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Current concepts and controversies in the management of early stage Hodgkin lymphoma

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Abstract

Over the past three decades, due to the recognition of late effects related to high-dose extended field radiotherapy and heavy alkylator chemotherapy, combined modality therapy with abbreviated chemotherapy and limited field radiotherapy has emerged as the standard of care for early stage Hodgkin lymphoma, with cure rates in excess of 80%. Currently, however, controversy remains over identifying the most appropriate criteria to risk-stratify patients with early stage disease, so that those with a favorable prognosis receive limited treatment without compromising cure rates and those with unfavorable risk receive more intensified therapy. The optimal risk stratification system remains unclear, with variable definitions of favorable and unfavorable disease used by research groups in North America and Europe. Thus, comparison of clinical trial results has been challenging, and additional controversies persist regarding optimal chemotherapy regimens, duration of therapy, and the role of radiotherapy. Investigations are ongoing to assess the potential of functional imaging and biomarkers as tools for risk stratification. The collective goal is to further refine current stratification strategies to allow for an individualized, risk-adapted treatment approach that minimizes long-term late effects without compromising high cure rates.

Keywords

Lymphoma and Hodgkin disease; pharmacotherapeutics; prognostication

Introduction

With the use of modern diagnostic evaluation and therapy, patients with early stage Hodgkin lymphoma (HL), defined as stage I or II disease, have a high likelihood of cure, with 5-year survival rates in excess of 90% [1]. Recognition of clinical prognostic factors for risk stratification led to the abandonment of the routine use of staging laparotomy. Concerns related to therapy-associated late effects have resulted in reductions of doses and volume of radiation therapy (RT) and minimizing exposure to alkylating agents. These paradigm shifts have led to a considerable evolution of therapy over the past three decades, resulting in combined modality therapy (CMT) of abbreviated chemotherapy and involved field radiotherapy (IFRT) as the current standard for early stage HL.

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Our review summarizes data that have established the current standard of care and then discusses controversies regarding the optimal stratification and management of early stage classical HL. A primary focus of contemporary clinical research is to tailor therapies based on risk, in order to minimize treatment-associated morbidity while maintaining an excellent rate of cure. We discuss the role of chemotherapy alone versus CMT, and the emerging role of risk-adapted therapy based on functional imaging that aims to identify a subset of patients who may benefit from more aggressive therapy. Finally, we review emerging data regarding optimal surveillance strategies and prognostic biomarkers.

Establishment of combined modality therapy as a ‘standard’ for early stage Hodgkin lymphoma

Several decades ago, early stage HL was treated reasonably effectively, with 5-year freedom from treatment failure (FFTF) of greater than 70% and a 5-year overall survival (OS) of greater than 90% with extended field RT (EFRT) alone [2,3]. By the early to mid-1990s, recognition of late effects largely due to EFRT and the efficacy of combination chemotherapy regimens for advanced stage disease led to paradigm shifts in therapy and the study of CMT for patients with stage I–II disease. The German Hodgkin Study Group (GHSG) HD7 trial randomized patients with favorable early stage disease to either EFRT (30 Gy followed by 10 Gy boost to involved sites) or two cycles of doxorubicin, bleomycin, vinblastine, and dactarbazine (ABVD) followed by EFRT [4]. A significantly improved 7-year FFTF was reported in the CMT arm (88% vs. 67%). No difference in OS was observed. The Southwest Oncology Group (SWOG) 9133 trial randomized patients to receive either subtotal lymphoid irradiation (STLI) or three cycles of doxorubicin and vinblastine (AV) followed by STLI. Similarly, a significantly higher 3-year failure-free survival (FFS) (94% vs. 81%) was reported on the CMT arm in comparison to the RT-alone arm [5]. The Stanford group reported similar outcomes for STLI when compared to IFRT (40–44 Gy) followed by six cycles of vinblastine, bleomycin, and methotrexate (VBM) [6]. At a median follow-up of 4 years, the freedom from progression (FFP) was 92% and 87%, respectively (p = not significant) [7].

Similar results were reported for patients with early stage disease treated on the European Organisation for Research and Treatment of Cancer (EORTC) H7 and H8-F studies for ‘favorable’ patients, as well as the EORTC H8-U and GHSG HD8 studies for unfavorable patients [8–10]. Therefore, across various studies significant improvements were seen in event-free survival (EFS) with CMT compared to EFRT alone. Even for a very favorable (VF) subset of patients in the EORTC H7-VF trial, mantle RT alone had an unacceptably low 3-year FFS of 82%, which led to closure of this arm of the trial [11] and to the abandonment of RT alone for the treatment of early stage HL.

Most of the earlier CMT trials used older chemotherapy regimens, such as mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) or its variants, that have since been replaced by less toxic regimens such as ABVD. Mature data from the Milan group reported that in 70 patients with stage I–II HL (21% bulky disease), four cycles of ABVD plus 36–40 Gy IFRT was equally effective as 30 Gy STLI, with a 12-year FFP of 94% vs. 93%, and OS of 94% vs. 96%, respectively [12]. These data established the CMT regimen as the standard

treatment for early stage HL and led to its acceptance as a control arm in the European studies EORTC H9 and GHSG HD10 and 11 [13–15].

Controversies in risk stratification: favorable versus unfavorable early stage Hodgkin lymphoma

Clinical prognostic factors for early stage HL were developed in an era when staging laparotomy was practiced and RT alone was used for therapy. The optimal method of risk stratification remains unclear, and variable definitions of favorable and unfavorable disease are applied by research groups in the USA, Canada, and Europe. Although historically based, recognition of these prognostic factors is important. They are the basis for stratification of patients in ongoing European clinical trials and, therefore, need to be appropriately considered when interpreting and applying clinical trial data to clinical practice [13–16].

In North America, patients with stage I or II HL are considered unfavorable if they have bulky lymphadenopathy and/or B symptoms (fever $>38^{\circ}\text{C}$, drenching night sweats, or unexplained weight loss $\geq 10\%$ of total body weight over 6 months). The presence of B symptoms is correlated with a higher likelihood of occult systemic disease, while bulky disease is a major prognostic factor for relapse [17–19]. Bulk is defined as a mediastinal mass ratio (MMR) more than one-third of the greatest intrathoracic diameter as measured on a standing posterior–anterior chest X-ray or a mass ≥ 10 cm on computed tomography (CT) imaging.

In Europe, in addition to B symptoms and bulk, the EORTC, GHSG, and Groupe d'Etudes des Lymphomes de l'Adulte (GELA) use other factors to define unfavorable subsets within early stage HL. There are minor differences between criteria employed to define unfavorable disease within the EORTC and GHSG. Both groups consider an erythrocyte sedimentation rate (ESR) ≥ 30 mm/h with B symptoms or ≥ 50 mm/h without B symptoms as unfavorable. The EORTC also considers >3 nodal sites or age ≥ 50 years, while the GHSG considers >2 nodal sites or the presence of any extranodal (EN) lesions as unfavorable. The GELA criteria vary considerably from the latter two European groups, and in addition to any elevation in ESR, age ≥ 45 years, and any EN lesion, also include elements of the International Prognostic Score (IPS) for advanced disease, such as hemoglobin <10.5 g/dL, lymphocytes <600 $\mu\text{g}/\mu\text{L}$, and male sex. Although there is consensus that bulky disease and B symptoms are markers of poor prognosis, there is debate on the significance of the additional prognostic factors when applied to asymptomatic patients with stage I–II non-bulky disease treated with modern CMT. In an analysis from Stanford, additional unfavorable factors as defined by the GHSG, EORTC, and GELA were used to retrospectively stratify 101 patients treated with an abbreviated regimen of 8 weeks of Stanford V chemotherapy and 20 or 30 Gy of IFRT. This stratification identified 33–60% of the patients as unfavorable by European criteria [20], yet despite their treatment with an abbreviated regimen, at a median follow-up of 8.5 years the outcome was excellent, with a FFP and OS of 94% and 97%, respectively, and comparable to European studies for unfavorable disease [13]. Differences in 10-year FFP between favorable and unfavorable patients were significant only for the GHSG criteria, 100% vs. 89% ($p = 0.02$), respectively,

with no difference in OS for any of the criteria applied. These data are provocative, since a majority of the patients in the Stanford study would have been considered unfavorable by European criteria and thus treated on more intense protocols.

A key controversy today is whether selected patients with early stage HL with high-risk features included within the European research groups could be managed with more limited treatment strategies. It is imperative that when comparing results from trials focused on patients with early stage disease, discordances in the definition of risk groups as favorable or unfavorable are accounted for. A consistent approach to risk stratification in early stage HL would provide more clarity in the allocation of limited intensity therapy and greater comparability of clinical trial results, and allow for optimization of surveillance strategies. Key studies addressing these issues are summarized in Table I.

Controversies regarding optimal management of ‘favorable’ early stage Hodgkin lymphoma

By and large, mature data support CMT with four cycles of ABVD and 30–36 Gy IFRT as the current standard of care for favorable early stage HL [1]. The current goal of clinical research for this patient population is to reduce treatment-related morbidity. This has resulted in a series of studies that have looked at altering the intensity and duration of chemotherapy, further reducing RT dose and fields, and also eliminating RT completely.

Studies reducing intensity or duration of chemotherapy

In patients with favorable early stage HL, the GHSG HD10 trial compared four cycles of ABVD (standard arm) to two cycles of ABVD (experimental arm) in a randomized trial involving 1190 patients. A second randomization compared two doses of IFRT [14]. In a recent update, at a median follow-up of 7.5 years there were no significant differences in the 5-year OS, FFTR, and progression-free survival (PFS) of patients treated with four or two cycles of ABVD followed by IFRT. These data suggest that for a highly selected group of patients with favorable early stage HL, as defined by GHSG criteria, chemotherapy with only two cycles of ABVD followed by IFRT may suffice.

While it appears that limiting the number of cycles of ABVD may be sufficient for patients with favorable disease, it is unknown whether all four agents in this combination are required for optimal results. This is addressed by the ongoing GHSG HD13 trial, with four arms comparing ABVD, AVD, ABV, or AV, all followed by 30 Gy IFRT. In an interim analysis, the ABV and AV arms were prematurely closed due to unacceptably high relapse rates, suggesting that dacarbazine is an important component of the ABVD regimen [21]. Results comparing ABVD to AVD are awaited and will clarify the role of bleomycin.

Alternatives to ABVD have been evaluated in patients with early stage HL. The Manchester group evaluated an abbreviated 4-week chemotherapy regimen with doxorubicin, cyclophosphamide, etoposide, vincristine, bleomycin, and prednisone (VAPEC-B) in combination with limited field RT. One hundred twenty-five patients with non-bulky asymptomatic early stage HL were treated at a median follow-up of 3.8 years, with an EFS >90% [22]. The Stanford group has reported excellent results in 87 patients treated with

abbreviated chemotherapy consisting of 8 weeks of Stanford V chemotherapy (nitrogen mustard, doxorubicin, vincristine, vinblastine, etoposide, bleomycin, and prednisone) followed by 30 Gy IFRT. At a median follow-up of 9 years, the FFP and OS were 94% and 96%, respectively [23]. These small series suggest that ABVD alternatives are effective; however, validation is necessary in randomized trials.

Studies reducing RT dose

For favorable patients, a major focus of research has been to limit RT to potentially ameliorate treatment-related late effects. Several groups have investigated reducing radiation doses from the standard 30–36 Gy to 20 Gy, or even omitting RT altogether for patients with very favorable risk.

In the GHSG HD10 trial, IFRT with 30 Gy (standard arm) was compared to 20 Gy (experimental arm) after chemotherapy of either two or four cycles of ABVD [14]. A total of 1163 patients were included, and at a median follow-up of 7.5 years there were no significant differences between FFP and OS between the two RT doses. Thus, chemotherapy with two cycles of ABVD and 20 Gy RT may suffice in a highly selected group of patients. As stated in the section above, it is critical to understand and recognize the eligibility criteria for these trials, as these results may not be applicable to ‘all’ patients with early stage HL treated in the USA.

In the EORTC H9F trial, patients with favorable early stage HL were treated with six cycles of epirubicin, bleomycin, vinblastine, and prednisone (EBVP). Patients achieving a complete response (CR) were subsequently randomized to one of three arms: no radiation, 20 Gy IFRT, or 36 Gy IFRT [24]. The arm without RT was closed prematurely due to significantly inferior outcomes compared to the combined modality arms. There was no difference in outcome between the two RT doses. The 4-year EFS for the no radiation arm versus the 36 and 20 Gy IFRT arms was 70%, 87%, and 84%, respectively. Thus, in this study, EBVP alone was significantly inferior to EBVP when used in CMT.

Studies eliminating RT

Use of ABVD alone has also been reported in a subset of patients treated on the National Cancer Institute-Canada (NCI-C) and Eastern Oncology Cooperative Group (ECOG) H6 trial. The definition of risk and patient selection varied from what is traditionally used by the GHSG or the EORTC and excluded patients with very favorable disease (stage IA with lymphocyte predominant or nodular sclerosis histology, bulk < 3 cm, ESR < 50 mm/h, and disease involving the high neck or epitrochlear region only) and high-risk disease (bulky or intra-abdominal disease) [25]. This complex study design compared standard RT-containing treatment (STLI alone for favorable disease and CMT with two cycles of ABVD and STLI for unfavorable disease) to an experimental treatment with chemotherapy alone (either four or six cycles of ABVD, depending on response by CT imaging after two cycles of therapy). It is important to note that the standard arm, as well as the type of RT used in combination with chemotherapy, is of historical interest only, since STLI is no longer used. The applicability of these data to patients treated in the modern era is difficult to determine. While the 5-year FFP was superior for patients who received RT compared to chemotherapy

alone (93% vs. 87%, respectively), there was no difference in OS. Of the 69 patients randomized to receive chemotherapy alone and assessed for response after two cycles of therapy, 83% achieved a CR after two cycles based on conventional imaging and had an excellent FFP and OS with an additional two cycles. Progression was more likely at sites within intended RT fields, which suggests that RT offered additional local control [26].

The concept of eliminating RT has also been evaluated with non-ABVD chemotherapy regimens. The Cancer and Leukemia Group B (CALGB) 50203 trial evaluated doxorubicin, vinblastine, and gemcitabine (AVG) in patients with stage I–II non-bulky HL. Ninety-nine patients were enrolled, and at a median follow-up of 1.1 years, the estimated 1- and 2-year PFS was 81% and 71%, respectively, substantially lower than that achieved with standard combined modality regimens [27].

Collectively, results from clinical trials studying chemotherapy alone are largely inferior to what is experienced with CMT. Likewise, alternative chemotherapy regimens, such as EBVP, AVG, or ABVD constituents, are also inferior. ABVD remains the standard backbone chemotherapy for patients with early stage HL. This is highlighted in a recent meta-analysis that included 1245 favorable and unfavorable patients with clinical stage I–II HL across five randomized controlled trials (three North American, one South American, and one European) and compared results from chemotherapy alone versus CMT. Chemotherapy regimens included ABVD, EBVP, and cyclophosphamide, vinblastine, procarbazine, and prednisone (CVPP), and RT regimens included both IFRT and EFRT [28]. While CR rates were similar between treatment groups, CMT provided improved tumor control (hazard ratio [HR] 0.41, 95% confidence interval [CI] 0.25–0.66) and OS (HR 0.40, 95% CI 0.27–0.59).

While the meta-analysis, as well as studies discussed above, supports CMT as the standard of care, debate continues on whether omission of RT after six cycles of ABVD will be as efficacious. In the ongoing CALGB 50604 trial, patients with a negative positron emission tomography (PET) scan after two cycles of ABVD receive an additional four cycles without RT. Until mature data from this trial are available, CMT with four cycles of ABVD and 30 Gy IFRT remains the gold standard. As therapy for favorable early stage disease evolves to include further reductions in treatment, prognostic factors used to stratify patients into risk categories must be carefully considered in the interpretation of clinical trial data and future study design.

Controversies regarding optimal management of ‘unfavorable’ early stage Hodgkin lymphoma

In the USA, patients with early stage HL with bulky disease or B symptoms are treated with regimens designed for advanced disease. The National Comprehensive Cancer Network (NCCN) guidelines recommend either 6–8 cycles of ABVD with IFRT or the combined modality Stanford V regimen in this subset of patients [29]. In Europe, subsets of patients within unfavorable disease are treated variably. Patients with bulky stage I–II disease with additional prognostic factors, such as a single EN site or >2 nodal sites, are treated on protocols for advanced disease, while those without the latter are treated on studies for

unfavorable early stage HL. As in the case of ‘favorable’ early stage HL, research into unfavorable early stage HL is largely focused on defining optimal chemotherapy and lowering the RT dose.

Studies defining optimal chemotherapy regimen

Currently, approximately 20% of patients with early stage HL will relapse after standard CMT, which raises the question whether a more aggressive upfront regimen might improve outcomes for patients with high-risk features. For advanced HL, the GHSG HD9 trial compared eight cycles of cyclophosphamide, vincristine, procarbazine, and prednisone (COPP)/ABVD, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) baseline, and the more intense BEACOPP escalated [30]. At a median follow-up of 111 months, the 10-year FFTF was 64%, 70%, and 82% with OS of 75%, 80%, and 86%, respectively ($p < 0.001$). BEACOPP escalated was significantly better than BEACOPP baseline and COPP/ABVD in terms of FFTF ($p < 0.0001$) and OS ($p = 0.0053$).

Several European studies have evaluated variations of BEACOPP for ‘unfavorable’ early stage HL. It is important to note that patients with early stage HL with either bulky disease and B symptoms or EN disease were excluded from these trials, and treated on trials for advanced disease. The EORTC/GELA H9U study compared four or six cycles of ABVD to four cycles of BEACOPP baseline followed by 36–40 Gy IFRT in 808 patients with unfavorable early stage HL. There were no significant differences in the 4-year EFS or OS between the three arms [13]. BEACOPP baseline was also studied in the GHSG HD11 trial that compared four cycles of ABVD or BEACOPP baseline followed by IFRT. Again, no significant differences were reported in 5-year FFTF between BEACOPP baseline and ABVD when followed by 30 Gy IFRT [31].

The GHSG HD14 trial evaluated the more intense BEACOPP escalated regimen. Patients with unfavorable early stage HL were randomized to receive either four cycles of ABVD or two cycles of BEACOPP escalated followed by two cycles of ABVD. Patients on both study arms received 30 Gy IFRT on completion of chemotherapy [32]. Final analyses at a median follow-up of 42.4 months on 1623 evaluable patients reported an improved estimated 4-year FFTF in the BEACOPP escalated arm versus ABVD, 94.7% and 89.3% ($p = 0.0001$), respectively, with no difference in OS. Until mature results of the GHSG HD14 study are available, the modest benefit of BEACOPP escalated in FFTF at the cost of excessive toxicity is not warranted outside of a clinical trial.

The Stanford V regimen, an abbreviated 12-week chemotherapy followed by 36 Gy RT to initial sites of disease ≥ 5 cm and/or macroscopic splenic disease, was reported for 46 patients with locally extensive early stage HL to have an estimated 5-year FFP of 89% and OS of 96% [33]. In a subset analysis, when bulk was compared to other unfavorable factors as defined by the EORTC or GHSG, no differences were observed in the 10-year FFP [34]. Similar results have been reported by the Memorial Sloan-Kettering Cancer Center and United Kingdom groups [35,36].

In comparison to ABVD, the cumulative doses of doxorubicin and bleomycin in Stanford V are significantly lower. Increased risk of several cardiovascular diseases by 3–5-fold has been reported in survivors of HL compared with the general population [37]. Longer follow-up will be required to assess the impact of reducing doxorubicin and bleomycin doses on cardiac and pulmonary sequelae. Additionally, initial results from the US Intergroup trial ECOG 2496 for advanced HL (including stage II bulky disease) comparing ABVD to the Stanford V regimen were recently reported [38,39]. At a median follow-up of 5.25 years for 812 patients, there was no significant difference in 5-year FFS or OS between the two arms. Mature data are awaited to assess treatment-related late effects.

Studies reducing RT dose

Similar to efforts aimed at reducing the RT dose in patients with favorable disease, the GHSG HD11 trial evaluated IFRT with either 20 or 30 Gy after chemotherapy with either four cycles of ABVD or BEACOPP baseline in patients with unfavorable early stage HL. The final analysis of 1395 patients reported no significant differences in the 5-year FFTF between 20 or 30 Gy IFRT after four cycles of BEACOPP baseline [31]. In contrast, after four cycles of ABVD, the 5-year FFTF with 20 Gy was inferior to 30 Gy IFRT (4.7% difference).

These results suggest that for patients with unfavorable disease, if the RT dose is reduced below the standard dose of 30 Gy, then more aggressive chemotherapy is warranted. Interpretation of European data must take into consideration that a subset of patients considered unfavorable, due to risk factors other than B symptoms and bulk, would not be considered unfavorable in the USA, and therefore intensification of therapy may not be warranted in all patients with unfavorable disease.

Future directions

While CMT is considered a standard approach, the impact of reduction of RT dose and field remains unknown, and will require at least another decade of follow-up. Stratification using functional imaging and molecular tools is gaining clinical relevance. As therapy is deescalated, close follow-up of patients takes on paramount importance so that relapses can be detected early, and the optimal method for surveillance in asymptomatic patients remains controversial.

Use of functional imaging for risk stratification and tailoring of RT fields

Fluorodeoxyglucose (FDG)-PET has emerged as an important imaging tool for staging and assessment of treatment response in HL. Several studies demonstrate that for patients with advanced disease, a positive interim and post-chemotherapy FDG-PET scan is prognostic and identifies patients with a higher risk of relapse [40–43]. With the recognition of late effects due to RT, it is speculative to consider whether FDG-PET imaging could be used to risk-stratify patients and eliminate RT in selected patients. In a randomized trial from Italy, 260 patients with predominantly early stage bulky disease who attained a CR by FDG-PET after chemotherapy with six cycles of vinblastine, etoposide, bleomycin, epirubicin, and prednisone (VEBEP) were randomized to RT or observation [44]. At a median follow-up of

40 months, EFS was significantly lower in the observation arm (86% vs. 96%), despite a complete response by FDG-PET imaging after chemotherapy. While this study employed an unconventional chemotherapy regimen, the results are consistent with the meta-analysis, and support the role of RT [28]. In a retrospective study by the Vancouver group, patients with advanced HL (stage III–IV and/or B symptoms and/or bulky disease) with a residual mass ≥ 2 cm on CT scan after completion of six cycles of ABVD underwent FDG-PET imaging and received RT only if the post-chemotherapy FDG-PET scan was positive. Of 52 patients, 77% had a negative post-chemotherapy FDG-PET scan and a superior PFS compared to those with a positive scan, 91% vs. 26%, respectively. For the patients with a negative FDG-PET scan, there were no differences in the 2-year PFS for bulky ($n = 17$) versus non-bulky disease ($n = 20$) (86% vs. 94%, respectively) [45].

PET scan-based trials utilizing ABVD chemotherapy are also ongoing. The GHSG HD16 trial is evaluating whether additional RT is needed in patients with early stage HL without risk factors and with a negative FDG-PET scan after two cycles of ABVD. In this study, patients with a positive FDG-PET scan after two cycles of ABVD receive IFRT (30 Gy), while those with a negative scan do not receive any further therapy. Planned US cooperative group trials are also specifically addressing whether mid-chemotherapy FDG-PET imaging can identify patients who may benefit from more intense treatment. Until mature results are available, omission of RT based on a mid- or post-chemotherapy FDG-PET scan remains a research question.

An emerging concept is the use of involved node RT (INRT), rather than IFRT, with the goal of further limiting RT toxicity. Isotropic margins for INRT vary from one cooperative group to another, with variability in cut-off values [46]. A retrospective study from Vancouver evaluated EFRT, IFRT, and INRT (≥ 5 cm) according to era-specific guidelines. At a median follow-up of 80 months, there were no significant differences in risk of relapse between the three modalities [47].

The concept of INRT after interim FDG-PET is the subject of investigation in ongoing European studies. Patients with favorable disease enrolled on the EORTC/GELA H10 study are imaged with FDG-PET after two cycles of ABVD. Patients with a negative scan receive an additional two cycles of ABVD without RT, while therapy is altered to two cycles of BEACOPP escalated followed by 30 Gy INRT in patients with a positive scan. For unfavorable disease a total of six cycles of ABVD without RT are administered if an interim FDG-PET scan is negative, and therapy escalated to four cycles of BEACOPP escalated followed by 30 Gy INRT for patients with a positive scan [48]. This trial is ongoing and results not yet reported.

Role of surveillance imaging after first complete response

NCCN guidelines recommend surveillance chest imaging with either an X-ray or CT scan every 6–12 months during the first 2–5 years after completion of therapy for patients in CR [29]. Recently, PET has been used increasingly for the purpose of surveillance, with a paucity of data regarding its role. The Dana-Farber Cancer Institute compared different surveillance methods in a retrospective analysis of 192 patients with HL in first CR. At a median follow-up of 31 months, the positive predictive value (PPV) of surveillance PET/CT

was 22.9%, compared with 28.6% for CT ($p = 0.73$) [49]. A retrospective review by Stanford University of 109 patients, the majority with early stage disease, reported that a surveillance FDG-PET had a 100% negative predictive value (NPV) while the PPV was only 36% [50]. At a median follow-up of 3.2 years, symptomatic relapses beyond 1 year were not observed.

In an analysis from the Memorial Sloan-Kettering Cancer Center, in 58 of 94 patients with relapsed HL referred for secondary therapy followed by high-dose transplant and stem cell support, relapse was classified based on either development of clinical symptoms or determined by imaging (CT or PET/CT) [51]. At a median follow-up of 7.4 years, there were no significant differences in 5-year FFS and OS between patients with asymptomatic relapses detected by surveillance scans versus those with clinical relapses.

Cumulatively, these data have important implications related to the interpretation of positive imaging during surveillance, potential effects of radiation exposure from repeated scanning, morbidity from unnecessary biopsies, increased patient anxiety, and escalating healthcare costs. At this time, data do not support the routine use of FDG-PET surveillance for patients with early stage disease. Whether early detection of asymptomatic relapse impacts outcome needs further investigation.

Emerging role of prognostic biomarkers

Elevations in levels of CD30, interleukin-10, Bcl-2, and CD68+ macrophages have been identified on multivariate analyses as unfavorable independent prognostic markers. Likewise, tumor necrosis factor- α and its receptor, and thymus and activating regulator chemokine (TARC), have been associated with a worse prognosis [52–54]. A recent study using gene expression profiling on 130 frozen samples obtained from patients with classical HL identified a signature of tumor-associated macrophages that was significantly associated with primary treatment failure. Findings were validated in an independent cohort, which demonstrated a correlation between an increased number of CD68+ macrophages and a shortened PFS, with an increased likelihood of relapse after autologous hematopoietic stem cell transplant [54]. These data, if confirmed, suggest that an elevated number of CD68+ macrophages could represent a new biomarker for HL, which may be useful for risk stratification.

Summary and conclusions

The treatment of early stage HL continues to evolve. For most patients, 4–6 cycles of ABVD and IFRT with 30 Gy remain the current standard, with excellent outcomes. Alternative combined modality regimens, such as Stanford V, have comparable results. For patients with unfavorable disease it is currently unclear whether the toxicities of more aggressive therapies such as BEACOPP escalated are warranted. The optimal method for risk stratification is debatable due to variable definitions of favorable and unfavorable disease between research groups in North America and Europe. It is important to recognize stratification factors used for patient selection in the recently published trials so that patients with a highly curable disease are not undertreated. Continued efforts to improve risk assessment in early stage HL are critical to future studies aimed at further reductions in

intensity and duration of chemotherapy and in radiation for a refined population of favorable-risk patients.

Prognostic biomarkers, if validated, will likely play an important role in the future management of HL. Ultimately, individualization of therapy in early stage HL will depend on matching the appropriate intensity of treatment to the correct patient populations. As newer more effective therapies are developed and more patients cured, an ongoing challenge will be to identify effective surveillance strategies to monitor such patients and optimize survivorship.

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Table I

Selected recent trials for early stage Hodgkin lymphoma (HL).

Group/trial	n	Treatment	FFTF, FFP, EFS, or PFS (%)	OS (%)	Median follow-up (months)
Favorable early stage HL					
EFRT versus combined modality therapy					
EORTC/GELA H7F [8]	333	STLI	78 at 10 yr	92 at 10 yr	108
		6 EBVP + 36–40 Gy IFRT	88 at 10 yr	92 at 10 yr	
EORTC/GELA H8F [9]	542	STLI	74 at 5 yr	92 at 10 yr	92
		3 MOPP/ABV + 36–40 Gy IFRT	98 at 5 yr	97 at 10 yr	
Reducing intensity or duration of chemotherapy					
Manchester [22]					
	125	IFRT	56 at 5 yr	89 at 5 yr	46
		4 VAPEC-B + IFRT	90 at 5 yr	94 at 5 yr	
GHSG HD10 [14]					
	1370	2 ABVD + 20 Gy IFRT	86 at 8 yr	95 at 8 yr	90
		2 ABVD + 30 Gy IFRT	86 at 8 yr	94 at 8 yr	
		4 ABVD + 20 Gy IFRT	90 at 8 yr	95 at 8 yr	
		4 ABVD + 30 Gy IFRT	87 at 8 yr	94 at 8 yr	
Stanford/G4 [23]	87	8 weeks Stanford V + 30 Gy IFRT	94 at 10 yr	96 at 10 yr	108
Reducing RT					
EORTC/GELA H9F [24]					
	783	6 EBVP*	70 at 4 yr	98 at 4 yr	33
		6 EBVP + 20 Gy IFRT	84 at 4 yr	98 at 4 yr	
		6 EBVP + 36 Gy IFRT	87 at 4 yr	98 at 4 yr	
GHSG HD10 [14]					
	1370	2 ABVD + 20 Gy IFRT	86 at 8 yr	95 at 8 yr	90
		2 ABVD + 30 Gy IFRT	86 at 8 yr	94 at 8 yr	
		4 ABVD + 20 Gy IFRT	90 at 8 yr	95 at 8 yr	
		4 ABVD + 30 Gy IFRT	87 at 8 yr	94 at 8 yr	
NCI-C HD6 [25]	399	4–6 ABVD	87 at 5 yr	96 at 5 yr	50
		2 ABVD + STLI	93 at 5 yr	94 at 5 yr	
Unfavorable early stage HL					
Alternatives to ABVD					
Stanford [33]	46	12 weeks Stanford V + 36 Gy RT to initial sites	89 at 5 yr	96 at 5 yr	65

Group/trial	<i>n</i>	Treatment	FFTF, FFP, EFS, or PFS (%)	OS (%)	Median follow-up (months)
Escalating chemotherapy					
EORTC/GELA H9U [13]	808	4 ABVD + 36–40 Gy IFRT	87 at 4 yr	94 at 4 yr	57
		6 ABVD + 36–40 Gy IFRT	91 at 4 yr	95 at 4 yr	
		4 BEACOPP baseline + 36–40 Gy IFRT	90 at 4 yr	93 at 4 yr	
GHSG HD14 [32]	1623	4 ABVD + 30 Gy IFRT	89 at 4 yr	Not significant	42
		2 BEACOPP escalated + 2 ABVD + 30 Gy IFRT	95 at 4 yr		
Reducing RT	1395	4 ABVD + 20 Gy IFRT	81 at 5 yr	94 at 5 yr	91
GHSG HD11 [31]		4 ABVD + 30 Gy IFRT	85 at 5 yr	94 at 5 yr	
		4 BEACOPP baseline + 20 Gy IFRT	87 at 5 yr	95 at 5 yr	
		4 BEACOPP baseline + 30 Gy IFRT	87 at 5 yr	95 at 5 yr	

* Closed early due to unacceptably high relapse rate.

yr, years; FFTF, freedom from treatment failure; EFS, event-free survival; FFP, freedom from progression; PFS, progression-free survival; OS, overall survival; RT, radiation therapy; IFRT, involved field radiation therapy; STLL, subtotal lymphoid irradiation; EBVP, eprubicin, bleomycin, vinblastine, and prednisone; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ABV, doxorubicin, bleomycin, and vinblastine; Stanford V, nitrogen mustard, doxorubicin, vincristine, etoposide, bleomycin, and prednisone; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; VAPEC-B, doxorubicin, cyclophosphamide, etoposide, vincristine, bleomycin, and prednisone.