Pediatric Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
1. Hodgson DC, Hudson MM, Constine LS. Pediatric hodgkin lymphoma: maximizing efficacy and minimizing toxicity. *Semin Radiat Oncol* 2007; 17(3):230-242.	7	N/A	Review of maximizing efficacy and minimizing toxicity in the treatment of pediatric HL.	Some generalizations regarding ongoing clinical trials for pediatric HL are as follows: (1) Patients with favorable risk disease have an excellent prognosis, and clinical trials are designed to limit exposure to anthracyclines, alkylating agents, and radiation to normal tissues while maintaining EFS rates of 90%. (2) Studies of patients with intermediate-risk disease are designed to increase efficacy without increasing toxicity (generally, this entails further subdividing this risk category according to early response, and modifying chemotherapy and/or RT accordingly). (3) Patients with high-risk disease require more effective treatment regimens. This may be achievable by increasing drug dose intensity or with innovative new treatments. Refining the role of RT in such trials will continue to be an important objective. The full extent to which contemporary low-dose IFRT will reduce late effects compared with full dose EFRT is not established, although growth and functional impairment is substantially reduced. Technical innovations in RT delivery and imaging provide the foundation for future advances, potentially allowing further reduction in the volume of normal tissue treated, while preserving the proven efficacy of RT in the management of HL.	4
2. Schellong G. The balance between cure and late effects in childhood Hodgkin's lymphoma: the experience of the German-Austrian Study-Group since 1978. German-Austrian Pediatric Hodgkin's Disease Study Group. *Ann Oncol* 1996; 7 Suppl 4:67-72.	7	1,241 patients	Review the results of five German Australian city group protocols with respect to cure and morbidity.	The survival rates exceeded 90% in all 5 study groups and exceeded 95% from the second study (H-85) onward.	4
3. Cleary SF, Link MP, Donaldson SS. Hodgkin's disease in the very young. *Int J Radiat Oncol Biol Phys* 1994; 28(1):77-83.	4	91 patients	Retrospective institutional review of all patients age ≥10 from 1961-1991 (4% of total patients). Wide treatment variations/compared outcomes and demographics to adolescents/adults.	Young children more often male (4:1) and histologies than older groups. Overall outcomes as good or better, most noted improvement with advanced stage. “Modern” approach with chemo and low-dose RT has 93% 11 year survival.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
4. Macmahon B. Epidemiological evidence of the nature of Hodgkin's disease. *Cancer* 1957; 10(5):1045-1054.	15	573 patients	To present data on some features of the descriptive epidemiology of HL and to discuss their relevance to the question of the nature of this disease.	It is suggested that HL as presently understood may be a syndrome including the common clinical and pathological end results of at least two distinct etiological processes. There is no evidence as to the nature of HL as it occurs in persons <40 and this portion of the age-incidence curve for the disease is quite unlike that of any known neoplastic disorder. On the other hand, the disease as it affects the older age groups (40 and more) has features characteristic of known neoplasms. It is suggested that there is a close relationship between Hodgkin's granuloma in persons more than 40, Hodgkin's sarcoma, and reticulum-cell sarcoma.	4
5. Mack TM, Cozen W, Shibata DK, et al. Concordance for Hodgkin's disease in identical twins suggesting genetic susceptibility to the young-adult form of the disease. *N Engl J Med* 1995; 332(7):413-418.	4	955 twins identified	To test concordance in twins for HL for genetic susceptibility to the young-adult form of the disease.	No such difference between pairs of monozygotic and dizygotic twins was seen with respect to the occurrence of other cancers after the diagnosis of HL in one twin. In pairs of twins in which one had non-HL or some other malignant condition, the same type of tumor subsequently occurred in the other twin no more than twice as often in the monozygotic group as in the dizygotic group.	3
6. Razzouk BI, Gan YJ, Mendonca C, et al. Epstein-Barr virus in pediatric Hodgkin disease: age and histiotype are more predictive than geographic region. *Med Pediatr Oncol* 1997; 28(4):248-254.	3b	26 Brazilian children; 26 U.S. children	To evaluate whether age and histiotype, rather than geographic region, are the major determinants of the association between Epstein-Barr virus and HL.	The same proportion of cases was positive (15/26 or 58%) in both groups of children. After adjustment for histiotype and age, the association between Epstein-Barr virus and HL remained independent of geographic location, but was more frequent in children aged ≤10 years at diagnosis. These findings support the multiple-etiology hypothesis for HL.	3
7. Kaplan HS. *Hodgkin's disease.* 2d ed. Cambridge, Mass.: Harvard University Press; 1980.	15	N/A	Textbook.	N/A	4

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8. Sandoval C, Venkateswaran L, Billups C, Slim M, Jayabose S, Hudson MM. Lymphocyte-predominant Hodgkin disease in children. *J Pediatr Hematol Oncol* 2002; 24(4):269-273.	3a	51 children	To describe the clinical biological features, treatment, treatment outcome, and sequela of children with LPHL.	Median duration of lymphadenopathy before diagnosis was 4 months. 36 children had stage I disease, 8 children stage II disease, 4 children stage III disease, and 4 children had stage IV disease. 4/15 children who underwent staging laparotomy were upstaged. 48 (94%) patients were alive and disease-free at a median follow-up of 8 years. 11 (22%) patients had long-term therapy related adverse effects (cardiac, infertility, pulmonary, and second malignancy). 4/5 second malignant neoplasms occurred in the field of radiation. 3 patients died, 2 patients died of complications of second malignant neoplasms and 1 died of infectious complications after HL recurrence.	2
9. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol* 1989; 7(11):1630-1636.	12	N/A	Classification system to evaluate and stage patients with HL.	It was concluded that the structure of the classification be maintained. It was particularly recommended: (1) that CT be included as a technique for evaluating intrathoracic and infradiaphragmatic lymph nodes; (2) that the criteria for clinical involvement of the spleen and liver be modified to include evidence of focal defects with two imaging techniques and that abnormalities of liver function be ignored; (3) that the suffix 'X' to designate bulky disease (>10 cm maximum dimension) be introduced; and (4) that a new category of response to therapy, unconfirmed/uncertain CR, be introduced to accommodate the difficulty of persistent radiological abnormalities of uncertain significance.	4
10. Castellino RA, Blank N, Hoppe RT, Cho C. Hodgkin disease: contributions of chest CT in the initial staging evaluation. *Radiology* 1986; 160(3):603-605.	10	203 patients	To evaluate the contributions of chest CT in the initial staging evaluation.	CT scans provided additional evidence of disease involvement, ranging from 0% to 15% at each of the designated anatomic sites. Treatment was altered in 9.4% of all patients (19 of 203), including 13.8% (nine of 65) of those undergoing RT alone and 8.2% (ten of 122) of those undergoing combined-modality treatment. Routine chest CT examinations are valuable in the clinical management of those patients for whom RT is planned.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
11. Jerusalem G, Beguin Y, Fassotte MF, et al. Whole-body positron emission tomography using 18F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. *Blood* 1999; 94(2):429-433.	12	N/A	A review of whether whole-body FDG-PET for post-treatment evaluation in HL and non-HL has higher diagnostic and prognostic value than classical CT imaging.	Even the most skeptical radiation oncologist becomes an enthusiast for PET when this technology becomes available for RT treatment planning. The very high rate of incremental information and the increased accuracy associated with this powerful imaging modality are rapidly changing our approach to some of the most common cancers. It is essential that we work hard to find the best ways to incorporate this new information into our everyday practice.	4
12. Smith RS, Chen Q, Hudson MM, et al. Prognostic factors for children with Hodgkin's disease treated with combined-modality therapy. *J Clin Oncol* 2003; 21(10):2026-2033.	2	328 patients	Evaluation of pretreatment factors to identify children at high risk for relapse after combined-modality therapy for HL.	Patients with stage I-IV HL were treated with chemotherapy and low-dose IFRT. With a median follow-up of 59 months, the 5-year DFS and OS for all patients were 83% and 93%, respectively. By multivariate analysis, male sex, stage IIB, IIIB, or IV disease, bulky mediastinal disease, WBC >13.5 x $10^3/mm^3$, and hemoglobin <11.0 g/dL were significant for inferior DFS. The prognostic index assigned one patient for each significant factor; 5-year DFS and OS for a prognostic score of 0 to 1 (94%, 99%); score 2 (85%, 96%); score 3 (71%, 92%); score 4 or 5 (49%, 72%). A prognostic index may be useful in assigning children with HL to risk-adapted therapy.	2

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13. Tubiana M, Henry-Amar M, Carde P, et al. Toward comprehensive management tailored to prognostic factors of patients with clinical stages I and II in Hodgkin's disease. The EORTC Lymphoma Group controlled clinical trials: 1964-1987. *Blood* 1989; 73(1):47-56.	2	1,579 consecutive patients from 4 controlled clinical trials	To identify the subsets of patients who could be treated safely by regional RT and to assess the impact on survival of a therapeutic strategy including staging laparotomy.	At a 4-year follow-up, no difference in survival was evidenced. In patients with unfavorable prognostic indicators, 3 MOPP-RT-3 MOPP were compared with 3 ABVD-RT-3 ABVD. From H1 to H5 trials, the proportion of patients having received chemotherapy during the course of the disease gradually decreased; the data suggest that a further reduction in the proportion of patients aggressively treated is conceptually possible. On the basis of the prognostic factors identified, one can delineate three subsets of patients and modulate toxic cost of the initial treatment according to the characteristics of these subsets. In the most favorable subgroup, RT alone produces high survival and chemotherapy is not justified.	2
14. Specht L. Prognostic Factors in Hodgkin's Disease. *Semin Radiat Oncol* 1996; 6(3):146-161.	7	N/A	To review prognostic factors in HL.	Prognostic factors for laparotomy findings in clinical stages I and II are: number of involved regions, disease confined to upper cervical nodes, B symptoms, gender, histology, age, and mediastinal disease (variable influence). In clinical stages I and II, the same prognostic factors apply as for pathological stages I and II and for laparotomy findings, and also some indirect indicators of extent of disease such as erythrocyte sedimentation rate, anemia, and serum albumin. In advanced disease the number of involved nodal and extranodal regions, the total tumor burden, B symptoms, age, gender, histology, and a number of hematologic and biochemical indicators are significant. Research into serum values of certain HL-associated antigens and cytokines may in the future provide valuable tumor markers in HL.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
15. Weiner MA, Leventhal B, Brecher ML, et al. Randomized study of intensive MOPP-ABVD with or without low-dose total-nodal radiation therapy in the treatment of stages IIB, IIIA2, IIIB, and IV Hodgkin's disease in pediatric patients: a Pediatric Oncology Group study. *J Clin Oncol* 1997; 15(8):2769-2779.	1	179 patients	Pediatric Oncology Group (POG) Trial for Advanced HL: (MOPP/ABVD) x 4 followed by +/- 2100 cGy total nodal RT. Design placed RT at end, randomization upfront so patients randomized to RT who failed prior to RT or refused RT still count as RT failures.	Approximately 80% long term EFS in both groups with no advantage to RT. Design may have limited ability to see RT effect by upfront randomization and 8 months of chemotherapy for all. CANNOT lead to lack of role for RT but suggests best role with shorter chemotherapy.	1
16. Kung FH, Schwartz CL, Ferree CR, et al. POG 8625: a randomized trial comparing chemotherapy with chemoradiotherapy for children and adolescents with Stages I, IIA, IIIA1 Hodgkin Disease: a report from the Children's Oncology Group. *J Pediatr Hematol Oncol* 2006; 28(6):362-368.	1	247 total patients from 52 POG institutions; 169 randomly assigned; 29 nonrandomly assigned	To determine if 6 courses of chemotherapy alone could achieve the same or better outcome than 4 courses of chemotherapy followed by RT (chemoradiotherapy) in pediatric and adolescent patients with HL.	The CR rate was 89%, with a CR and partial response rate of 99.4%. There was no statistically significant difference in EFS or OS between arms. The EFS for those who achieved an early CR was significantly higher than for those who did not. For pediatric patients with asymptomatic low-stage and intermediate-stage HL, chemotherapy and chemoradiotherapy both resulted in 3-year EFS of approximately 90% and statistically indistinguishable 8-year EFS and OS, without significant long-term toxicity. Early response to therapy was associated with higher EFS, a concept that has led to the Children's Oncology Group paradigm of response-based risk-adapted therapy for pediatric HL.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
17. Mauz-Korholz C, Hasenclever D, Dorffel W, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: the GPOH-HD-2002 study. *J Clin Oncol* 2010; 28(23):3680-3686.	3a	573 patients	To evaluate the effectiveness of Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls.	Toxicity of OEPA-COPDAC was tolerable overall. Hematotoxicity was more pronounced with OEPA than OPPA, whereas it was less pronounced with COPDAC compared with COPP. The median observation time was 58.6 months. OS and EFS rates (+/- SE) at 5 years were 97.4% +/- 0.7% and 89.0% +/- 1.4%, respectively. In TG-1, overall EFS was 92.0% +/- 2.0%. EFS of patients without irradiation (93.2% +/- 3.3%) was similar to that of irradiated patients (91.7% +/- 2.5%), confirming results of the previous GPOH-HD-95 study. In TG-2+3, EFS did not significantly differ between boys and girls (90.2% +/- 2.3 vs 84.7% +/- 2.7, respectively; P=.12). In TG-2+3, results in boys and girls are superimposable. OPPA-COPP and OEPA-COPDAC seem to be exchangeable regimens in intermediate- and advanced-stage classical HL in pediatric patients.	2
18. Longo DL, Young RC, Wesley M, et al. Twenty years of MOPP therapy for Hodgkin's disease. *J Clin Oncol* 1986; 4(9):1295-1306.	3a	198 patients	To evaluate MOPP therapy for HL.	Throughout the period of follow-up, 103 patients have remained continuously free of disease. Review of biopsy specimens of 43 patients originally classified as HL, lymphocyte-depleted type, revealed that 10 of these patients actually had diffuse immunoblastic or large cell non-HL. Of the 188 patients with HL, 157 achieved a CR (84%), and 66% of them (101 patients) have remained disease-free more than 10 years from the end of treatment. Absence of B symptoms and receiving higher doses of vincristine were factors associated with a higher CR rate and longer survival. Patients entering CR in 5 cycles or less had significantly longer remissions than those requiring 6 or more cycles. 48% of the HL patients have survived between 9 and 21 years (median, 14 years) from the end of treatment. 19% of the CRs have died of intercurrent illnesses, free of HL.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
19. Santoro A, Bonadonna G, Valagussa P, et al. Long-term results of combined chemotherapy-radiotherapy approach in Hodgkin's disease: superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy. *J Clin Oncol* 1987; 5(1):27-37.	1	232 patients	To evaluate the long-term results of a combined chemotherapy-RT approach in HL.	The CR rate was 80.7% following MOPP and 92.4% following ABVD (P<.02). The 7-year results indicated that ABVD was superior to MOPP in terms of freedom from progression (80.8% vs 62.8%; P<.002), relapse-free survival (87.7% vs 77.2%; P=.06), and OS (77.4% vs 67.9%; P=.03). Moreover, the comparative iatrogenic morbidity showed that irreversible gonadal dysfunction as well as acute leukemia occurred only in patients subjected to MOPP, while cardiopulmonary studies failed to document significant laboratory differences between the two treatment groups. Present findings indicate that ABVD followed by extensive RT represents a valid therapeutic alternative to the widely used alkylating agent-containing regimens plus RT.	1
20. LaMonte CS, Yeh SD, Straus DJ. Long-term follow-up of cardiac function in patients with Hodgkin's disease treated with mediastinal irradiation and combination chemotherapy including doxorubicin. *Cancer Treat Rep* 1986; 70(4):439-444.	4	41 patients	To evaluate cardiac function in patients with HL treated with mediastinal irradiation and combination chemotherapy including doxorubicin.	15 patients had unequivocally normal left ventricular function by all these parameters. Two patients had minimally reduced left ventricular ejection fraction at rest with a normal increment with exercise. In two other patients with high normal resting left ventricular ejection fraction and subnormal increment with exercise, the elevated resting values implied initial measurement in a nonbasal state. A twentieth patient (the oldest; one of two with active HL at the time of evaluation and the stimulus for this study) had markedly reduced left ventricular ejection fraction as determined by radionuclide cardiac angiography and had developed clinical congestive heart failure shortly before evaluation. Despite this patient, the study indicates that treatment with MOPP/ABVD and low-dose mediastinal irradiation entails low risk for cardiac complications.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
21. Nachman JB, Sposto R, Herzog P, et al. Randomized comparison of low-dose involved-field radiotherapy and no radiotherapy for children with Hodgkin's disease who achieve a complete response to chemotherapy. *J Clin Oncol* 2002; 20(18):3765-3771.	1	829 patients	Determine if excellent EFS and survival produced with combined modality therapy can be maintained with chemotherapy alone in children achieving a CR to initial chemotherapy.	501 patients who achieved a CR after risk-adapted combination chemotherapy (Group 1-COPPABV x 4 courses; Group 2-COPPABV x 6 courses; Group 3-AraC/VP-16/COPPABV/CHOP) were randomized to low-dose IFRT or no further treatment. Estimated 3-year EFS is 92% ± 1.9% for patients randomized to low-dose IFRT vs 87% ± 2.2% for those randomized to receive no further therapy. Estimated 3-year EFS is 93% ± 1.7% for those treated with LD-IFRT compared to 85%±2.3% for patients receiving no further therapy. Three-year survival estimates showed no advantage for low-dose IFRT (98% ± 1.1% for patients treated with combined modality therapy vs chemotherapy alone (99% ± 0.5%).	1

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22. Dorffel W, Luders H, Ruhl U, et al. Preliminary results of the multicenter trial GPOH-HD 95 for the treatment of Hodgkin's disease in children and adolescents: analysis and outlook. *Klin Padiatr* 2003; 215(3):139-145.	3a	1,018 patients from 5 consecutive trials	To analyze the preliminary results of a multicenter trial for the treatment of HL in children.	36 tumor progressions and 49 relapses occurred over a period of 7 1/2 years (median follow-up 3 years, data deadline 12/19/02). Kaplan-Meier-analysis after 5 years showed a probability for EFS for all patients of 0.88 and for probability for OS of 0.97. For the total group the probability for DFS was lower in 222 non irradiated patients than in the 758 irradiated patients (0.88 vs 0.92, P=0.049). But there was a difference between the individual treatment groups. In TG1 there was no difference between nonirradiated and irradiated patients (0.97 vs 0.94) and the non-irradiated patients showed a better trend. In TG2, and in TG2 and TG3 combined, the probability for DFS was significantly worse for nonirradiated patients in comparison with the irradiated patients (TG2:0.78 vs 0.92; TG2 +3:0.79 vs 0.91). Compared to former DAL-HD trials the probability for OS stayed stable despite therapy reduction. A reduction of RT to 20 Gy for patients in all stages with good response to chemotherapy is possible without deterioration of the results. The omission of RT for patients in CR after chemotherapy is recommended only for patients in early stages (TG1). In future trials the possibility of a wider selection for chemotherapy alone for this group needs to be evaluated. In intermediate (TG2) and advanced (TG3) stages omission of RT for patients incomplete remission results in a lower probability for EFS, but the probability for OS is not significantly reduced. Only with knowledge of the long term effects of today's therapy we can give a satisfactory answer to the question whether in future trials the primary aim should be probability for EFS as high as possible due to front-line-therapy or reduction of late effects.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
23. Donaldson SS, Link MP, Weinstein HJ, et al. Final results of a prospective clinical trial with VAMP and low-dose involved-field radiation for children with low-risk Hodgkin's disease. *J Clin Oncol* 2007; 25(3):332-337.	4	110 patients	To evaluate outcome and assess complications in children and adolescents with low-risk HL treated with VAMP chemotherapy and low-dose IFRT.	With median follow-up of 9.6 years (range, 1.7 to 15.0), 5- and 10-year OS were 99.1% and 96.1%, respectively, and 5-and 10-year EFS were 92.7% and 89.4%. Factors contributing to 10-year EFS were: early CR (P=.02), absence of B symptoms (P=.01), lymphocyte predominant histologic subtype (P=.04), and less than three initial sites of disease (P=.02). Organ toxicity has been limited to correctable hypothyroidism in 42% of irradiated patients, and one case of cardiac dysfunction. 17 healthy babies have been born to 106 survivors. There have been two malignant tumors: one thyroid cancer within the RT field and one Ewing's sarcoma outside the RT field. Risk-adapted, combined-modality therapy using VAMP chemotherapy with RT is effective and well tolerated. Pediatric patients with low-risk HL can be cured with therapy without an alkylating agent, bleomycin, etoposide, or high-dose, EFRT. Thus, these children are expected to retain normal fertility, organ function, and be at low risk of a second malignant tumor.	2
24. Tebbi CK, Mendenhall N, London WB, Williams JL, de Alarcon PA, Chauvenet AR. Treatment of stage I, IIA, IIIA1 pediatric Hodgkin disease with doxorubicin, bleomycin, vincristine and etoposide (DBVE) and radiation: a Pediatric Oncology Group (POG) study. *Pediatr Blood Cancer* 2006; 46(2):198-202.	3a	51 patients	To evaluate the feasibility of reducing therapy, while maintaining treatment efficacy, in the context of a cooperative group clinical trial that allowed for clinical staging in early stage HL.	With a median follow-up of 8.4 years, the 6-year OS and EFS rates for the 46 patients treated with combination therapy were 98 +/- 2% and 91 +/- 5%, respectively. All patients achieved remission after completion of therapy. There have been four recurrences and a remission death due to gunshot wound. Combined modality therapy was well tolerated. Predominant side effects were gastrointestinal and hemopoietic. There have been no clinically significant cardio-pulmonary side effects so far. In clinically staged children with early-stage HL, DBVE and low-dose IFRT was effective therapy with tolerable side effects and reduced potential for long-term adverse events.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
25. Tebbi CK, Mendenhall NP, London WB, et al. Response-dependent and reduced treatment in lower risk Hodgkin lymphoma in children and adolescents, results of P9426: a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2012;59(7):1259-1265.	1	255 patients	To demonstrate that a reduction in treatment was possible without compromising survival outcomes.	There were 294 patients enrolled, with 255 eligible for analysis. The 8-year EFS between the dexrazoxane randomized groups did not differ (EFS 86.8 ± 3.1% with dexrazoxane, and 85.7 ± 3.3% without dexrazoxane (P=0.70). 45% of patients demonstrated CR after 2 cycles of chemotherapy. There was no difference in EFS by histology, rapidity of response, or number of cycles of chemotherapy. 6/8 secondary malignancies in this study have been previously reported.	2
26. Keller FG, Nachman J, Constine LS, et al. A Phase III Study for the Treatment of Children and Adolescents with Newly Diagnosed Low Risk Hodgkin Lymphoma (HL): American Society of Hematology; December, 2010.	2	275 patients	Phase III study designed to investigate: 1) the rate at which 3 cycles of AVPC induces CR, 2) whether achieving CR after 3 cycles of chemotherapy alone allows elimination of IFRT, while maintaining excellent disease control and 3) whether very early response as measured by FDG-PET after the first course of chemotherapy is predictive of outcome.	The CR rate after 3 cycles of AVPC was 63.6%, lower than the goal rate of 80%. However, EFS for the entire cohort at 2 years was 84%, and OS was 100%. At a median follow-up of 25 months, 46% of the entire cohort remains in CR without receiving any RT. These outcomes are similar to other published pediatric regimens for low risk HL (excluding LP histology), even those that incorporated RT for all or most patients. The OS of 100% suggests that those who did recur after limited therapy were quite salvageable, many without aggressive salvage regimens or stem cell transplant. CR status after 9 weeks of chemotherapy may not optimally identify patients in whom IFRT can be avoided. Very early response, as measured by FDG-PET after 3 weeks of therapy, had significant prognostic implications in both CR and PR subjects, suggesting that this assessment may have a role in identifying a cohort of patients for whom limited volume/low dose RT remains an important component of therapy. Alternatively, AVPC may require intensification to optimize EFS while limiting need for IFRT. The role of a limited intensity chemotherapy regimen with low-dose IFRT for those subjects that experience localized recurrence after chemotherapy alone is the subject of an ongoing investigation.	2

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27. Hudson MM, Poquette CA, Lee J, et al. Increased mortality after successful treatment for Hodgkin's disease. *J Clin Oncol* 1998; 16(11):3592-3600.	3a	387 patients	To determine the impact of treatment toxicity on long-term survival in pediatric HL.	The 5-year estimated EFS for the entire cohort was 79.6% +/- 2.1 %, which declined to 63.1% +/- 4.4% by 20 years. Cumulative incidences of cause-specific deaths at 25 years were 9.8% +/- 1.6% for HL, 8.1% +/- 2.6% for second malignancy, 4.0% +/- 1.8% for cardiac disease, 3.9% +/- 1.5% for infection, and 2.1% +/- 0.8% for accidents. Standardized incidence ratios showed excess risk for all second malignancies (12; 95% CI, 8 to 17), acute myeloid leukemia (81; 95% CI, 16 to 237), solid tumors (11; 95% CI, 7 to 16), and breast cancer (33; 95% CI, 12 to 72). Standardized mortality ratios also showed excess mortality from cardiac disease (22; 95% CI, 8 to 48) and infection (18; 95% CI, 7 to 38). Compared with age- and sex-matched control populations, survivors of pediatric HL who were treated before 1990 face an increased risk of early mortality related to second cancers, cardiac disease, and infection	2
28. Schwartz CL, Constine LS, Villaluna D, et al. A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: the results of P9425. *Blood* 2009; 114(10):2051-2059.	4	216 patients <22 years old	To evaluate ABVE-PC for children and adolescents with intermediate and high-risk HL.	5-year EFS was 84%: 86% for the RER and 83% for the SER (P=.85). Only 1% of patients had progressive disease. 5-year OS was 95%. With this regimen, cumulative doses of alkylators, anthracyclines, and epipodophyllotoxins are below thresholds usually associated with significant long-term toxicity. ABVE-PC is a dose-dense regimen that provides outstanding EFS/OS with short duration, early-response-adapted therapy.	2

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29. Friedman DI, wolden SL, Constine LS, al. E. AHOD0031: A Phase III Study of Dose-Intensive Therapy for Intermediate Risk Hodgkin Lymphoma: A Report From the Children's Oncology Group: American Society of Hematology; December, 2010.	1	1,712 patients	Phase III trial to evaluate dose-intensive therapy for intermediate risk HL.	The EFS at 3 years was 85.6% (95% CI, 83.6%-87.3%) for all patients, 87.1% (95% CI, 84.9%-89.0%) for RER patients vs 77.8% (95% CI, 72.0%-82.5%) for SER patients (P=0.0001). OS at 3 years was 98.2% (95% CI, 97.3%-98.8%) for all patients and differed between RER (98.7%) and SER patients (96.9%) (P=0.02). IFRT following 4 cycles of ABVE-PC did not appreciably improve outcome for RER/CR patients: 3-year EFS was 87.9% (95% CI, 83.3%-91.4%) for patients randomized to receive IFRT vs 85.4% (95% CI, 80.8%-89.0%) for those randomized to no IFRT (P=0.07). For SER patients randomized to DECA, 3-year EFS was 80.2% (95% CI, 71.9%-86.2%), and did not differ statistically from those who were randomized to no DECA, where the 3-year EFS was 75.6% (95% CI, 67.1%-82.2%). Early response to chemotherapy is important in the optimization of subsequent treatment intensity in patients with HL. Patients with RER followed by CR, particularly those who were PET2–, may not benefit from 21 Gy IFRT. In addition, CT and PET both play an important role in defining response and titration of therapy. Augmentation with DECA did not improve the overall EFS for SER (which remained inferior to outcome for RER), but there was a trend toward improved outcome with DECA in SER patients who were PET2+. Alternative augmentation regimens may prove more effective than DECA; an ongoing Children's Oncology Group trial is evaluating this hypothesis.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
30. Kelly KM, Sposto R, Hutchinson R, et al. BEACOPP chemotherapy is a highly effective regimen in children and adolescents with high-risk Hodgkin lymphoma: a report from the Children's Oncology Group. *Blood* 2011; 117(9):2596-2603.	4	99 patients	To evaluate BEACOPP chemotherapy in the treatment of children and adolescents with high-risk HL.	Rapid response was achieved by 74% of patients. 5-year EFS 94%, IFRT with median follow-up of 6.3 years. There were no disease progressions on study therapy. Secondary leukemia's occurred in 2 patients. OS is 97%. Early intensification followed by less intense response-based therapy for rapidly responding patients is an effective strategy for achieving high EFS in children with high-risk HL.	2
31. NCCN Clinical Practice Guidelines in Oncology. Hodgkin Lymphoma. Version 1.2013. Available at: http://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf. Accessed April 12, 2013.	7	N/A	To provide NCCN practice guidelines on Hodgkin Lymphoma.	No abstract available.	4

Pediatric Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
32. Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA* 2003; 290(4):465-475.	3c	3,817 patients	To quantify the long-term risk of breast cancer associated with use of RT and chemotherapy to treat young women with HL.	A radiation dose of 4 Gy or more delivered to the breast was associated with a 3.2-fold (95% CI, 1.4-8.2) increased risk, compared with the risk in patients who received lower doses and no alkylating agents. Risk increased to 8-fold (95% CI, 2.6-26.4) with a dose of more than 40 Gy (P<.001 for trend). Radiation risk did not vary appreciably by age at exposure or reproductive history. Increased risks persisted for 25 or more years following RT (RR, 2.3; 95% CI, 0.5-16.5; P=.03 for trend with dose). Treatment with alkylating agents alone resulted in a reduced risk (RR, 0.6; 95% CI, 0.2-2.0) of breast cancer, and combined alkylating agents and RT in a 1.4-fold (95% CI, 0.6-3.5) increased risk. Risk of breast cancer decreased with increasing number of alkylating agent cycles (P =.003 for trend). Risk also was low (RR, 0.4; 95% CI, 0.1-1.1) among women who received 5 Gy or more delivered to ovaries compared with those who received lower doses. Hormonal stimulation appears important for the development of radiation-induced breast cancer, as evidenced by the reduced risk associated with ovarian damage from alkylating agents or radiation. The high radiation-related risk, which did not diminish at the highest doses or the longest follow-up, however, suggests the need for lifetime surveillance and programs of patient and public awareness.	2

Pediatric Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
33. Koh ES, Sun A, Tran TH, et al. Clinical dose-volume histogram analysis in predicting radiation pneumonitis in Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys* 2006; 66(1):223-228.	3a	64 consecutive patients	To quantify the incidence of radiation pneumonitis in a modern HL cohort and to identify any clinically relevant parameters that may influence the risk of radiation pneumonitis.	At a median follow-up of 2.1 years, the actuarial survival for all patients was 91% at 3 years. There were 2 (2/64) cases of RTOG Grade 2 radiation pneumonitis (incidence 3.1%). Both index cases with corresponding V(20) values of 47.0% and 40.7% were located in the upper quartile (2/16 cases), defined by a V(20) value of ≥36%, an incidence of 12.5% (P=0.03). Similarly for total mean lung dose, both index cases with values of 17.6 Gy and 16.4 Gy, respectively, were located in the upper quartile defined by mean lung dose ≥14.2 Gy, an incidence of 11.8% (2/17 cases, P=0.02). Despite relatively high V(20) values in this study of HL patients, the incidence of radiation pneumonitis was only 3%, lower compared with the lung cancer literature. We suggest the following clinically relevant parameters be considered in treatment plan assessment: a V(20) greater than 36% and an mean lung dose >14 Gy, over and above which the risk of RTOG Grade 2 or greater radiation pneumonitis would be considered clinically significant.	2

Pediatric Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
34. Shahidi M, Kamangari N, Ashley S, Cunningham D, Horwich A. Site of relapse after chemotherapy alone for stage I and II Hodgkin's disease. *Radiother Oncol* 2006; 78(1):1-5.	3a	61 patients	To assess the site of relapse after chemotherapy alone for stage I and II HL.	After a median follow-up of 6.5 years, 24 patients had relapsed giving a 5-year relapse rate of 40%. The 5 and 10-year actuarial survival rates were 94% and 89%, respectively with cause-specific survival being 94% at 5 and 10 years. Two-thirds of the relapses were nodal and supradiaphragmatic. 20 patients (83%) relapsed in the initially involved sites of disease and this was the sole site of recurrence in 11 (45%) of patients. In retrospect, it appeared that at least 12 recurrences could have been prevented by IFRT. Review of detailed imaging data (available in 9/11 patients with recurrences in initial sites of disease) showed that the relapses were always in the initially involved nodes. After chemotherapy alone in early stage HL most initial recurrences are nodal. Loco-regional recurrences are in the originally involved nodes. Based on limited data it appears that involved nodal RT is equivalent to IFRT and may halve the risk of recurrence.	2
35. Girinsky T, van der Maazen R, Specht L, et al. Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: concepts and guidelines. *Radiother Oncol* 2006; 79(3):270-277.	7	N/A	To describe new concepts for radiation fields in patients with early stage HL treated with a combined modality.	Radiation fields are designed to irradiate the initially involved lymph nodes exclusively and to encompass their initial volume. In some cases, radiation fields are slightly modified to avoid unnecessary irradiation of muscles or organs at risk. The concept of INRT described here is the first attempt to reduce the size of radiation fields compared to the classic involved fields used in adult patients. Proper implementation of INRT requires adequate training and an efficient prospective or early retrospective quality assurance program.	4

Pediatric Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
36. Eich HT, Muller RP, Engenhart-Cabillic R, et al. Involved-node radiotherapy in early-stage Hodgkin's lymphoma. Definition and guidelines of the German Hodgkin Study Group (GHSG). *Strahlenther Onkol* 2008; 184(8):406-410.	15	N/A	Guidelines comparing INRT with standard IFRT in early-stage HL.	The clinical target volume encompasses the initial volume of the lymph node(s) before chemotherapy and incorporates the initial location and extent of the disease taking the displacement of the normal tissues into account. The margin of the planning target volume should be 2 cm in axial and 3 cm in craniocaudal direction. If necessary, it can be reduced to 1-1.5 cm. To minimize lung and cardiac toxicity, the target definition in the mediastinum is different. The concept of INRT has been proposed as a means to further improve the therapeutic ratio by reducing the risk of radiation-induced toxicity, including second malignancies. Field sizes will further decrease compared to IFRT.	4
37. Girinsky T, Specht L, Ghalibafian M, et al. The conundrum of Hodgkin lymphoma nodes: to be or not to be included in the involved node radiation fields. The EORTC-GELA lymphoma group guidelines. *Radiother Oncol* 2008; 88(2):202-210.	15	N/A	To develop easily applicable guidelines for the determination of initially involved lymph nodes to be included in the radiation fields.	The classic guidelines for determining the involvement of lymph nodes were not easily applicable and did not seem to reflect the exact extent of HL. Three simple steps were used to pinpoint involved lymph nodes. First, FDG-PET scans were meticulously analyzed to detect lymph nodes that were overlooked on CT imaging. Second, any morphological and/or functional asymmetry was sought on CT and FDG-PET scans. Third, a decrease in size or the disappearance of initially visible lymph nodes on the prechemotherapy CT scan as compared to the postchemotherapy CT scan was considered as surrogate proof of initial involvement. All the radiological procedures should be performed on patients in the treatment position for proper coregistration. It is highly advisable that all CT and/or CT/PET scans be performed with intravenous contrast. Using the above-mentioned three simple guidelines, initially involved lymph nodes can be detected with very satisfactory accuracy. It is also emphasized that the classic guidelines (2, 3, 4) can always be used when deemed necessary.	4

Pediatric Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
38. Campbell BA, Voss N, Pickles T, et al. Involved-nodal radiation therapy as a component of combination therapy for limited-stage Hodgkin's lymphoma: a question of field size. *J Clin Oncol* 2008; 26(32):5170-5174.	3a	325 patients	To evaluate INRT as a component of combination therapy for limited-stage HL.	Median follow-up of living patients was 80 months. Median time to relapse was 37 months. 12 relapses occurred: four after EFRT (3%); five after IFRT (5%); and three after INRT ≤5 cm (3%; P=.9). No marginal recurrences occurred after INRT ≤5 cm. Locoregional relapse (LRR) occurred in five patients: three after EFRT; two with IFRT; and none with INRT ≤5 cm. At 5 years, PFS was 97%, and OS was 95%. At 10 years, PFS and OS were 95% and 90%, respectively. Reduction in field size appears to be safe, without an increased risk of LRR in patients receiving INRT ≤5 cm.	2

Pediatric Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
39. Bodis S, Kraus MD, Pinkus G, et al. Clinical presentation and outcome in lymphocyte-predominant Hodgkin's disease. *J Clin Oncol* 1997; 15(9):3060-3066.	3a	75 patients with LPHL	Patterns of presentation, histologic pattern (nodular or diffuse), treatment, and long-term outcome were studied in patients with LPHL to determine whether these patients should be treated differently than patients with other subtypes of HL.	The 10-year actuarial freedom-from-first-relapse and 10-year OS rates for the 71 patients with LPHL treated at the JCRT were 80% and 93%, respectively. The 10-year actuarial freedom-from-first-relapse by nodular (n=51), diffuse (n=14), and unspecified (n=6) histologic pattern was 74%, 100%, and 60%, respectively. Overall, 14/71 patients have relapsed: 9/61 with stage IA, IB, or IIA disease and 5/10 with stage IIB to IVB disease have relapsed. The median time to relapse was 53 months. 9/71 patients have died. Only 1 death has been from HL: 5 patients died of second cancers, two of cardiac disease, and one of alcoholic liver cirrhosis. Of 7 patients with second malignancies, 5 died. None of the second malignancies were non-Hodgkin's lymphoma. Patients with LPHL have different patterns of presentation, sex and age distribution, and likelihood of occult abdominal disease than patients with nodular-sclerosing or mixed-cellularity disease. The median time to relapse for LPHL patients was later than reported for other histologic subtypes; however, there was no pattern of continuous late relapse. With pathologic staging and standard treatment, mortality from LPHL is low; nearly all deaths have been cardiac- or second tumor-related. This suggests that less aggressive treatment for LPHL might continue to yield excellent results, while perhaps lowering the long-term risk of complications.	3

Pediatric Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
40. Bodis S, Henry-Amar M, Bosq J, et al. Late relapse in early-stage Hodgkin's disease patients enrolled on European Organization for Research and Treatment of Cancer protocols. *J Clin Oncol* 1993; 11(2):225-232.	3a	1,044 patients	To describe the characteristics and outcome of patients who had late relapses, which was defined as relapses that, occurred 5 or more years after initial treatment start.	The 10- and 15-year cumulative probabilities of late relapse in patients who were disease-free at 5 years were 4.8% and 8.3%, respectively. Patients treated on more recent protocols had a higher incidence of late relapse; possibly due to an attempt to tailor therapy to the specific prognostic factors (10-year cumulative probabilities, 4.6%, 2.6%, and 7.5% in trials H1, H2, and H5, respectively). Incidence of late relapses significantly correlated with male sex, B symptoms, mediastinal involvement, and treatment modality. Salvage treatment induced a CR in 27 patients (79%) and a prolonged complete remission in 24 patients (71%). 20-years after initial treatment start, similar OS rates were observed for late relapsing (72%) and nonrelapsing patients (75%). Late relapses of HL are uncommon, but may be more frequent with recent protocols tailored to specific prognostic factors. If treated, their outcome is favorable. Late relapse is therefore another factor indicating that careful, long-term follow-up is needed for patients with HL.	2
41. Chan WC. Cellular origin of nodular lymphocyte-predominant Hodgkin's lymphoma: immunophenotypic and molecular studies. *Semin Hematol* 1999; 36(3):242-252.	7	N/A	Review LPHL.	Challenge for the future is to obtain a more comprehensive molecular profile of L&H cells and their associated T lymphocytes, so as to provide a framework for eventual elucidation of the pathogenesis of this type of HL.	4
42. Nogova L, Reineke T, Eich HT, et al. Extended field radiotherapy, combined modality treatment or involved field radiotherapy for patients with stage IA lymphocyte-predominant Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Study Group (GHSG). *Ann Oncol* 2005; 16(10):1683-1687.	3a	131 patients	Study reviewed all LPHL cases registered in the database of the German Hodgkin Study Group (GHSG) and compared the different treatment approaches, such as EFRT, IFRT and combined modality treatment for LPHL stage IA patients.	129 patients achieved complete remission: 98% after EFRT, 100% after IFRT and 95% after combined modality. With a median follow-up of 43 months there were 5% relapses and only 3 patients died. Toxicity of treatment was generally mild with most events observed after combined modality. In terms of remission induction IFRT for stage IA LPHL patients is as effective as EFRT or combined modality treatment. However, longer follow-up is needed before final conclusion as the optimal therapy.	3

Pediatric Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
43. Wirth A, Yuen K, Barton M, et al. Long-term outcome after radiotherapy alone for lymphocyte-predominant Hodgkin lymphoma: a retrospective multicenter study of the Australasian Radiation Oncology Lymphoma Group. *Cancer* 2005; 104(6):1221-1229.	3a	202 patients	Retrospective multicenter study to examine the long-term results of initial RT alone, to identify favorable patient subsets, and to explore the effect of reducing RT field size on treatment efficacy.	The OS rate at 15 years was 83%, and freedom from progression was observed in 82% of patients, including 84% of patients with stage I disease and 73% of patients with stage II disease. No recurrent LPHL and only 1 patient with non-Hodgkin lymphoma were reported after 15 years. Adverse prognostic factors that were identified on multifactor analysis were as follows: for OS, age 45 years or older ($P<0.0005$), the presence of B symptoms ($P=0.002$), increasing number of sites ($P=0.015$); for freedom from progression, increasing number of sites ($P=0.002$). No significant difference was found in freedom from progression in a comparison of patients who received elective mediastinal RT with patients who did not receive mediastinal RT ($P=0.11$). Causes of death at 15 years were LPHL in 3% of patients, non-Hodgkin lymphoma in 2% of patients, in-field malignancy in 2% of patients, in-field cardiac/respiratory in 4% of patients, and other in 6% of patients. The current data suggested that RT potentially may be curative for patients with Stage I-II LPHL and raise the possibility that limited-field RT may be used without loss of treatment efficacy. IFRT warrants further investigation for patients with early-stage LPHL.	3

Pediatric Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
44. Karayalcin G, Behm FG, Gieser PW, et al. Lymphocyte predominant Hodgkin disease: clinico-pathologic features and results of treatment--the Pediatric Oncology Group experience. *Med Pediatr Oncol* 1997; 29(6):519-525.	4	26 cases of LPHL in 613 patients	A review on the Pediatric Oncology Group (POG) experience with LPHL in children.	Histologic subtypes were 17 nodular, 8 diffuse pattern; 1 was indeterminate. The sites involved at diagnosis were primarily the peripheral lymph nodes. 14 patients had stage I disease; 9 had stage II; 3 had stage III; there was no stage IV disease. Only 4/26 patients had B symptoms. All 26 patients achieved complete remission, 10 with RT, 6 with chemotherapy and 10 with combined modality therapy. Treatment was not uniform since patients were registered on different protocols. EFS after 5 years was 86.5%. Two patients developed and succumbed to large cell, T-cell type, non-Hodgkin lymphoma. Optimal treatment for LPHL should focus on efforts to limit the risk of second malignancy.	3
45. Murphy SB, Morgan ER, Katzenstein HM, Kletzel M. Results of little or no treatment for lymphocyte-predominant Hodgkin disease in children and adolescents. *J Pediatr Hematol Oncol* 2003; 25(9):684-687.	3a	12 patients	To see if children and adolescents could be spared the adverse sequelae of treatment, the authors adopted a policy of little or no treatment of localized LPHL in 1989.	All patients are alive, without evidence of disease, for periods ranging from 2 to 13+ years after diagnosis (median 6 years). One patient recurred locally with LPHL 6 years after initial brief chemotherapy and was then treated with IFRT, achieving a prolonged second remission. Children and adolescents with localized LPHL have an excellent prognosis and may be safely approached either with a wait-and-see attitude of no initial therapy after initial adenectomy or with less aggressive treatments.	3

Pediatric Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
46. Mauz-Korholz C, Gorde-Grosjean S, Hasenclever D, et al. Resection alone in 58 children with limited stage, lymphocyte-predominant Hodgkin lymphoma-experience from the European network group on pediatric Hodgkin lymphoma. *Cancer* 2007; 110(1):179-185.	3a	58 children	European study groups reported their experience of surgery alone used in the treatment of pediatric LPHL in order to clarify the optimum treatment strategy in children.	With a median follow-up of 43 months (range, 2-202 months), the OS rate was 100%, and the PFS rate was 57%. 51/58 patients achieved complete remission after surgery. In the complete remission group, the overall PFS rate was 67% (95% CI, 51%-82%). All 7 patients who had residual disease after initial surgery developed recurrences (P=.003). Among 18 patients with stage IA LPHL who developed recurrent disease, 11 patients had local recurrences, and 7 patients recurred in stage IIA. One patient with stage IIIA disease presented with high-grade B-cell non-Hodgkin lymphoma at 10 years of follow-up. When complete resection was achieved, a substantial proportion of patients with surgically treated, early-stage LPHL experienced long-term remission and actually may have been cured.	3
47. Appel B, Ehrlich P, Chen L, et al. Treatment of pediatric stage IA lymphocyte-predominant Hodgkin lymphoma with surgical resection alone: A report from the Children's Oncology Group. *J Clin Oncol* 2012; 30(suppl; abstr 9524).	4	52 patients	To report the results of a large prospective study using a treatment algorithm in which a selected subset of patients received surgery alone.	Between January 2006 and November 2010, 52 patients with stage IA, single node LPHL were enrolled with confirmed total resection. Nine patients have experienced a relapse; 8 were stage I and 1 was stage II at relapse. The median time to relapse was 10 (range 1-17) months. The median follow-up among the 43 remaining patients is 26 (range 4-60) months. The current 2 year EFS estimate among these patients is 80.3% (95% CI: 65.3%-89.3%). OS for the 52 patients is 100%.	3
48. Constine LS, Rapoport AP. Hodgkin's disease, bone marrow transplantation, and involved field radiation therapy: coming full circle from 1902 to 1996. *Int J Radiat Oncol Biol Phys* 1996; 36(1):253-255.	7	N/A	To review HL, bone marrow transplantation, and IFRT.	The applicability of IFRT in the setting of HL and stem-cell rescue may increase as a consequence of the more common use of chemotherapy in early-stage HL and a trend toward RT field and dose reductions. It is likely that no single strategy of IFRT will be ideal for all patients.	4

Pediatric Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
49. Reece DE, Connors JM, Spinelli JJ, et al. Intensive therapy with cyclophosphamide, carmustine, etoposide +/- cisplatin, and autologous bone marrow transplantation for Hodgkin's disease in first relapse after combination chemotherapy. *Blood* 1994; 83(5):1193-1199.	3a	58 patients	To evaluate the optimal timing in which to use intensive chemotherapy and autologous bone marrow transplantation in HL.	Treatment-related deaths occurred in only 3 patients. 13 patients have relapsed at median 0.7 years (range 0.1 to 3.5) post-bone marrow transplantation. At a median follow-up of 2.3 years (range 0.4 to 7.2), the actuarial PFS is 64% (95% CI, 46%-78%). In the statistical analysis, three similarly weighted but independent prognostic factors were identified: "B" symptoms at relapse, extranodal disease at relapse, and initial remission duration of <1-year. Patients with no risk factors had a 3-year PFS of 100%, compared with 81% in patients with one factor, 40% in those with two factors, and 0% in patients with all three factors. CBV +/- P and autologous bone marrow transplantation is highly effective salvage therapy for HL patients in a first relapse, particularly in the subset of patients with less than two adverse factors. Therapy must be improved in the future for patients with ≥2 adverse factors.	2
50. Yahalom J. Management of Relapsed and Refractory Hodgkin's Disease. *Semin Radiat Oncol* 1996; 6(3):210-224.	7	N/A	To review standard-dose salvage as well as current development in high-dose therapy with particular attention to the role of RT.	Although it appears that further dose escalation of chemotherapy is limited by nonhematologic toxicity, the benefit from incorporation of RT into high-dose programs has only recently been recognized. Because of the availability of hematopoietic growth factors and easier mobilization and collection of peripheral blood stem cells, these have become the preferred source for hematopoietic support. The use of peripheral blood stem cells and growth factors was shown to correlate with more rapid recovery of granulocytes and platelets and a shorter hospitalization period. Still, many patients remain refractory to salvage despite intensive therapy. These patients can be identified by their response to re-induction chemotherapy before transplant and should be considered for alternative approaches such as allogeneic bone marrow transplantation, sequential bone marrow transplant, and other experimental programs.	3

Pediatric Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
51. Claviez A, Canals C, Dierickx D, et al. Allogeneic hematopoietic stem cell transplantation in children and adolescents with recurrent and refractory Hodgkin lymphoma: an analysis of the European Group for Blood and Marrow Transplantation. *Blood* 2009; 114(10):2060-2067.	3a	91 patients	To assess allogenic hematopoietic stem cell transplantation in children and adolescents with recurrent and refractory HL.	Reduced intensity conditioning was associated with an increased relapse risk compared with myeloablative conditioning; most apparent beginning 9 months after hematopoietic stem cell transplantation (P=.01). PFS was 40% (+/- 6%) and 30% (+/- 6%) and OS was 54% (+/- 6%) and 45% (+/- 6%) at 2 and 5 years, respectively. Disease status at hematopoietic stem cell transplantation was predictive of PFS in multivariate analysis (P<.001). Beyond 9 months, PFS after reduced intensity conditioning was lower compared with myeloablative conditioning (P=.02). Graft-vs-host disease did not affect relapse rate and PFS. In conclusion, children and adolescents with recurring HL show reasonable results with allogeneic hematopoietic stem cell transplantation. Especially patients allografted in recent years with good performance status and chemosensitive disease show highly encouraging results (PFS: 60% +/- 27%, OS: 83% +/- 15% at 3 years). Because relapse remains the major cause of treatment failure, additional efforts to improve disease control are necessary.	2
52. Trippett TM, Chen A. Treatment of Relapsed/Refractory Hodgkin Lympoma. In: Weinstein HJ, Hudson MM, Link MP, eds. *Pediatric oncology*. Berlin ; New York: Springer; 2007:67-84.	15	N/A	Textbook.	N/A	4

Pediatric Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
53. Cole PD, Schwartz CL, Drachtman RA, de Alarcon PA, Chen L, Trippett TM. Phase II study of weekly gemcitabine and vinorelbine for children with recurrent or refractory Hodgkin's disease: a children's oncology group report. *J Clin Oncol* 2009; 27(9):1456-1461.	3a	30 patients	Phase II study to assess the efficacy and toxicity of gemcitabine and vinorelbine in pediatric patients with heavily pretreated relapsed/refractory HL. Both agents have significant single-agent response rates in this setting.	30 eligible patients with a median age of 17.7 years (range, 10.7 to 29.4 years) were enrolled. All patients had received at least two prior chemotherapy regimens, and 17 patients had undergone prior autologous stem-cell transplantation. Hematologic toxicity was predominant in all treatment cycles. Nonhematologic grade 3 to 4 toxicity, including elevated hepatic enzymes and hyperbilirubinemia, was less common. Pericardial and pleural effusions developed in one patient after cycles 4 and 5 of gemcitabine and vinorelbine, consistent with gemcitabine-induced radiation recall. There were no toxic deaths. Measurable responses were seen in 19 (76%) of 25 assessable patients (95% exact binomial CI, 55% to 91%), including six CRs, 11 very good partial responses, and two partial responses. Gemcitabine and vinorelbine is an effective and well-tolerated reinduction regimen for children with relapsed or refractory HL.	2
54. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med* 2010; 363(19):1812-1821.	2	45 patients	To enhance the antitumor activity of CD30-directed therapy, the antitubulin agent monomethyl auristatin E was attached to a CD30-specific monoclonal antibody by an enzyme-cleavable linker, producing the antibody-drug conjugate brentuximab vedotin.	The maximum tolerated dose was 1.8 mg per kilogram, administered every 3 weeks. Objective responses, including 11 CRs, were observed in 17 patients. Of 12 patients who received the 1.8-mg-per-kilogram dose, 6 (50%) had an objective response. The median duration of response was at least 9.7 months. Tumor regression was observed in 36/42 patients who could be evaluated (86%). The most common adverse events were fatigue, pyrexia, diarrhea, nausea, neutropenia, and peripheral neuropathy. Brentuximab vedotin induced durable objective responses and resulted in tumor regression for most patients with relapsed or refractory CD30-positive lymphomas in this phase 1 study. Treatment was associated primarily with grade 1 or 2 (mild-to-moderate) toxic effects.	3

Pediatric Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
55. Donaldson SS, Hudson MM, Lamborn KR, et al. VAMP and low-dose, involved-field radiation for children and adolescents with favorable, early-stage Hodgkin's disease: results of a prospective clinical trial. *J Clin Oncol* 2002; 20(14):3081-3087.	2	110 patients	To evaluate outcome and assess toxicity of children and adolescents with early-stage, favorable HL treated with VAMP and low-dose IFRT.	Patients received 4 cycles of VAMP plus 15 Gy to 25.5 Gy RT. With a median follow-up of 5.6 years, the 5 year OS and EFS were 99% and 93%, respectively. Nodular sclerosing HL was found to be unfavorable. Risk-adapted, combined-modality therapy for patients with early-stage/favorable HL is highly effective and without demonstrable late effects. Pediatric patients with stage I and II favorable HL can be cured with limited therapy that does not include an alkylating agent, bleomycin, etoposide, or high-dose EFRT.	2
56. Hutchinson RJ, Fryer CJ, Davis PC, et al. MOPP or radiation in addition to ABVD in the treatment of pathologically staged advanced Hodgkin's disease in children: results of the Children's Cancer Group Phase III Trial. *J Clin Oncol* 1998; 16(3):897-906.	1	111 patients	A randomized trial designed to compare MOPP/ABVD (regimen A) with ABVD plus low-dose regional EFRT (regimen B) for the treatment of children and adolescents with stages III and IV HL.	OS is 87% at 4 years and EFS is 82%. Patients randomized to ABVD plus EFRT have a 4-year EFS of 87% compared with 77% for patients randomized to MOPP/ABVD (P=.09, two-sided). Patients randomized to ABVD plus EFRT have a 4-year OS of 90% compared with 84% for patients randomized to MOPP/ABVD (P=.45, two-sided). Significant prognostic factors in multivariate analysis for EFS are stage of disease, erythrocyte sedimentation rate at diagnosis, liver size at diagnosis, and, among stage III patients, the size of the mediastinal mass at diagnosis. The acute toxicities of treatment are largely hematopoietic in nature, whereas acute pulmonary and cardiac toxicities are modest and not limiting. The results of this study show that, in advanced-stage HL in children, equivalent results can be obtained by the addition of either MOPP or low-dose EFRT to the ABVD regimen; whether the addition of either contributes to outcome was not addressed in this study and will require additional testing. It is clear, however, that MOPP chemotherapy can safely be eliminated from front-line combination chemotherapy regimens for advanced HL in pediatric patients.	1

Evidence Table Key

Study Type Key

Numbers 1-7 are for studies of therapies while numbers 8-15 are used to describe studies of diagnostics.

1. Randomized Controlled Trial — Treatment
2. Controlled Trial
3. Observation Study
    a. Cohort
    b. Cross-sectional
    c. Case-control
4. Clinical Series
5. Case reviews
6. Anecdotes
7. Reviews
8. Randomized Controlled Trial — Diagnostic
9. Comparative Assessment
10. Clinical Assessment
11. Quantitative Review
12. Qualitative Review
13. Descriptive Study
14. Case Report
15. Other (Described in text)

Strength of Evidence Key

- Category 1 - The conclusions of the study are valid and strongly supported by study design, analysis and results.
- Category 2 - The conclusions of the study are likely valid, but study design does not permit certainty.
- Category 3 - The conclusions of the study may be valid but the evidence supporting the conclusions is inconclusive or equivocal.
- Category 4 - The conclusions of the study may not be valid because the evidence may not be reliable given the study design or analysis.

Abbreviations Key

ABVD = Doxorubicin, bleomycin, vinblastine, and dacarbazine

ABVE-PC = Doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide

AVPC = Doxorubicin, vincristine, prednisone and cyclophosphamide

BEACOPP = Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone

CI = Confidence interval

CR = Complete response

CT = Computed tomography

DBVE = Doxorubicin, bleomycin, vincristine and etoposide

DECA = Dexamethasone, etoposide, cisplatin and cytarabine

DFS = Disease-free survival

EFRT = Extended-field radiation therapy

EFS = Event-free survival

FDG-PET = Fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography

HL = Hodgkin’s lymphoma

IFRT = Involved-field radiation therapy

INRT = Involved-node radiation therapy

LPHL = Lymphocyte-predominant Hodgkin's lymphoma

MOPP = Mechlorethamine, vincristine, procarbazine, and prednisone

OEPA/COPDAC = Vincristine, etoposide, prednisone, and doxorubicin/cyclophosphamide, vincristine, prednisone, and dacarbazine

OPPA/COPP = Vincristine, procarbazine, prednisone, and doxorubicin/cyclophosphamide, vincristine, procarbazine, and prednisone

OS = Overall survival

PFS = Progression-free survival

RER = Rapid early responder

RR = Relative risk

RT = Radiation therapy

SER = Slow early responder

VAMP = Vinblastine, doxorubicin, methotrexate, and prednisone

WBC = White blood cell