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ANALYSIS OF OUTCOMES OF COMBINATION THERAPY IN CHILDHOOD HODGKIN LYMPHOMA: A LITERATURE-BASED REVIEW

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Abstract. *Childhood Hodgkin lymphoma is one of the most curable pediatric malignancies, with long-term overall survival now approaching 90%–98% in modern cooperative-group series.*

Because cure is achieved in the great majority of patients, the central question in contemporary management is no longer whether children can be cured, but how they can be cured with the lowest possible burden of late toxicity. Combination therapy has therefore evolved from broad-field radiotherapy plus intensive chemotherapy toward risk-adapted, response-based multiagent regimens in which chemotherapy intensity, use of radiotherapy, and more recently incorporation of targeted agents are tailored according to stage, tumor bulk, B symptoms, and early treatment response. This review analyzes the results of combination treatment in childhood Hodgkin lymphoma with emphasis on major pediatric trials, including P9425, AHOD0031, GPOH-HD-2002, EuroNet-PHL-C1, AHOD0831, and AHOD1331. A narrative review methodology was used to identify landmark studies, late-effect cohorts, and contemporary reviews relevant to combined-modality therapy in children and adolescents.

The published evidence shows that multiagent chemotherapy remains the therapeutic backbone, while radiotherapy can be safely omitted in selected patients with favorable early response. At the same time, targeted augmentation of chemotherapy with brentuximab vedotin has improved outcomes in high-risk disease without a clear increase in acute toxicity. The major challenge remains balancing event-free survival with long-term risks such as infertility, cardiotoxicity, pulmonary damage, and second malignant neoplasms. Current data support a modern paradigm of biologically and clinically individualized combination therapy, in which disease control and survivorship are considered equally important endpoints [1-17].

Keywords: *childhood Hodgkin lymphoma; pediatric Hodgkin lymphoma; combination therapy; combined-modality therapy; chemotherapy; radiotherapy; brentuximab vedotin; response-adapted treatment; late effects; survivorship.*

Introduction

Hodgkin lymphoma in children and adolescents occupies a distinctive position in pediatric oncology. Unlike many childhood cancers, it shares important biologic and clinical features with the adult disease, yet its treatment philosophy has developed along a uniquely pediatric path. In the past, children were often treated with adult-style extended-field radiotherapy, which produced durable remissions but caused serious late complications, including endocrine dysfunction, infertility, cardiopulmonary injury, and secondary cancers. Recognition of these harms shifted the field toward combined-modality approaches using lower-dose radiation and increasingly effective multiagent chemotherapy. In the contemporary era, pediatric Hodgkin lymphoma is treated with risk-based, response-adapted regimens that seek to preserve excellent survival while reducing the cumulative burden of therapy [1].

In the United States, Hodgkin lymphoma accounts for approximately 6.5% of childhood cancers, and its incidence rises sharply with age, peaking in adolescents 15 to 19 years old.

Between 2013 and 2019, the 5-year overall survival rate for patients younger than 20 years reached 98%, underscoring how strongly modern management has shifted toward the long-term quality of survivorship [1].

From a clinical perspective, classical Hodgkin lymphoma in children is heterogeneous.

Treatment decisions are influenced by Ann Arbor stage, number of involved nodal sites, bulky mediastinal disease, extranodal extension, erythrocyte sedimentation rate, and B symptoms such as fever, weight loss, and drenching night sweats [1]. These variables are not merely descriptive; they guide the intensity of frontline therapy and strongly influence whether radiotherapy will be used after chemotherapy.

The most important practical development in the last two decades has been the integration of early response assessment—especially PET-based metabolic response—into treatment algorithms. This has enabled clinicians to distinguish patients who can safely receive less therapy from those who need intensification. As a result, modern pediatric Hodgkin lymphoma therapy is best understood not as a fixed regimen but as a family of combination-treatment strategies that adjust chemotherapy, radiotherapy, and, increasingly, targeted agents according to risk and response [1,2,5,6].

Materials and Methods

This article was prepared as a narrative review of the literature. The aim was to synthesize the evidence most relevant to combination-treatment outcomes in children and adolescents with Hodgkin lymphoma, rather than to perform a formal meta-analysis. Sources were identified through structured review of major pediatric Hodgkin lymphoma trial publications, health-professional treatment summaries, and survivorship studies published from 2000 through April 2026. Priority was given to landmark cooperative-group investigations from the Children's Oncology Group (COG), the German Society of Pediatric Oncology and Hematology (GPOH), and EuroNet-PHL, as well as to publications specifically addressing chemotherapy-radiotherapy combinations, response-adapted treatment, targeted therapy integration, and late toxicity.

The literature base was centered on studies of ABVE-PC-based regimens, OEPA-COPDAC/COPP strategies, brentuximab vedotin-containing combinations, and relapsed/refractory response-adapted salvage approaches [1-17].

Eligible studies included pediatric or adolescent populations, generally from early childhood through 21 years of age, with newly diagnosed or relapsed/refractory Hodgkin lymphoma. Adult-only studies were not emphasized unless they directly informed the adolescent and young adult transition or comparative treatment paradigms.

Data extracted for interpretation included study design, risk group, treatment regimen, role of radiotherapy, early response strategy, survival outcomes, toxicity patterns, and late-effect endpoints. Studies focusing only on rare subtypes such as isolated nodular lymphocyte-predominant Hodgkin lymphoma were not a major focus unless they informed the broader concept of de-escalation.

By design, this review privileges clinically practice-shaping pediatric evidence over small retrospective series and unspecific narrative commentary [1-17].

Discussion

Historical development of combination therapy in pediatric Hodgkin lymphoma

The modern pediatric strategy arose from a clear historical lesson: excessive reliance on radiotherapy cured many patients but at an unacceptable long-term cost. Combined-modality therapy emerged as the compromise that preserved disease control while reducing radiation exposure. One of the pivotal studies clarifying the value and limits of radiotherapy was CCG 5942. In this trial, patients who achieved a complete response to chemotherapy were randomly assigned to receive involved-field radiotherapy (IFRT) or no further therapy.

Long-term follow-up showed that IFRT improved event-free survival, but not overall survival; in an as-treated analysis, 10-year EFS was 91.2% with IFRT versus 82.9% without further therapy, whereas OS remained similar [10]. The importance of this result is conceptual as much as numerical. It demonstrated that local consolidation can reduce relapse risk, but it also suggested that some relapses can still be salvaged, thereby weakening the case for universal irradiation in all complete responders. In other words, cure alone could no longer justify routine radiation when late toxicity remained substantial [10].

North American pediatric groups then refined multiagent chemotherapy to shorten treatment duration and intensify early disease control. The P9425 study, which used the ABVE-PC regimen (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide) in intermediate- and high-risk patients, was especially important because it showed that a short, dose-dense strategy could maintain excellent results.

Five-year EFS was 84%, including 86% in rapid early responders and 83% in slow early responders, while only 1% of patients experienced progressive disease during therapy [3]. P9425 therefore established several principles that still shape current practice: multiagent chemotherapy is the therapeutic backbone; early response is clinically meaningful; and treatment can be titrated according to that response without compromising the majority of outcomes [3].

The study also reinforced a broader pediatric philosophy: compress treatment to maximize efficacy early, but avoid unnecessarily prolonged exposure to agents associated with infertility, cardiopulmonary toxicity, and second neoplasms.

These ideas were further tested in AHOD0031, the first large COG trial to randomize intermediate-risk patients according to early response. Among 1,712 eligible patients, the 4-year EFS was 85.0%; rapid early responders had better outcomes than slow early responders (86.9% vs 77.4%) [2]. However, the most practice-defining observation came from the subgroup of rapid early responders who also achieved complete response.

In these patients, IFRT did not significantly improve 4-year EFS compared with no IFRT (87.9% vs 84.3%, P=.11), and in the PET-assessed subgroup with PET-negative response there was likewise no apparent EFS benefit from radiotherapy [2]. This finding was central to the evolution of response-adapted treatment. It did not prove that radiotherapy is unnecessary in every case, but it strongly supported its omission in carefully selected children with favorable early and complete response.

Thus, AHOD0031 transformed combined-modality therapy from a uniform two-part strategy into a conditional strategy, in which the second modality—radiotherapy—is delivered only to those who appear to need it [2].

Brentuximab vedotin and the next generation of combination therapy

The next major phase in pediatric Hodgkin lymphoma therapy has been the addition of targeted agents to standard chemotherapy backbones. Brentuximab vedotin (BV), an anti-CD30 antibody-drug conjugate, is especially attractive because CD30 is uniformly expressed on classical Hodgkin Reed-Sternberg cells. Its incorporation into pediatric frontline therapy reflects a broader shift in oncology: rather than escalating conventional cytotoxic intensity alone, investigators are increasingly using biologically directed agents to improve efficacy while hoping to limit long-term damage.

That targeted step was foreshadowed by the 2021 study from Metzger and colleagues, in which BV was integrated into frontline treatment for high-risk pediatric Hodgkin lymphoma together with risk-adapted residual-node radiotherapy. Of the 77 enrolled patients, 27 (35%) achieved complete remission at early response assessment and were spared radiotherapy [8].

The study concluded that frontline BV was highly tolerable, reduced radiation exposure, and produced excellent outcomes [8]. This trial was important not only because the results were good, but because it suggested a new treatment logic: a targeted agent could potentially improve systemic disease control enough to permit less radiotherapy, thereby combining efficacy escalation with local-treatment de-escalation.

Role of early response assessment in tailoring combined treatment

A defining feature of modern pediatric Hodgkin lymphoma therapy is that combination treatment is no longer static. Instead, it is dynamically adapted according to early response. This principle runs through P9425, AHOD0031, AHOD0831, and EuroNet-PHL-C1. Rapid early response, complete anatomic response, and adequate metabolic response have become central decision points for treatment de-escalation. The practical consequence is that the same nominal diagnosis—say, stage IIB or stage IIIA Hodgkin lymphoma—may lead to quite different final treatment depending on interim imaging. The biologic logic is straightforward: tumors that clear rapidly under initial chemotherapy are likely more chemosensitive and may not require consolidation radiotherapy, whereas slow responders may benefit from augmented chemotherapy and/or local treatment [2,3,5-7].

Late effects, fertility, and long-term survivorship

Because survival is so high in childhood Hodgkin lymphoma, late effects are not secondary concerns; they are core treatment outcomes. This fact fundamentally changes how combination therapy must be evaluated. A regimen that produces only a marginal gain in EFS at the cost of substantially higher infertility, cardiomyopathy, pulmonary fibrosis, or second cancers may not represent a true therapeutic advance. Pediatric Hodgkin lymphoma is therefore one of the clearest examples in oncology where cure quality matters almost as much as cure frequency.

Second malignant neoplasms remain a serious survivorship issue, although modern response-adapted treatment appears to be reducing this burden. In the AHOD0031 survivor cohort, among 1,711 intermediate-risk survivors treated with response-adapted therapy, the 10-year cumulative incidence of subsequent malignancy was 1.3%, and the cumulative incidence of secondary myelodysplastic syndrome or acute myeloid leukemia was 0.2% [12].

These numbers are lower than those reported in older eras of broader radiation exposure, supporting the belief that contemporary de-escalation can produce real survivorship gains [1,12].

Likewise, cardiac toxicity modeling has shown that modern pediatric protocols are associated with lower projected long-term cardiac risk than historical regimens, largely because of reductions in mediastinal radiotherapy and cumulative anthracycline exposure [11]. The key message is that response-adapted combination therapy is not simply a way to lower toxicity in theory; it appears to be lowering measurable long-term risk.

Fertility is another major determinant of therapeutic quality. Procarbazine-containing regimens are well known to be gonadotoxic, which is why the development of COPDAC was so important [4]. A 2023 review of reproductive ability in survivors of childhood, adolescent, and young adult Hodgkin lymphoma concluded that treatment negatively affects gonadal function and emphasized the need for fertility counseling, fertility preservation when appropriate, and long-term reproductive monitoring [13]. This has direct implications for regimen choice in pediatric practice. When two combinations appear oncologically similar, the regimen with lower gonadotoxic potential has a strong survivorship advantage. Thus, the success of procarbazine-sparing strategies is not a minor pharmacologic detail; it is a major outcome measure for children who may live many decades after cure.

In addition to reproductive and cardiac effects, late pulmonary, endocrine, psychosocial, and quality-of-life outcomes must also be considered. Survivorship is especially important in girls and young women with chest irradiation, in boys exposed to alkylators, and in adolescents whose schooling, identity formation, and future family planning coincide with cancer treatment. For this reason, any rigorous analysis of combination-therapy results in pediatric Hodgkin lymphoma should include not only EFS and OS but also radiotherapy rate, alkylator burden, cumulative anthracycline dose, need for salvage treatment, and expected late-effect profile. Modern success in pediatric Hodgkin lymphoma should be defined as durable remission with minimized biological cost [1,4,11-13].

Adolescents, relapse, and future directions

An additional challenge in pediatric Hodgkin lymphoma is age-related heterogeneity.

Adolescents often fare worse than younger children even when treated on pediatric protocols. In a pooled COG analysis, patients aged 15 years or older had worse 5-year EFS than younger patients (80% vs 86%), and age 15 years or older conferred a markedly increased risk of death [14]. Similarly, comparison of a pediatric COG trial with an adult cooperative-group study suggested that younger adolescent and young adult patients had better outcomes when treated on a pediatric protocol than on an adult trial [15].

These observations imply that adolescents should not simply be treated as “small adults.” Instead, they may benefit from pediatric-inspired, response-adapted regimens and supportive care frameworks that account for differences in tumor biology, host factors, and treatment adherence [14,15].

Relapsed or refractory disease remains the principal cause of treatment failure.

Although outcomes in newly diagnosed disease are excellent, approximately 10% of patients with early-stage disease and up to 25% of those with advanced-stage disease will relapse [16]. Historically, this led to high-dose therapy and autologous stem-cell transplantation in many patients. More recently, salvage combination therapy has become more sophisticated and less uniformly transplant-dependent.

In CheckMate 744, nivolumab plus brentuximab vedotin, with bendamustine added only for suboptimal responders, produced high complete metabolic response rates with limited toxicities in children, adolescents, and young adults with relapsed/refractory classical Hodgkin lymphoma; most patients did not require bendamustine intensification [16]. In 2025, Daw and colleagues reported a transplant-free, risk-adapted, response-based approach with nivolumab plus BV and involved-site radiotherapy that achieved high complete metabolic response rates and a high 3-year EFS in low-risk relapsed disease [17].

These studies matter even for frontline therapy because they redefine what is considered an acceptable relapse risk. If salvage becomes more effective and less toxic, frontline regimens may be safely de-escalated further in selected patients. Conversely, highly effective frontline BV-containing therapy may reduce the future number of children needing salvage at all [9,16,17].

Taken together, current evidence suggests that pediatric Hodgkin lymphoma is moving toward increasingly individualized combination therapy based on three pillars: biologic targeting, response adaptation, and survivorship preservation. Future directions likely include broader integration of immunotherapy, better use of circulating tumor DNA and metabolic biomarkers, quantitative response assessment, and more refined selection of patients who can forgo radiotherapy or alkylating agents. The main strategic challenge will be to push cure rates incrementally upward without recreating the late-effect burden of earlier decades. This is precisely why pediatric Hodgkin lymphoma remains an important model disease in oncology: it forces clinicians to treat not only the lymphoma of today, but also the adult survivor of tomorrow [1,9,11,13-17].

Conclusion

The literature demonstrates that combination therapy in childhood Hodgkin lymphoma has undergone a profound transformation. Earlier combined-modality strategies established the curability of the disease, but they also revealed the long-term cost of indiscriminate radiotherapy and gonadotoxic chemotherapy. Subsequent pediatric trials refined this model by using dose-dense multiagent chemotherapy, early-response assessment, and selective radiotherapy, thereby preserving excellent survival while reducing treatment burden.

P9425 and AHOD0031 showed that chemotherapy intensity and radiotherapy need can be guided by response. GPOH-HD-2002 and EuroNet-PHL-C1 demonstrated that treatment composition can be modified to reduce gonadotoxicity and, in selected patients, radiotherapy can be safely omitted. AHOD1331 then marked a new stage in therapeutic evolution by proving that incorporation of brentuximab vedotin into frontline chemotherapy improves outcomes in high-risk disease without clearly increasing overall acute toxicity [2-9].

For a dissertation analyzing combination-treatment outcomes in pediatric Hodgkin lymphoma, the most meaningful framework is therefore multidimensional. Classical oncologic endpoints such as EFS, PFS, OS, and relapse pattern must be combined with survivorship endpoints including radiotherapy exposure, fertility risk, cardiac toxicity, and subsequent malignant neoplasms. The best contemporary treatment is not simply the regimen with the highest short-term disease control, but the regimen that achieves durable remission with the lowest lifelong biologic cost.

On the basis of current evidence, the modern standard can be summarized as response-adapted, risk-stratified, multiagent chemotherapy with selective radiotherapy, and targeted intensification for high-risk patients. Future advances will likely depend on integrating biomarkers and immunotherapy so that pediatric Hodgkin lymphoma treatment becomes even more precise, less toxic, and more survivorship-conscious [1,9,11-17].

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