated as necessary. Lifestyle advice should also be given, i.e., patients should be advised to refrain from smoking (from the start of treatment of Hodgkin lymphoma), maintain a healthy body weight, and exercise regularly [78].

27.1.3.3 Management of Radiation-Associated Carotid Artery Damage

The management of radiation-associated carotid artery disease should be as for that due to other causes. Experience shows that intervention for carotid artery stenosis as for non-radiation-associated disease can be successful. Both open endarterectomy [79] and angioplasty with stenting [80] have been used. There may be particular challenges with an open surgical approach following radiotherapy including fibrosis and

poor healing of irradiated tissue. Additionally, the disease may be situated more proximally in the carotid artery, and restenosis has been reported to be more common [81]. As such it could be recommended that radiation-associated disease is best managed by vascular surgeons with experience of the condition.

27.1.4 Radiation-Associated Damage to Other Major Arteries

Other major arteries are also susceptible to damage from doses of radiation above 30 Gy, including the subclavian and axillary arteries following supradiaphragmatic irradiation [46] and renal, mesenteric, and iliac vessels following subdiaphragmatic irradiation [82]. The clinical manifestations depend on the site and severity of the disease. Due to the potential for complications caused by radiation-induced fibrosis, management of radiation-associated vascular disease is best decided by a vascular surgeon with particular experience. As for other forms of radiation-related cardiovascular disease, good control of cardiovascular risk factors (e.g., smoking cessation, treatment of hypertension and hypercholesterolemia) should be maintained and antiplatelet therapy considered based on the severity of disease.

27.2 Late Pulmonary Toxicity

Both chemotherapeutic agents and radiation exposure of the lungs may lead to pulmonary morbidity and mortality. Significant mortality may be seen in the first months up to 1 year after chemotherapy [83]. During long-term follow-up, the mortality from second pulmonary neoplasms is significantly increased (see Chap. 26, Hodgson DC et al.), but not from other pulmonary diseases [8, 9]. Longer-term increased morbidity from pulmonary toxicity, as suggested by an increased risk of hospital admissions due to respiratory conditions, has also been observed among Hodgkin lymphoma survivors [84].

27.2.1 Chemotherapy-Associated Pulmonary Toxicity

27.2.1.1 General Aspects of Chemotherapy-Associated Pulmonary Toxicity

Several frequently used chemotherapeutic agents may cause pulmonary toxicity. Bleomycin is the most frequently used agent in treatment of patients with Hodgkin lymphoma that causes pulmonary toxicity.

27.2.1.2 Bleomycin

The pulmonary toxicity of bleomycin has been recognized since it was used in clinical trials in the 1960s for testicular cancer. Acute pulmonary toxicity following bleomycin-containing chemotherapy usually presents with dyspnea, dry cough, and fever. Long-term pulmonary toxicity is predominantly fibrotic and may be associated with pulmonary impairment and a dry cough. The classic radiographic pattern of bleomycin-induced interstitial fibrosis on chest X-ray is bibasilar reticular or fine nodular infiltrates. On CT scans, infiltrative changes, nodules, and patchy ground-glass opacities may be seen (see Fig. 27.3). Nowadays, FDG-PET can identify early bleomycin-related pulmonary toxicity, and it may also be used for follow-up of this toxicity. Conventional CT scanning is not able to distinguish between residual changes and active

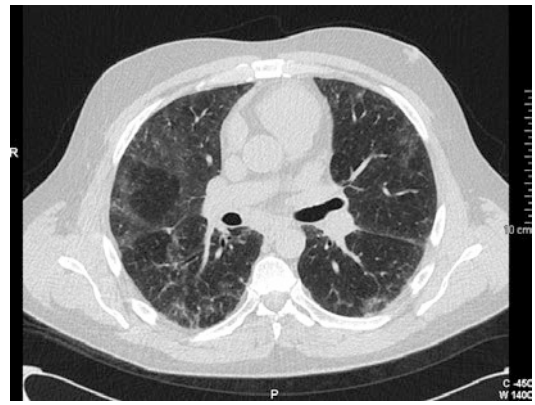

Fig. 27.3 CT scan of the chest showing interstitial pulmonary changes attributed to bleomycin

inflammation. Thus, PET represents a useful diagnostic tool and, independently of CT, indicates the resolution of disease activity, even in the presence of residual pulmonary scarring [85].

The severity of bleomycin toxicity may vary. Martin et al. [83] reported a bleomycin pulmonary toxicity incidence rate of 18% in patients treated with ABVD (25 of 141 patients), and one-quarter of the patients with bleomycin pulmonary toxicity died from pulmonary toxicity within 9 months of their Hodgkin lymphoma diagnosis. Risk factors for bleomycin toxicity included age >40 years, smoking, previous lung or renal impairment, thoracic radiotherapy, and G-CSF treatment. A detrimental impact on 5-year overall survival rates in Hodgkin lymphoma patients who developed bleomycin pulmonary toxicity was observed; the 5-year overall survival was 90% in unaffected patients and 63% in patients with bleomycin pulmonary toxicity ($p = 0.001$). In patients who survived the pulmonary toxicity, bleomycin pulmonary toxicity had no effect on outcome.

The BEACOPP regimen, which contains lower doses of bleomycin and higher steroid doses, has a lower incidence of pulmonary toxicity [86]. The recently reported RATHL trial in advanced Hodgkin lymphoma randomized omission of bleomycin from subsequent cycles if a complete metabolic response was obtained on FDG-PET following two cycles of ABVD. The pulmonary toxicity of continued ABVD was greater than AVD, with more grade 3 or 4 respiratory events and a larger reduction in the diffusing capacity of the lung for carbon monoxide (DLco) [87]. Importantly, the omission of bleomycin from cycles 3 to 6 did not result in significantly lower treatment efficacy.

27.2.1.3 Other Agents Leading to Pulmonary Toxicity

Carmustine is used in high-dose regimens, such as in combination with etoposide, cytarabine, and melphalan (BEAM), and may also induce pulmonary toxicity. The toxic reaction in the lung caused by carmustine usually manifests as chronic interstitial fibrosis that occurs after prolonged treatment and high cumulative doses.

The substitution of etoposide for gemcitabine in the escalated BEACOPP regimen was reported as non-feasible due to severe acute pulmonary toxicity. This increased toxicity was probably related to the concomitant application of gemcitabine and bleomycin [88]. No long-term follow-up is available for this treatment yet. In the same patient population [89], no increased toxicity was observed following radiation treatment. The authors therefore concluded that integration of radiotherapy in gemcitabine-containing regimens for Hodgkin lymphoma is feasible provided there is an interval of at least 4 weeks between the two modalities and that radiotherapy follows chemotherapy.

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 (MMAE). BV is associated with acute pulmonary toxicity which, although rare, can be potentially fatal. In 2015, on the basis of improved progression-free survival results in the phase III AETHERA trial, BV was approved for consolidation therapy after autologous transplant in patients deemed to be of high risk of relapse. The rate of pulmonary toxicity in this study was reported as 5% [90]; however due to heavy pretreatment, this likely represents a high-risk group. Small studies using BV as first-line treatment have reported no pulmonary toxicity [91]. BV should not be given in combination with bleomycin because this leads to a high risk of pulmonary toxicity [92].

27.2.1.4 Prevention of Chemotherapy-Associated Pulmonary Toxicity

Information on how to prevent long-term toxicity is scarce. High inspired concentrations of oxygen after prior treatment with bleomycin have been reported to be toxic [93]. The best strategy to avoid chemotherapy-associated pulmonary toxicity may simply be minimization of the use of these agents as demonstrated by the RATHL trial [87].

27.2.1.5 Management of Chemotherapy-Associated Pulmonary Toxicity

There is no accepted standard treatment for acute bleomycin toxicity. Corticosteroids, withholding bleomycin from subsequent chemotherapy, and proceeding with a regimen not containing bleomycin, if possible, are the most common approach [83]. Long-term corticosteroid treatment may be necessary to avoid recall pneumonitis.

27.2.2 Radiation-Associated Pulmonary Toxicity

27.2.2.1 General Aspects of Radiation-Associated Pulmonary Toxicity

Radiation may damage both the lung and the pleura leading to different clinical symptoms. Lung irradiation can cause subacute pneumonitis resulting in a dry cough and shortness of breath 2–3 months following treatment. Corresponding changes on chest X-rays and CT scans of the thorax may be observed (see Fig. 27.4). In the longer term, this may progress to chronic pulmonary fibrosis.

The risk for radiation pneumonitis is related to both the radiation dose and irradiated volume. Generally accepted clinical parameters related to radiation pneumonitis within 1 year after treatment include mean lung dose (MLD) and the volume of lung tissue receiving at least 20 Gy (V20). Koh et al. reported that a V20 ≥ 36% and an MLD of ≥14.2 Gy predicted a risk of RTOG grade 2 or greater that would be considered clinically significant (10–25% vs. 3% overall) [94]. Fox et al. reported similar cutoffs (V20 ≥ 33.5% and MLD ≥ 13.5 Gy) and also noted that those treated with mediastinal radiotherapy for relapsed Hodgkin lymphoma pretransplant had a higher risk of RP than those treated post transplant (57% vs. 0%, $p = 0.015$) [95]. More recently, Pinnix et al. reported predictors of radiation pneumonitis in patients receiving intensity-modulated radiotherapy (IMRT) [96]. Similar to the previous studies, an MLD > 13.5Gy and a V20 > 30% was predicted for radiation pneumonitis, but of note, the strongest predictor was for the volume of lung tissue receiving at least 5 Gy (V5) with a cutoff of V5 > 55%.

A Dutch study on breast cancer and Hodgkin lymphoma patients reported a partial recovery from early local perfusion, ventilation, and density changes that were seen between 3 and 18 months after radiotherapy. In lymphoma patients, local lung function did not further improve after 18 months [97].

Although minor radiological and pulmonary function abnormalities may be seen regularly

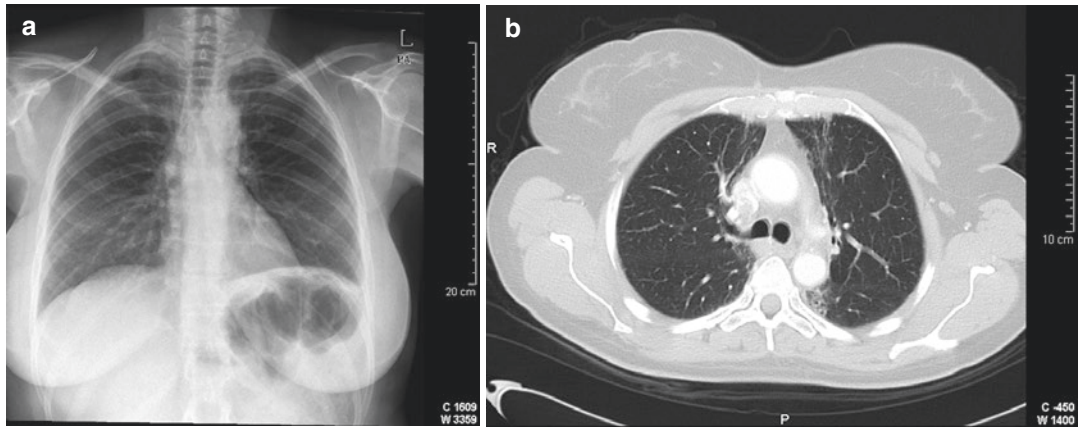

Fig. 27.4 (**a**) Chest X-ray 11 years after mediastinal radiation showing paramediastinal radiation fibrosis. (**b**) CT scan of the chest of the same patient also 11 years after mediastinal radiation showing interstitial pulmonary changes limited to the mediastinal radiation field

following radiation therapy for Hodgkin lymphoma, clinically significant symptoms are rare.

27.2.2.2 Prevention of Radiation-Associated Pulmonary Toxicity

The best way to minimize the risk of radiation-associated pulmonary toxicity is to minimize incidental radiation dose to the normal lung. The mean lung dose and V20 should be kept as low as possible, ideally well below recognized levels that are associated with increased risk [96]. This can be achieved by utilizing modern concepts of target volume definition and advanced treatment planning and delivery techniques where appropriate. IMRT can help reduce the higher radiation dose to the lungs, but care must be taken to limit the low dose received by the lung particularly in patients with non-modifiable risk factors for radiation pneumonitis such as bulky mediastinal disease and use of salvage treatment. Deep-inspiration breath-hold techniques may be particularly useful in these circumstances [98]. Proton beam therapy can also help reduce lung doses particularly for large mediastinal target volumes. Patients should be advised to refrain from smoking as this may increase the risk of acute and late pulmonary effects.

27.2.2.3 Management of Radiation-Associated Pulmonary Toxicity

Treatment of symptomatic radiation pneumonitis, occurring within the first year following treatment, generally consists of high-dose corticosteroids given for at least 2 weeks and then tapered over 3–12 weeks dependent on response. In the long term, no specific treatment is currently available, and pulmonary fibrosis following radiation is generally irreversible.

27.2.2.4 Combined Toxicity

Combined modality treatment is frequently used in patients with Hodgkin lymphoma. As the pulmonary toxicity of bleomycin and radiotherapy may interact, bleomycin dose modification may be required [99], and radiotherapy may have to be similarly adapted.

27.3 Conclusion

The cure rate of Hodgkin lymphoma patients today exceeds 80% with risk-adapted treatment using modern chemotherapy and radiotherapy regimens. Effective chemotherapy combinations have been developed, and ability to manage acute toxicities has improved significantly. Much of the knowledge regarding long-term cardiovascular and pulmonary toxicities relates to historical treatment regimens that are no longer applied. By utilizing the data available on toxicity and delivering patient-tailored treatment, we expect to observe lower risks of cardiovascular and pulmonary toxicity in the future for patients being treated today. However, it is important that treating physicians and patients remain aware of these possible late effects following cure.

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28 Gonadal Dysfunction and Fertility Preservation in Hodgkin Lymphoma Patients

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_28

28.1 Introduction

Patients with Hodgkin lymphoma (HL) are generally young, and high cure rates can be achieved. Thus, HL diagnosis and therapy frequently occur at a time of life when family planning plays an important role. It is therefore of major importance for the patients to discuss this subject and to consider fertility preservation techniques as early as possible after diagnosis. Furthermore, not discussing fertility issues and experiencing infertility after therapy can lead to depression, anxiety, and a general negative impact on quality of life in young cancer patients [1–4].

28.2 Gonadal Dysfunction in Men

28.2.1 Male Reproductive Physiology

Sperm production in males is stimulated via secretion of follicle-stimulating hormone (FSH) by the pituitary gland, regulated by a negative feedback mechanism via inhibin produced from the Sertoli cells and/or seminiferous tubules. Impaired or absent sperm production can be anticipated based on progressive elevation of FSH levels. Testicular androgen production is regulated by pituitary secretion of luteinizing hormone (LH) and controlled by a comparable feedback mechanism via testosterone production of the testicular Leydig cells.

Gonadal function can be evaluated by measuring FSH and LH together with the morning testosterone level. A semen analysis is a more definitive test of fertility, with normal values of $>15 \times 10^6$/mL, a total sperm motility of >40%, and with >3% of normal forms.

28.2.2 Hodgkin Lymphoma and Male Gonadal Dysfunction

Inadequate pretreatment semen quality due to the lymphoma itself has been reported by several authors. Some report on a high percentage between 78% of male HL patients, more frequently in patients with elevated erythrocyte sedimentation rate (ESR) and advanced stage [5–8]. However according to the results of a more recent analysis in 504 HL patients, only a total of 25% had an impaired spermatogenesis, while 75% had a normal total sperm number. The semen volume and total sperm number were significantly lower in the more advanced stages compared with the early stages, respectively [9].

The mechanisms involved are still unknown; however, possible factors include damage to the germinal epithelium, disturbances in the hypothalamic–hypophysial axis, immunological processes associated with cancer that impair spermatogenesis, and the impact of cytokines [5, 10–14]. In a study by the German Hodgkin Study Group (GHSG), male fertility was assessed in a total of 243 patients. In pretreatment semen analysis, only 20% of patients had normal sperms. Azoospermia was observed in 11% of patients and other dysspermia in 69% [6].

28.2.3 Treatment-Related Gonadal Dysfunction

Posttreatment gonadal damage is most often associated with chemotherapy regimens that include alkylating agents such as cyclophosphamide and procarbazine. The degree of damage

and recovery of spermatogenesis depends on the choice of drugs and the dose given. In multiple analyses, the rate of azoospermia after cyclophosphamide, vincristine, procarbazine, and prednisone (COPP); Mustargen, vincristine, procarbazine, and prednisone (MOPP); or cyclophosphamide, vincristine, procarbazine, prednisone, Adriamycin, bleomycin, vinblastine, and dacarbazine (COPP/ABVD) is high, ranging from 80% to 100% [7, 15–18]. Recovery of spermatogenesis can occur and has been recorded in 11–14% of males after these regimens [7, 18–20]. This rate was 40% when dysspermia was included [7]. Da Cunha and colleagues assessed MOPP-induced gonadotoxicity, demonstrating a significantly higher rate of azoospermia in patients treated with more than five cycles of MOPP compared to those receiving three or fewer cycles [21]. Newer and more intensive alkylating-agent-based combinations such as bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) are highly gonadotoxic in males. A study by the GHSG performing posttreatment sperm analyses at a median of 17.4 months after the end of therapy revealed azoospermia in 64% of patients, other forms of dysspermia in 30%, and normal sperm analysis results in only 6% of cases [6]. Thirty-eight patients with advanced-stage disease were examined, and 89% were azoospermic after treatment. None of these patients had a normal sperm status. There was no statistically significant difference in the posttreatment fertility status between a group of patients treated with eight cycles of BEACOPP baseline (with a cumulative cyclophosphamide dose of 5200 mg/m^2) and a group treated with eight cycles of BEACOPP escalated regimens (with a cumulative cyclophosphamide dose of 10,000 mg/m^2) [8].

In contrast, ABVD is less gonadotoxic, with gonadal damage that might be only transient [18, 22, 23]. However, more detailed data in advanced-stage patients receiving eight cycles of ABVD is needed.

Pelvic radiotherapy is now infrequently used in the management of HL. The testes are highly sensitive to irradiation in a dose-dependent manner. Doses above 4–6 Gy can result in permanent azoospermia, and doses of more than 6 Gy have a significant risk of this complication. Direct testicular radiation is usually not necessary in HL patients, and scattered radiation can be reduced by shielding the testes.

28.2.4 Predictive Factors for Gonadal Dysfunction and Damage

In a multivariate analysis of HL patients at initial diagnosis, Rueffer and colleagues described an elevated erythrocyte sedimentation rate (ESR) and poor prognostic risk groups as predictive for severe dysspermia [5]. A comparable study by Gandini and colleagues evaluated the semen quality in 106 untreated HL patients showing a significant decrease in sperm concentration, total sperm count, and forward motility in the later stages of HL (stages III–IV) compared to early stages (stages I–II). Interestingly, of 53 patients with elevated ESR, 79.2% had a normal sperm count, suggesting this parameter was not predictive for semen quality or potential infertility [24]. In an analysis of the GHSG risk groups, extranodal involvement and treatment with chemotherapy and BEACOPP were predictive factors for posttreatment azoospermia only in a univariate model. The fertility status prior to therapy was not predictive for posttreatment fertility [8].

28.2.5 Hormonal Analyses to Assess Testicular Function After Therapy

Achievement of paternity and sperm counts provide the strongest evidence of male fertility; however, gonadotropin measurement can also provide useful surrogate information. Most studies in male patients show that the FSH levels correlate with testicular function after treatment [6, 7, 16, 23, 25]. In a study by van der Kaaij and colleagues, FSH was measured in a total of 355 patients with early-stage disease at least 12 months after the end of treatment. FSH was elevated in 35% of all patients and in 3% of those

receiving radiotherapy only. In contrast, 60% of patients treated with alkylating agents had elevated FSH levels, whereas this was observed in only 8% of patients receiving chemotherapy without alkylators. Recovery of fertility was also poorer in patients treated with alkylating-agent-containing chemotherapy [25]. Kreuser and colleagues reported increased FSH levels in 80% of patients after treatment with COPP/ABVD [16]. In a retrospective GHSG analysis, abnormal FSH levels after chemotherapy were found in 79% of patients. In this group, the majority of patients were azoospermic (78%; $p = 0.001$), suggesting an indirect correlation between FSH level and testicular dysfunction after therapy [6]. In contrast, normal levels of LH and testosterone were found in 86% and 63% of patients after treatment. This underlines the hypothesis that spermatogonium cells are sensitive, whereas Leydig cells are more resistant to the toxic effects of cytostatic drugs [6, 16, 19]. Another important hormone in the assessment of infertility in men is inhibin B, which is produced by the Sertoli cells. Some studies support the use of inhibin B and inhibin B/FSH ratios as markers of male infertility [26, 27]. According to the results of a study by van Casteren and colleagues, 65% of male cancer survivors had low inhibin B values as compared to 26% in the control group [28]. Inhibin B levels significantly correlated with sperm concentration [28–30]. In a more recent GHSG study, fertility status in men was assessed using hormonal levels of FSH and inhibin B. A total of 761 male survivors younger than 50 years at diagnosis were analyzed after a mean observation time of 48 months. Inhibin B and FSH values significantly correlated with chemotherapy intensity. Half of the survivors after early-stage treatment (2–4 × ABVD or 2 × BEACOPP escalated + 2 × ABVD) had FSH and inhibin B levels corresponding to proven fertile men, whereas 88.8% of survivors after advanced-stage treatment had levels indicating oligospermia. An effect of follow-up time on inhibin B and FSH levels was found in men after 2 × BEACOPP escalated + 2 × ABVD, suggesting a recovery up to 4 years after intermediate aggressive treatment. In contrast to the dose-dependent effect of chemotherapy on spermatogenesis, mean testosterone levels were within the normal range [31].

28.2.6 Endocrine Hypogonadism After Chemotherapy in Men

Little is known on the endocrine status of men after chemotherapy for HL. A study by Kiserud and colleagues investigated posttreatment exocrine and endocrine gonadal function in 165 HL and 129 non-Hodgkin lymphoma (NHL) patients. In almost one-third of the patients, the hormone levels were compatible with endocrine hypogonadism, defined as low testosterone with or without elevated LH or elevated LH and normal testosterone. Interestingly, only three patients were receiving testosterone replacement at the time of analysis [32]. Comparable findings after chemotherapy for testicular cancer in young males were linked with a subsequent risk of developing metabolic syndrome [33].

According to the results of the GHSG study, aging male symptoms were not different between patients in the trials and reference values [31].

28.2.7 Fertility Preservation in Men: Preventative Pretreatment Strategies and Management After Chemotherapy

Sperm banking is a widely available and successful pretreatment preventative strategy [34]. All postpubertal males should thus be offered sperm banking prior to potentially gonadotoxic chemotherapy. This also needs to include patients planned for ABVD, although this regimen has a lower risk of treatment-related infertility. The reason for this is that in the event of early relapse, sperm quality and quantity might not have recovered, rendering banking impossible prior to gonadotoxic salvage treatment. Sperm should be banked regardless of count as intracytoplasmic sperm injection (ICSI) can be successfully used as part of in vitro fertilization (IVF) where counts

are low. If azoospermia is present and time permits, testicular sperm retrieval can be successful, particularly in the presence of a normal or only modestly elevated FSH level.

Cryopreservation of testicular tissue in prepubertal boys is still highly experimental, and pregnancies in humans have not been achieved. However, due to recent success in animal models [35], this technique is already offered in specialized centers to boys, expecting that the scientific progress will allow using the tissue to generate sperm or to reactivate the testes in the future.

28.3 Gonadal Dysfunction in Women

28.3.1 Female Reproductive Physiology

In premenopausal menstruating women, ovarian function is controlled by pituitary secretion of FSH and LH. FSH activates the granulosa cells of growing ovarian follicles which in turn begin to proliferate and to produce estradiol. This reduces the FSH levels by feedback inhibition, maintaining them at low levels. A mid-cycle LH surge induces ovulation following the formation of the luteal body that produces progesterone. Follicle development takes place over several months prior to ovulation. The growing follicles produce not only estradiol but also inhibin, which prevents the growth of too many follicles by down-regulating FSH.

At puberty, approximately 300,000 follicles are present in the ovary. This number declines with age to around 1000 at menopause (around 50–52 years of age), when FSH levels are insufficiently suppressed due to declining estrogen levels and therefore rise. The decline accelerates after the age of 35.

The number of follicles present in the ovary is known as the ovarian reserve and reflects reproductive capacity. Anti-Müllerian hormone (AMH) is produced by early developing follicles, and its levels vary slightly during the menstrual cycle. It acts directly on other follicles in the ovary and inhibits the growth of too many follicles. The levels of this hormone are increasingly used in clinical studies to assess long-term gonadal damage and ovarian reserve.

28.3.2 Treatment-Related Infertility

While the mechanisms underlying the ovariotoxic effects of cytostatic drugs are still largely unknown, it is clear that the development of primary ovarian failure after chemotherapy is caused by accelerated attrition of the ovarian primordial follicles. As described above, this is age-dependent and relates to the ovarian reserve. For alkylating agents, a direct dose-dependent cytotoxic effect has been described. Acute toxicity reduces the number of follicles, whereas chronic toxicity affects the quality of follicles resulting in early atresia [36].

Very similar to male patients, alkylating agents are most commonly involved in female gonadal damage. This is well documented after treatment with older chemotherapy regimens such as MOPP or MVPP (Mustargen, vinblastine, procarbazine, and prednisone). In an early study, only 17 of 44 women maintained regular menses when either of these regimens was used [37]. In a similar study, Schilsky and colleagues investigated ovarian function after treatment with MOPP and documented persistent amenorrhea in 11 of 24 women [38]. Similarly, after treatment with alternating COPP/ABVD for advanced-stage HL, therapy-induced ovarian failure was described in 17 of 22 women (77%) [16]. A further analysis included a total of 84 female patients with HL and NHL treated with at least three cycles of chemotherapy including alkylating agents. Premature ovarian insufficiency (POI) was defined as persistent amenorrhea for at least 2 years after the end of chemotherapy and elevated FSH levels. After a median follow-up of 100 months, 31 (37%) women with preserved fertility achieved natural pregnancy; in 34 women (40.5%), premature ovarian insufficiency was reported [39]. A study by Haukvik and colleagues

reported POF defined as persistent amenorrhea before the age of 41 in 37% of women after HL treatment. This occurred more commonly in alkylating-agent-treated patients [40]. In a retrospective GHSG analysis, the menstrual status after HL treatment of 405 female patients younger than 40 years was analyzed. With a median follow-up of 3.2 years, 51.4% of women who received eight cycles of escalated BEACOPP had continuous amenorrhea. Amenorrhea was significantly less common in women treated with two cycles of ABVD (3.9%), two cycles of alternating COPP/ABVD (6.9%), four cycles of alternating COPP/ABVD (37.5%), or eight cycles of BEACOPP baseline (22.6%). In a multivariate analysis, amenorrhea was most pronounced in women with advanced-stage HL, women older than 30 years of age at treatment, and women who did not take oral contraceptives during chemotherapy [41]. In a more recent analysis of the GHSG, hormonal levels and fertility questionnaires were analyzed in a total of 562 female survivors after a mean observation time of 46 months. Women were younger than 40 years at HL diagnosis. Normal mean AMH levels (>2 μg/L) were observed in women younger than 30 years after two to four cycles of ABVD early-stage treatment, but AMH levels were compromised in survivors ≥30 years old. After treatment with six to eight cycles of BEACOPP, mean AMH levels were 0 μg/L in both age groups, and highest FSH levels were measured in women older than 30 years. Regular menstrual cycle was reported by more than 90% of women after early-stage treatment and was mostly completed within 1 year. In contrast, after advanced-stage treatment, age at therapy onset was a decisive factor, and time to resumption of menstrual activity was considerably longer (Table 28.1). The risk of sustained amenorrhea 4 years after chemotherapy was 25% in 25-year-old women and 50% in 30-year-old women [31].

Van der Kaaij and colleagues analyzed POF defined as menopause before age 40 years in a total of 460 survivors after HL therapy within the EORTC-GELA trials using the Life Situation Questionnaire (LSQ). This questionnaire addressed in detail fertility and parenthood.

Table 28.1 Regular cycle after therapy depending on age at treatment and chemotherapy regimen in advanced-stage HL (Behringer et al.) [31]

Age (years)	Chemotherapy regimen	Regular cycle after therapy (%)
<30	8 × BEACOPP escalated	85
≥30		35
<30	6 × BEACOPP escalated	88
≥30		55
<30	8 × BEACOPP-14	70
≥30		44

Median follow-up was 16 years. The cumulative risk of POF for treatment with alkylating chemotherapy was 60% (95% CI, 41–79%) and only 3% (95% CI, 1–7%) or 6% (95% CI, 2–20%) for treatment with nonalkylating chemotherapy (ABVD or EBVP) or radiotherapy only, respectively [42].

Furthermore, Falorio and colleagues analyzed gonadal function in 238 HL patients. The median age of the patients at the time of diagnosis was 25 (14–40 years). The median follow-up was 7 years (1.5–25 years). Overall, 25% of the patients were considered to have impaired gonadal function. Older age (>30 years), advanced stage, front-line treatment with alkylating agents, and number of treatments were associated with an increased risk of impaired gonadal function [43].

After ABVD alone, chemotherapy-induced ovarian failure is less likely, especially when women are younger than 30 years at the time of treatment [22, 42, 44–47]. Older women have a significantly lower likelihood of ovarian recovery than those of younger age [16, 31, 37–39, 41, 48, 49]. In a recent analysis by Anderson and colleagues, a reduced ovarian recovery was detected in women ≥35 years after ABVD/AVD treatment compared to women <35 years [50].

Interestingly, the study by Haukvik and colleagues demonstrated a high cumulative percentage of POF in the youngest group of women. Compared to women diagnosed at the age of 30 years or older, those younger than 30 years developed POF approximately 5 years later. These findings suggest that younger age at HL treatment delays the development of POF but that the lifetime risk of POF is not decreased [40].

In a recent analysis by Weibull and colleagues, childbearing potential in 449 contemporarily treated relapse-free patients with HL was compared to childbirth rates in the general population. Childbirth during follow-up was found in a total of 101 patients (22.5%). Authors detected an increasing cumulative probability of childbirth over time in survivors since diagnosis. While patients had a lower childbirth rate in relation to comparators over the full follow-up period, 3 years or more after diagnosis, no difference in childbirth rates was observed. Even after BEACOPP therapy, childbirth rates approached those of the comparators later than 3 years after therapy; in contrast, none of the women experiencing relapse had a childbirth after relapse [51].

28.3.3 Posttreatment Assessment of Ovarian Reserve with Anti-Müllerian Hormone Levels

In the literature, the definition of gonadal toxicity varies. As described in the prior section, gonadal toxicity is defined by amenorrhea only in some reports, whereas in others also, hormonal parameters such as FSH or LH were used. However, all of these parameters only measure the ovarian reserve indirectly and have little sensitivity. Recent studies suggested that AMH is the most sensitive marker of gonadal function. This hormone is produced by the granulosa cells of early developing preantral and antral follicles in the ovary. The serum AMH levels can be used as a marker for the number of growing follicles—the levels decrease when the number of follicles declines. The AMH levels are not influenced by the day of the menstrual cycle. They are therefore a potentially convenient and useful marker [52–54].

28.3.3.1 Reduced Ovarian Reserve Prior to Therapy

Authors investigated AMH levels in HL patients before therapy. Interestingly, they report on significantly lower AMH concentrations in patients than in controls and a strong negative correlation between AMH and certain cytokines. This finding suggests a reduced ovarian reserve due to the lymphoma itself. However, in practical terms, this difference was only limited. Women with HL who were stimulated to freeze their oocytes had one oocyte less than control women [55–57].

28.3.3.2 Hypogonadism in Women

In the study of the GSHG, hypogonadism was analyzed using the menopause rating scale (MRS). Results demonstrated an age-dependent raise in severe menopausal symptoms for all HL stages and therapies. Severe menopausal symptoms in women >30 years were three- to fourfold higher than in an older (45–60 years) German reference population [31].

28.3.4 Radiation Therapy

Due to the increasing use of combined modality or chemotherapy-only approaches, infradiaphragmatic radiation is rarely used in the treatment of HL. According to a mathematical model described by Wallace and colleagues, the dose of radiation required to destroy approximately 50% of oocytes has been estimated to be less than 2 Gy [58]. The estimated effective sterilizing radiation dose to the ovary at birth is 20.3 Gy, at the age of 10 years 18.5 Gy, at the age of 20 years 16.5 Gy, and at the age of 30 years 14.3 Gy [59].

The uterus is more radioresistant than are the ovaries. Nonetheless, partial or complete uterine irradiation, though rarely required, can result in uterine fibrosis with an increased rate of miscarriage. Gonadal and organ damage can be reduced by shielding and other techniques, and pretreatment oophoropexy may also have a role in this process (see Sect. 28.3.8).

28.3.5 Preventative Treatment Strategies in Women

After HL diagnosis, strategies for ovarian protection should be offered to all women who have not completed their family planning. Women should

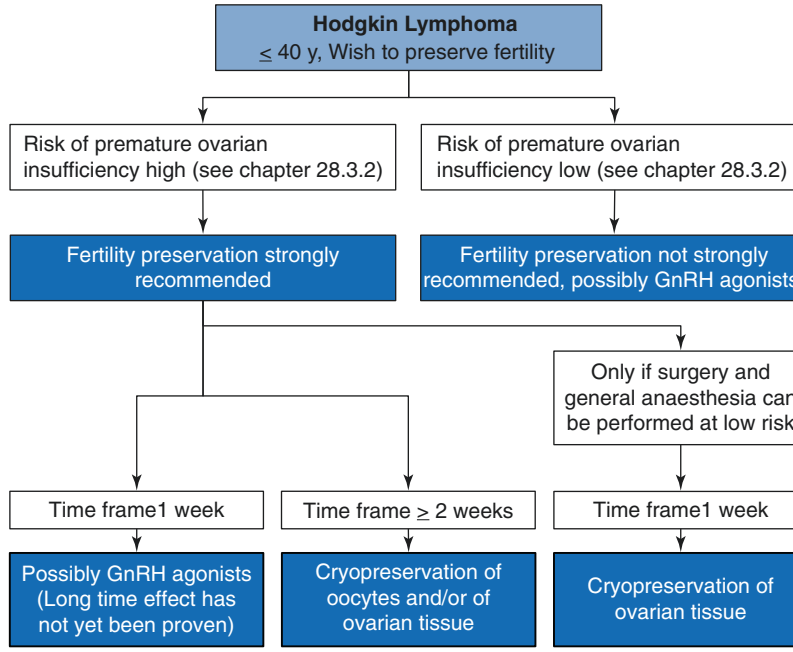

Fig. 28.1 Fertility preservation in women with HL

be referred to an experienced center for counseling on protective procedures, after which management approaches should also be discussed with the attending oncologist. Figure 28.1 summarizes the options to preserve fertility in women with HL.

28.3.6 Pharmacological Prevention of Gonadal Damage

28.3.6.1 GnRH Agonists (GnRHa) During Chemotherapy

A simple and commonly used method of fertility protection is chemotherapy-concomitant treatment with GnRH agonists. This method is based on the hypothesis that pituitary downregulation leads to an "inactivation" of ovarian activity and hence to reduced sensitivity of the germinal tissue to cytotoxic effects. The medication should be started at least 5–7 days before the start of chemotherapy due to the initial increased gonadotropin release from the pituitary gland (so-called "flare-up" effect), an effect which should last at least 1–2 weeks after the administration of the last cycle of chemotherapy. The benefits are quick availability and no serious side effects. Side effects can include reversible menopausal symptoms.

The fertility-protective effect of GnRHa has been the subject of controversial debate for years, as data from the mainly small and retrospective studies was heterogeneous. Meanwhile, five large prospective randomized studies, all of which were performed in women with breast cancer, have provided clarity. A meta-analysis incorporating these five studies showed reduction in the risk of chemotherapy-induced premature ovarian failure of approximately 50% within the first 1–2 years after initiation of chemotherapy (adjusted odds ratio, 0.38; 95% CI, 0.26–0.57, $p < 0.001$) and the chance of later pregnancy is increased (incidence ratio, 1.83; 95% CI, 1.06–3.15, $p = 0.030$) [60]. Even though these studies have been performed with breast cancer patients, it can be assumed that the same effect can be expected in Hodgkin lymphoma.

However, it is still unclear whether the protective effect of GnRHa persists for several years [61]. Because of this, GnRHa should not, if possible, be given as the sole option for fertility protection, especially in younger women who will still have to wait several years to realize their desire to have children [62].

28.3.7 Cryopreservation of Oocytes/Ovarian Tissue

There have been remarkable advances in recent years in the field of cryopreservation of oocytes and ovarian tissue. But which technique (if any) should be recommended to a young woman before chemotherapy? This depends on the treatment to be used, age, availability of a partner, and the clinical condition of the patient and time available. It should be emphasized that results are likely to significantly improve during the reproductive span of patients currently undergoing harvest and storage.

28.3.7.1 Ovarian Stimulation and Cryopreservation of Fertilized and Unfertilized Oocytes

In accordance with the procedure of in vitro fertilization (IVF), oocytes can be retrieved by ovarian stimulation and follicular puncture, which can then be cryopreserved in an unfertilized or fertilized state.

Hormonal stimulation for pure egg cell retrieval can be carried out independently of the patient's cycle day ("random start stimulation") so that the time frame until the beginning of chemotherapy is only about 2 weeks [63, 64]. The stimulation plans differ only slightly, depending on whether the stimulation is started in the early follicular phase, the late follicular phase, or the luteal phase [57]. By using GnRH antagonists and ovulation induction with GnRH agonists, ovarian hyperstimulation can be avoided, which would have previously led to postponement of chemotherapy. Double stimulation can also be performed, which takes 4 weeks to complete and doubles the chances of success [65].

Unfertilized oocytes are usually conserved, but preservation is also possible after fertilization. However, it must be considered that fertilized oocytes can only be transferred later after the approval of both partners.

The risks of ovarian stimulation are low. Severe hyperstimulation during stimulation of patients in the FertiPROTEKT network occurred only once in 684 stimulations [64]. The malformation rate of children born from cryopreserved oocytes does not differ from those after spontaneous conception.

28.3.7.2 Cryopreservation of Ovarian Tissue

Cryopreservation of ovarian tissue is now an established method to restore fertility after oncological treatment [62]. Cryopreservation of ovarian tissue is particularly suitable for younger patients, since their ovarian reserve and thus the follicular density are very high.

The procedure can be performed independently of the cycle and therefore does not lead to any delay in oncological treatment. Fifty percent of the ovarian cortex of an ovary is usually resected laparoscopically. The ovarian tissue is cryopreserved immediately after removal, or it can be transferred to a specialized ovarian tissue cryopreservation center with an attached cryobank. A transport time of 4–5 h before cryopreservation is possible without any problems [66]. Even with longer periods (overnight transport), the vitality of the tissue appears to be preserved [67].

If a patient with ovarian failure wishes to have children after a sufficiently long recurrence-free interval, the tissue can be retransplanted. Transplantation is usually performed in the usual location (orthotopic) either in or on the remaining ovary or in a peritoneal pocket in the ovarian fossa. According to recent studies, tissue remains active for about 6 months to more than 7 years [68]. Pregnancies can occur during this time. In principle, natural conception is possible with the orthotopic transplantation sites; assisted reproductive technique (ART) measures (ICSI) can be used if necessary.

A case report has been published that describes a birth after cryopreservation of ovarian tissue at the age of 13 (premenarchal) and transplantation at age 27 [69]. This case report shows that transplantation can lead to pregnancies, even after prepubertal cryopreservation of ovarian tissue. This is also supported by two case reports that have demonstrated puberty induction by transplantation of prepubertal cryopreserved ovarian tissue [70, 71].

Autotransplantation of ovarian tissue in cancer patients poses a theoretical risk of recurrence

from the cryopreserved tissue [72]. The extent of the risk of recurrence of malignancies after transplantation depends mainly on the type of disease, the stage, and the amount of transferred malignant cells. Overall, the risk of re-transplantation of malignant cells is considered very low if strict quality assurance measures are ensured.

A purely experimental option for these patients would be the maturation of oocytes without tissue transplantation in vitro. The possibility of obtaining mature, fertilizable oocytes from the primordial follicles of the ovarian tissue with the entire use of in vitro maturation has so far only been possible in animal experiments; in humans, it is currently not possible; however, great progress is being made [73]. Another possibility is the also purely experimental xenotransplantation of human ovarian tissue. Ovarian tissue is transplanted into immunodeficient mice (e.g., SCID mice) which do not exhibit any rejection reaction against foreign tissue, where the follicles mature and can be punctured to retrieve the oocytes [74].

Combination of Different Fertility-Preserving Techniques

A combination of fertility-preserving measures should be discussed, especially in patients at high risk of primary ovarian insufficiency. For example, the combination of the removal and cryopreservation of ovarian tissue, directly followed by ovarian stimulation for the cryopreservation of oocytes, is possible [75]. This theoretically increases the chance of a future pregnancy.

28.3.8 Transposition of the Ovaries

If pelvic radiotherapy is planned, ovarian transposition may be performed by moving one or both ovaries out of the radiotherapy field. This can significantly reduce ovarian radiation exposure and reduce the risk of radiogenic ovarian failure [76]. The procedure is normally performed laparoscopically, and it is usually necessary to completely separate the adnexa from the uterus. Various surgical techniques have been described in the literature, including cranial, lateral, medial, and anterior transpositions. Due to the inhomogeneity of the collectives and the lack of prospective randomized studies, no reliable statement on the comparison of the different techniques is possible, although cranial transposition is the safest technique for reducing the radiation dose during pelvic radiotherapy.

The success rate regarding preserved ovarian function was reported as 80.8% (min 17%, max 95%) in a meta-analysis with 32 publications and a total of 1189 patients [77]. However, a considerable publication bias is suspected since many cases or trials with poor success rates should not have been published [78].

The level at which the ovaries are suspended is considered one of the biggest prognostic factors for the preservation of ovarian function. The ovaries should be located at least 2 cm above the iliac crest [79]. The question of whether bilateral or unilateral ovarian transposition should be performed can only be decided on a strictly individual basis in cooperation with radiologists. In addition to the expected gonadal toxicity, the eventual wish to have a unilateral transposition plays a role in enabling spontaneous conception via the remaining side.

Although the effectiveness of ovarian transposition in maintaining ovarian function is considered to be high, pregnancies (e.g., after radiotherapy for cervical cancer) are rare for various reasons after ovarian transposition [80]. Therefore, it is important to know whether there is still a wish to conceive after oncological treatment and, if necessary, to consider reproductive medical measures [81]. Reversing ovarian transposition is technically difficult and is associated with a high risk of loss of ovarian function. Furthermore, radiotherapy to the uterus significantly reduces the chance of pregnancy.

Oncological safety is not significantly affected by transposition. The surgical risks of ovarian transposition are low. Ovarian cysts can develop in 25% of cases postoperatively, which usually relates to disturbed ovarian function. The frequency of metastases at the trocar insertion sites ("port site metastasis") is stated as <1%.

28.3.9 Premature Menopause

Early onset of menopause in female patients after treatment for childhood cancer is well described showing higher cumulative incidence of premature menopause by the age of 40 for survivors compared to control siblings (8% vs. 0.8%) [82]. Alkylating-agent-based combination chemotherapy will very likely lead to premature menopause in female patients [83, 84]. In younger patients at treatment, data reveal a longer period after therapy over which premature menopause could occur compared to patients treated at older age [84]. It is important to note that occasionally transient cessation of menses, with or without hot flushes, can occur. Hormone replacement may be indicated to reduce symptoms and prevent osteoporosis. If fertility is desired in younger women and if conventional low-dose HRT is used, it is possible to monitor ovarian recovery with FSH levels. If oral contraceptives are used, treatment breaks with re-evaluation of ovarian function may be reasonable.

28.3.10 Fertility and Late Effects in HL Survivors

During the follow-up period, it is still very important to discuss fertility issues with HL survivors. First, family planning after cancer therapy often needs special medical attendance and reproductive counseling. Second, many late effects caused by an early decline of hormone levels (estradiol, testosterone) may occur during this period, e.g., cardiotoxicity, bone health, and further endocrine late effects [2].

28.4 Conclusions

Remarkable advances have occurred in the management of HL, and today cure can be anticipated for the vast majority of young adults. When alkylating-agent-based combination chemotherapy was first introduced in the 1960s, almost any late effect on fertility was acceptable in the context of the hitherto grim prognosis of HL, particularly in advanced stages. Then, regimens such as ABVD proved to be equivalent or superior, inducing less gonadotoxic effects. After the introduction of highly effective alkylating-agent-based therapy such as BEACOPP, impressive tumor control and overall survival rates were achieved but were associated with substantial gonadal toxicity, necessitating the development of adjunctive fertility-supporting technology. Current trials evaluate risk-adapted treatment, reserving more effective but more toxic treatment for subgroups of patients with poorer prognosis as judged by positron emission tomography (PET) scanning.

The remarkable advances in the management of HL are paralleled by advances in fertility preservation techniques. It is of particular importance that these are considered and discussed as early as possible after diagnosis in the context of the patient's wishes with regard to treatment and future fertility.

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Cancer-Related Fatigue in Hodgkin Lymphoma

29

Stefanie Kreissl, Anton Hagenbeek, Hans Knoop, and Peter Borchmann

Contents

29.1 Introduction

With stage-adapted treatment including polychemotherapy with or without consolidation radiotherapy, Hodgkin lymphoma (HL) has become a curable malignancy for most patients [1–3]. With a median age of about 30 years at first diagnosis, the disease mainly affects young adults, and the improved curability has led to a continuously growing number of long-term survivors at risk for long-term sequelae and impairments of their health-related quality of life (HRQoL) [4–7]. Cancer-related fatigue (CRF) is known to be one of the most common patient-reported impairments in survivors of HL.

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A. Engert, A. Younes (eds.), *Hodgkin Lymphoma*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-32482-7_29

Available data suggest that patients with HL experience significant physical and psychological distress including high levels of CRF, which often remain considerably elevated even years after treatment [7–10]. Persistent fatigue has been observed in up to 40% of survivors of HL and has been reported to be 2.5–3 times higher in HL survivors than in the general population [9, 11, 12].

CRF is defined as a persistent subjective feeling of strong physical, emotional and/or intellectual exhaustion, which cannot be explained by previous activities. It implies reduced energy level, reduced muscle strength and cognitive impairments [13].

Symptoms of CRF in patients with HL deserve attention because they are associated with adverse effects on psychological well-being and everyday life including family, work and social participation [14, 15]. CRF often remains a relevant problem even years after successful lymphoma treatment. Moreover, persistent severe fatigue prevents survivors from social reintegration and return to their work or education life [16]. Thus, CRF requires specific focus, both for the early identification of patients suffering from CRF and for the development of distinct treatment approaches.

29.2 Assessment of CRF

In HL, most recently published studies on CRF used validated questionnaires either measuring fatigue specifically, e.g., by the use of the Fatigue Questionnaire (FQ) or the Multidimensional Fatigue Inventory (MFI), or HRQoL questionnaires such as the 36-Item Short Form Survey (SF-36) or the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [17–21].

To generate a better understanding of CRF, the German Hodgkin Study Group (GHSG) implemented the assessment of health-related quality of life, including self-reported fatigue, systematically and prospectively in all first-line trials since 1998.

In 2016, the GHSG published the results of a 5-year longitudinal analysis of CRF in 5306 HL patients and survivors enrolled in the three prospective, randomised controlled clinical trials HD13–HD15 for early-favourable, early-unfavourable and advanced stages [1, 2, 11, 22]. CRF assessment was performed using a validated quality of life questionnaire for survivors (QLQ-S). Part of the QLQ-S is the EORTC QLQ-C30, and its fatigue scale was used as a continuous outcome parameter. The fatigue scale of the EORTC-QLQ-C30 is reliable, validated and sensitive to chance. The respective German reference values were used for normalisation in the descriptive part of the analyses [21, 23, 24].

Fatigue scores range from 0 to 100, with higher scores indicating worse fatigue. Differences of ten points or more are generally deemed to be clinically relevant [25]. Furthermore, an absolute threshold value of fifty points was used for describing very high fatigue scores as severe fatigue [26].

Patients and survivors completed the questionnaires at the following timepoints: immediately after diagnosis (baseline), after two to four cycles of chemotherapy, immediately after end of treatment, and at predefined follow-up examinations up to 5 years after end of treatment.

29.3 Prevalence of CRF and Time of Occurrence

Despite the clinical importance of this problem, little was known about the longitudinal development of CRF, as clinical and reliable data from prospective and controlled trials were lacking for a long time. Two prospective studies on HRQoL in HL patients reporting on CRF were restricted to early-stage patients, and CRF assessment started at the end of treatment. Therefore, no firm conclusions could be made on the effect of anti-lymphoma treatment or on the longitudinal course of fatigue due to missing pretreatment data [8, 27].

One of the key findings of the GHSG analysis was that clinically relevant fatigue is prevalent in HL patients even before the onset of

chemotherapy. Baseline fatigue levels increased with higher-stage disease, reflecting higher tumour burden. Mean fatigue scores at baseline were lowest in patients with early-stage favourable Hodgkin lymphoma (HD13 trial, mean fatigue score 30·8 [SD 28·0]), higher in patients with early-stage unfavourable disease (HD14 trial, 39·8 [29·4]) and highest in patients with advanced-stage disease (HD15 trial, 49·0 [30·2]). Accordingly, the proportion of patients with severe fatigue (fatigue score ≥ 50) also increased with higher disease stage from 24% patients in the HD13 trial, to 37% in the HD14 trial, to 48% in the HD15 trial, respectively.

29.4 The Longitudinal Course of CRF

By contrast, the large effect of the disease stage on the extent of baseline fatigue did not translate into different fatigue levels during treatment. Against expectation, all different treatment intensities used in the three trials induced very severe fatigue symptoms. This finding was surprising because the intensity of two cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) in early stages is very different from six to eight cycles of escalated-dose bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone ($BEACOPP_{escalated}$) in HD15.

After the end of treatment, survivors reported a rapid decrease in fatigue scores up to 1 year after the end of treatment, and fatigue scores remained stable after that, irrespective of disease stage and treatment received: year 1, mean FAref 21·4 (SD 25·3) in HD13, 20·3 (SD 23·5) in HD14 and 23·3 (SD 24·5) in HD15 (Fig. 29.1).

The mean long-term fatigue scores of survivors (i.e., at 2 and 5 years after the end of treatment) were very similar across the three trials (mean FAref in the second year 16·6 [SD 24·5] in HD13, 17·0 [24·1] in HD14 and 19·5 [23·9] in HD15; in the fifth year, 17·7 [25·7] in HD13, 14·8 [24·6] in HD14 and 16·3 [24·4] in HD15). Although long-term fatigue was decreased compared with baseline scores in patients in the HD14 and HD15 trials, the fatigue scores were still higher than the reference population by a clinically relevant amount (FAref ≥ 10 points) in all three trials (combined FAref scores for all three trials 21·7 [SD 24·3] in year 1 to 16·0 [24·7] in year 5, respective data for year 2 17·9 [24·1]).

29.5 The Impact of Treatment Intensity on Long-Term CRF

The potentially negative effect of intensified first-line treatment on the development of long-term fatigue has long been a cause for concern among patients as well as oncologists. Previously published data suggested that there is no correlation between treatment intensity and the extent of long-term fatigue [8, 9, 28, 29]. However, this question needed to be answered by a large prospective trial with randomly assigned treatments in all stages of HL.

To assess the effect of treatment on long-term fatigue, the GHSG analysis compared fatigue scores of patients treated with the best experimental treatments (i.e., the treatment group in each respective trial that showed the best outcome among the experimental treatments in the final analysis) of the trials to their respective reference treatments. Fatigue scores in the second and fifth year after end of treatment were analysed and adjusted for sex, age and fatigue score at baseline.

Treatment intensity within the investigated range of interventions did not significantly affect the extent of long-term fatigue in any of the three trials. In particular, considering patients with early-stage unfavourable Hodgkin lymphoma, there was no increase of long-term fatigue after the relevant intensification of chemotherapy with $BEACOPP_{escalated}$ as compared with ABVD only [11].

29.6 Predictors of Long-Term CRF

The EORTC H8 trial for early-stage HL formerly concluded that fatigue at the end of treatment predicts subsequent persistent fatigue [8]. The

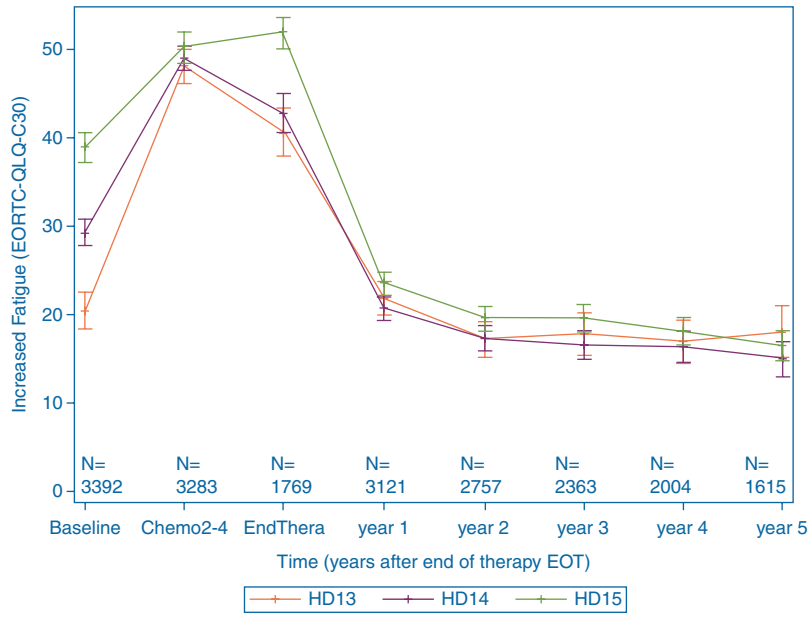

Fig. 29.1 Longitudinal development of fatigue in the HD13, HD14 and HD15 trials up to 5 years after treatment. Mean fatigue score normalised to the German population reference values (FAref) and 95% CIs. EORTC, European Organisation for Research and Treatment of Cancer

GHSG analysis of patients of all stages revealed that fatigue at baseline was a significant predictor for long-term fatigue. Additionally, age was a significant and relevant risk factor within the respective studies, and its effect on long-term fatigue increased with more advanced disease [11]. This is in line with previously published data reporting higher fatigue levels in older patients [8, 9, 28].

For clinical practice, the early identification of patients being at high risk for developing long-term fatigue seems to be of utmost importance. In the GHSG analysis, subgroups of patients with significantly different fatigue trajectories were identified in each trial (three subgroups in HD13 and four subgroups in HD14 and HD15). Irrespective of stage and treatment, the subgroups detected resulted primarily from different baseline levels translating into different long-term fatigue. None of the three subgroups in early-stage patients had a notable improvement in fatigue after treatment compared with baseline fatigue. Conversely, subgroups of patients with early-stage unfavourable and advanced-stage disease showed distinct improvements in fatigue after treatment, if baseline fatigue scores did not markedly exceed 50 (severe fatigue). Thus, considerable improvement of moderate baseline fatigue can be expected for around 70% of survivors after treatment of early-stage unfavourable and advanced-stage HL. Patients suffering from severe fatigue at baseline showed typically no improvement in fatigue irrespective of disease stage. The proportion of survivors in the subgroups with severe persistent fatigue ranged from 17% (95% CI 12–22) of patients with early-stage favourable disease, to 27% (95% CI 22–32) of patients with early-stage unfavourable disease, to 22% (95% CI 12–32) of patients with advanced-stage disease. Accordingly, about 20% of all patients will report persistent severe fatigue even 5 years after successful treatment for HL [11] (Figs. 29.2, 29.3, and 29.4).

29.7 Impact of Persistent CRF on Treatment Outcome and Social Reintegration

It has been shown that HRQoL can help to predict survival in cancer patients [30, 31]. However, there was very little knowledge on the consequences of baseline or persistent severe fatigue for patients and survivors with HL during the follow-up period.

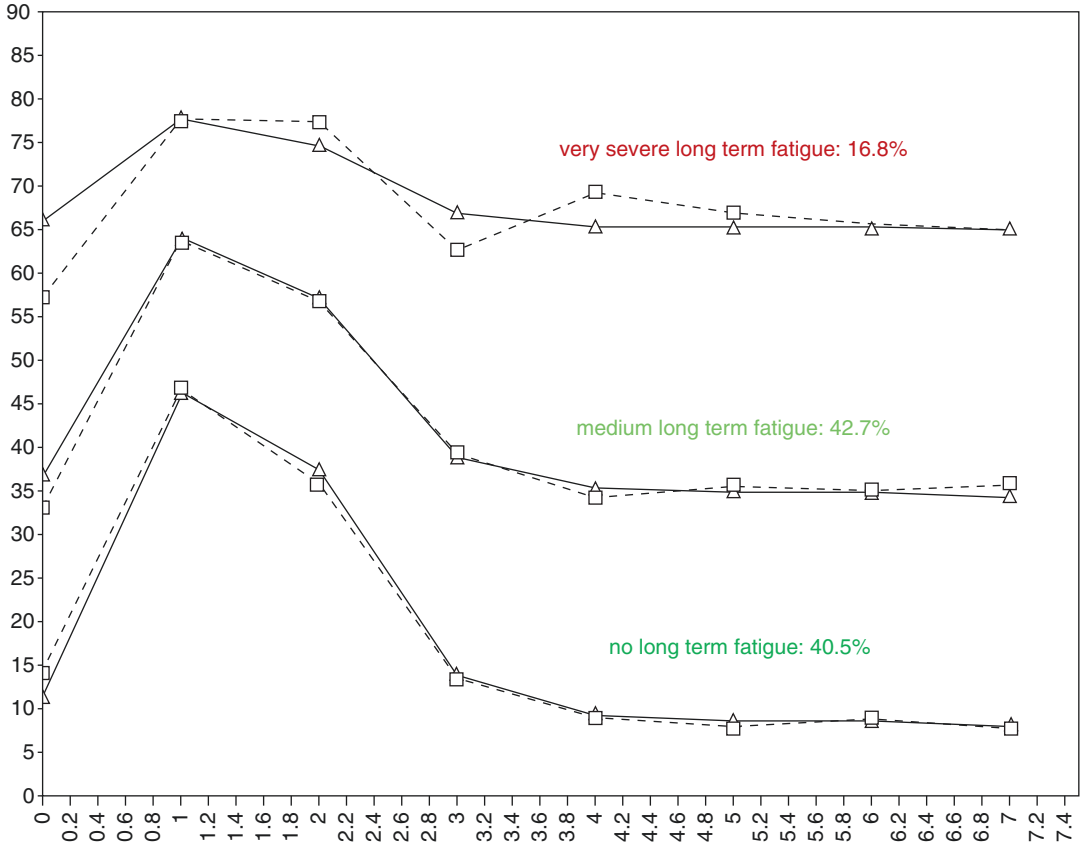

Fig. 29.2 Subgroups with different fatigue trajectories in HD13

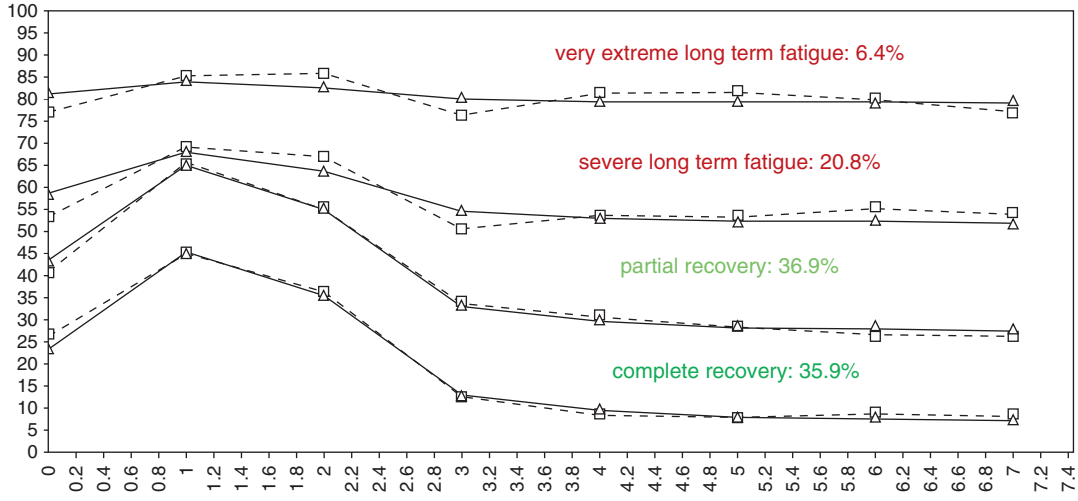

Fig. 29.3 Subgroups with different fatigue trajectories in HD14

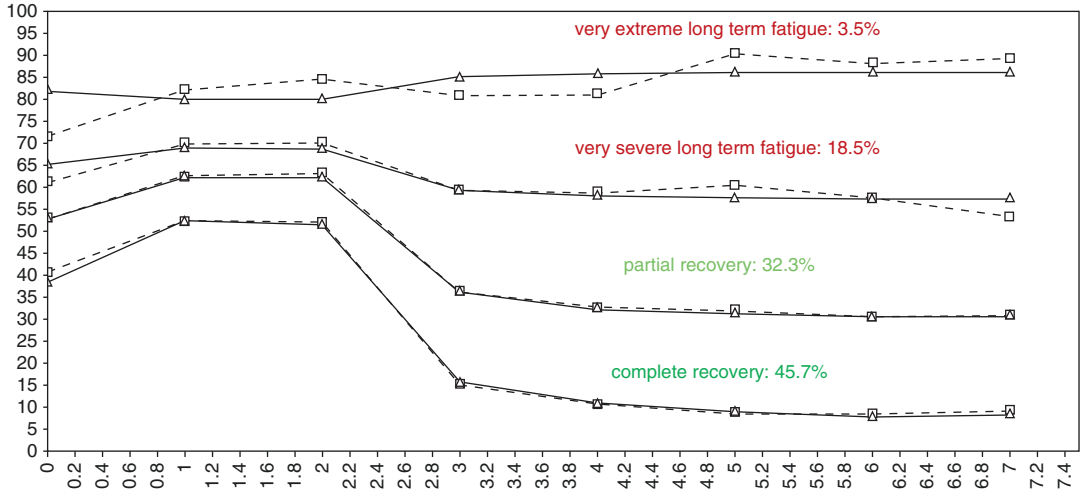

Fig. 29.4 Subgroups with different fatigue trajectories in HD15

Another GHSG analysis of HL patients and survivors treated in the HD13–HD15 trials focused on the consequences of persistent fatigue in terms of treatment outcome and social reintegration. The authors demonstrated that fatigue at baseline is a significant risk factor for treatment outcome: higher levels of fatigue at baseline translate into lower progression-free survival (PFS) and overall survival (OS) in patients receiving standard treatment at the time the trials were conducted. This may be a problem especially when less effective chemotherapies, such as ABVD in advanced-stage HL, are applied. However, within the HD13–HD15 trials, the impact of fatigue on the treatment outcome could be overcome when using the most effective HL treatment [16]. Nonetheless, baseline fatigue remains a very important measure as it has been shown to have a very high predictive value on the development of persistent fatigue [11].

Another key finding of this analysis was that persistent severe fatigue had a significant negative association with the survivors' employment and financial status. The number of severely fatigued survivors working or in training was nearly 30% lower compared to those without severe fatigue even at 5 years after end of treatment (84% vs. 57%, $p < 0.0001$). This significant difference applies for both women and men. Five years after the end of treatment, a total of 49% of female survivors and 36% of male survivors with severe persistent fatigue were not employed, and their financial distress was significantly higher (mean financial distress score 46.5) than in survivors without severe fatigue (mean financial distress score 17.3; $p < 0.0001$). Additionally, the number of visits to general practitioners and medical specialists per year was also much higher in fatigued survivors, underlining the fact that survivors with severe fatigue often suffer from further somatic distress [16].

29.8 Management of CRF

Patients with HL and clinically significant CRF are often not detected and, consequently, do not receive specific or adequate treatment. In order to improve low rates of detection, referral and treatment, routine screening for CRF has been widely recommended as a standard in cancer care [32]. A clinical practice guideline to help standardising screening, assessment and management of severe fatigue in adult cancer survivors has been published recently [33]. However, its benefit inevitably depends upon the systematic availability of effective interventions that follow it.

At present, there are no standard treatment intervention for chronically fatigued cancer sur-

vivors. Various therapeutic approaches have been evaluated for the treatment of CRF. Physical activity has been shown to be an effective intervention [34–36]. However, it doesn't address a relevant number of patients, and the feasibility of sports in patients suffering from severe CRF remains problematic. The evidence for pharmacological agents such as psychostimulants is controversial. Thus, current guidelines do not routinely recommend their use in survivors with CRF [33].

Comprehensive models to understand the multicausal development and course of CRF during cancer treatment and survivorship include both somatic and psychosocial factors [37]. Available data suggest that, in contrast to fatigue at the time of diagnosis, long-term fatigue is not related to disease or treatment but predominantly to psychosocial factors [11, 38, 39].

The research group of Knoop and Gielissen successfully performed a randomised controlled trial to investigate the effect of cognitive behavioural therapy (CBT) in severely fatigued cancer survivors. The rationale of this intervention was based on the assumption that cancer itself and/or cancer treatment may trigger fatigue (precipitating factors), but other factors are responsible for the persistence of fatigue in the long term (perpetuating factors). CBT was focused on six perpetuating factors (six modules) of post-cancer fatigue, which were based on existing literature and experience in clinical practice. They involve insufficient coping with the experience of cancer, fear of disease recurrence, dysfunctional cognitions concerning fatigue, dysregulation of sleep, dysregulation of activity and low social support and negative social interactions. The authors demonstrated that the intervention of CBT had a clinically relevant effect in reducing fatigue and functional impairment, and this effect persisted for up to 2 years after finishing CBT. The authors also report that even a full recovery from chronic fatigue syndrome after CBT is possible [40, 41]. Additionally, Knoop and colleagues developed a web-based intervention for severely fatigued cancer survivors based on the explanatory model of the CBT protocol. E-health interventions have been widely developed during recent years and have created new possibilities including flexibility in terms of time and availability [42]. Web-based CBT has been specifically designed for patients with severe post-cancer fatigue, but it has not been evaluated in terms of efficacy in HL survivors.

Therefore, the GHSG is currently planning to perform a randomised, controlled trial on CBT in HL survivors with severe persistent fatigue in cooperation with the Department for Medical Psychology and Sociology at the University of Leipzig.

29.9 Summary and Conclusion

CRF is prevalent in HL patients even before the onset of chemotherapy and differs significantly between disease stages. In sharp contrast to these different fatigue levels at baseline, fatigue during therapy and more importantly long-term fatigue are remarkably similar across all different stages of HL. Accordingly, there is no negative impact of treatment intensity on the development of long-term fatigue. Fatigue at baseline is a strong predictor of fatigue after treatment. Subtypes of long-term fatigue development result primarily from different baseline fatigue levels. Survivor groups with severe baseline fatigue tend to remain at high fatigue levels during the observation period of 5 years. However, the vast majority of survivors of more advanced-stage HL with moderate fatigue at baseline can expect remarkable improvement after successful therapy of HL.

The presence of severe fatigue prevents HL patients from social reintegration and thus has major implications for their life as survivors. In the fifth year after therapy, the number of survivors without severe fatigue working or in education was nearly 30% higher compared to those with severe fatigue. There is evidence that exercise programs and cognitive behaviour therapy help to ameliorate CRF.

Further randomised, clinical trials are needed to improve the outcome and quality of life of HL survivors suffering from CRF.

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