Hodgkin Lymphoma-Stage III and IV
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC Press; 2008.	Review/Other-Dx	N/A	N/A	N/A	4
2. 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.	Review/Other-Dx	N/A	To review the classification and modify it in the light of experience gained in its use and new techniques for evaluating disease.	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 2 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
3. Richardson SE, Sudak J, Warbey V, Ramsay A, McNamara CJ. Routine bone marrow biopsy is not necessary in the staging of patients with classical Hodgkin lymphoma in the 18F-fluoro-2-deoxyglucose positron emission tomography era. *Leuk Lymphoma.* 2012;53(3):381-385.	Observational-Dx	50 patients	To assess current UK practice in classical HL staging by questionnaire and retrospectively analyze patients staged at a single center with bone marrow biopsy and FDG-PET/CT.	From 34 questionnaire responses 50% used FDG-PET/CT routinely. Bone marrow biopsy was employed in 97% with advanced-stage and 30% of patients with limited-stage disease (70% of those not using routine FDG-PET/CT). 10/50 patients were bone marrow+, all of which were identified by FDG-PET/CT (PET+). Conventional bone marrow biopsy changed management in 2% of cases. There were no clinically significant FDG-PET/CT false positives. Conventional routine bone marrow biopsy staging in classical HL is extremely insensitive. FDG-PET/CT can rule out marrow/bone involvement in classical HL.	3

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4. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32(27):3059-3068.	Review/Other-Dx	N/A	To modernize recommendations for evaluation, staging, and response assessment of patients with HL and NHL.	PET/CT should be used for response assessment in FDG-avid histologies, using the 5-point scale; CT is preferred for low or variable FDG avidity. A complete metabolic response even with a persistent mass is considered a CR. A partial response requires a decrease by more than 50% in the sum of the product of the perpendicular diameters of up to 6 representative nodes or extranodal lesions. Progressive disease by CT criteria only requires an increase in the perpendicular diameters of a single node by 50%. Surveillance scans after remission is discouraged, especially for diffuse large B-cell lymphoma and HL, although a repeat study may be considered after an equivocal finding after treatment. Judicious use of follow-up scans may be considered in indolent lymphomas with residual intra-abdominal or retroperitoneal disease.	4
5. Edwards-Bennett SM, Jacks LM, Moskowitz CH, et al. Stanford V program for locally extensive and advanced Hodgkin lymphoma: the Memorial Sloan-Kettering Cancer Center experience. *Ann Oncol.* 2010;21(3):574-581.	Observational-Tx	126 patients	To examine whether treatment at Memorial Sloan-Kettering Cancer Center carefully following Stanford V guidelines would confirm the original Stanford outcome data.	The 5- and 7-year OS were 90% and 88%, respectively. The 5-year FFS was 78%. IPS ≥4 was a significant independent predictor of worse OS and PFS. The FF2R was 64% at 3 years.	2
6. Horning SJ. Risk, cure and complications in advanced hodgkin disease. *Hematology Am Soc Hematol Educ Program.* 2007:197-203.	Review/Other-Tx	N/A	To review the characteristics and outcomes of patients treated with ABVD in randomized controlled trial compared with COPP/ABVD in HD9; to review the clinical and biologic prognostic factors, including PET imaging; and to discuss newer strategies targeted at minimizing treatment complications while maximizing cure rates.	Although enthusiasm for PET imaging is great, the challenges for using this diagnostic tool for risk-adapted therapies are substantial. Importantly, physicians and patients should be aware of these challenges, support the randomized controlled trial that seek to address them, and carefully weigh risks and benefits for individual patients.	4

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7. Horning SJ, Williams J, Bartlett NL, et al. Assessment of the stanford V regimen and consolidative radiotherapy for bulky and advanced Hodgkin's disease: Eastern Cooperative Oncology Group pilot study E1492. *J Clin Oncol.* 2000;18(5):972-980.	Experimental-Tx	47 patients	To evaluate the efficacy and feasibility of the Stanford V chemotherapy regimen plus RT to bulky HL sites.	With a median follow-up of 4.8 years, 45 patients are alive and 40 have been continuously disease-free. The estimated FFP was 87% at 2 years and 85% at 5 years. OS was 96% at 2 and 5 years. There was 1 death from HL and 1 death from an M5 acute leukemia. 6 of 7 relapsed patients received high-dose therapy and autologous stem-cell transplantation. The freedom from second progression for the 7 relapsed patients was estimated at 98% at 3 years.	2
8. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med.* 1998;339(21):1506-1514.	Observational-Tx	1,618 patients	To develop a scoring system for patients treated with combination chemotherapy, with or without RT.	The prognostic score was defined as the number of adverse prognostic factors present at diagnosis. 7 factors had similar independent prognostic effects: a serum albumin level of <4 g/dL, a hemoglobin level of <0.5 g/dL, male sex, an age of 45 years or older, stage IV disease (according to the Ann Arbor classification), leukocytosis (a white-cell count of at least 15,000 per cubic millimeter), and lymphocytopenia (a lymphocyte count of <600 per cubic millimeter, a count that was <8% of the white-cell count, or both). The score predicted the rate of FFP of disease as follows: 0, or no factors (7% of the patients), 84%; 1 (22% of the patients), 77%; 2 (29% of the patients), 67%; 3 (23% of the patients), 60%; 4 (12% of the patients), 51%; and 5 or higher (7% of the patients), 42%.	4
9. Moccia AA, Donaldson J, Chhanabhai M, et al. International Prognostic Score in advanced-stage Hodgkin's lymphoma: altered utility in the modern era. *J Clin Oncol.* 2012;30(27):3383-3388.	Observational-Dx	740 patients	To assess the prognostic relevance of the IPS in patients with advanced-stage HL treated in the modern era.	In all, 740 patients were identified. 5-year FFP and OS were 78% and 90%, respectively. The IPS was prognostic for both FFP (P<.001) and OS (P<.001), with 5-year FFP ranging from 62% to 88% and 5-year OS ranging from 67% to 98%. Analysis limited to patients age 16 to 65 years (n = 686) demonstrated a narrower range of outcomes, with 5-year FFP ranging from 70% to 88% and 5-year OS ranging from 73% to 98%.	4

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10. Diefenbach CS, Li H, Hong F, et al. Evaluation of the International Prognostic Score (IPS-7) and a Simpler Prognostic Score (IPS-3) for advanced Hodgkin lymphoma in the modern era. *Br J Haematol.* 2015;171(4):530-538.	Observational-Dx	854 patients	To assess the utility of the individual IPS-7 factors in the contemporary era, we analyzed data from a prospective phase III randomized trial, ECOG 2496 (E2496), a study that evaluated ABVD vs Stanford V in advanced HL.	The IPS-7 remained prognostic however its prognostic range has narrowed. On multivariate analysis, 2 factors (age, stage) remained significant for FFP and 3 factors (age, stage, hemoglobin level) for OS. An alternative prognostic index, the IPS-3, was constructed using age, stage and hemoglobin level, which provided 4 distinct risk groups [FFP (P=0.0001) and OS (P<0.0001)]. IPS-3 outperformed the IPS-7 on risk prediction for both FFP and OS by model fit and discrimination criteria. Using reclassification calibration, 18% of IPS-7 low risk patients were re-classified as intermediate risk and 13% of IPS-7 intermediate risk patients as low risk.	3
11. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med.* 1992;327(21):1478-1484.	Experimental-Tx	361 patients; 123 received MOPP, 123 received MOPP alternating with ABVD, and 115 received ABVD alone	To compare 3 regimens of primary systemic therapy for newly diagnosed advanced HL in stages IIIA2, IIIB, and IVA or IVB: (1) MOPP alone given for 6 to 8 cycles, (2) MOPP alternating with ABVD for 12 cycles, and (3) ABVD alone for 6 to 8 cycles.	The overall response rate was 93%, with complete responses in 77%: 67% in the MOPP group, 82% in the ABVD group, and 83% in the MOPP/ABVD group (P=0.006 for the comparison of MOPP with the other 2 regimens, both of which contained doxorubicin). The rates of FFS at 5 years were 50% for MOPP, 61% for ABVD, and 65% for MOPP/ABVD. Age, stage (III vs IV), and regimen influenced FFS significantly. OS at 5 years was 66% for MOPP, 73% for ABVD, and 75% for MOPP/ABVD (P=0.28 for the comparison of MOPP with the doxorubicin regimens). MOPP had more severe toxic effects on bone marrow than ABVD and was associated with greater reductions in the prescribed dose.	1
12. Carde P. Who are the high-risk patients with Hodgkin's disease? *Leukemia.* 1996;10 Suppl 2:s62-67.	Review/Other-Tx	N/A	To review the concerns with the prognosis of relapsing HL.	No results stated in abstract.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
13. Cooper MR, Pajak TF, Gottlieb AJ, et al. The effects of prior radiation therapy and age on the frequency and duration of complete remission among various four-drug treatments for advanced Hodgkin's disease. *J Clin Oncol.* 1984;2(7):748-755.	Observational-Tx	408 patients	To examine the clinical response observed in 137 patients with advanced HL who had relapsed from an initial complete response following RT in comparison to 280 patients with no prior therapy.	The frequency of CR was 75% for the RT group compared to 60% of those with no prior therapy (*P*=.005). In the RT group, those patients receiving a nitrosourea had a significantly greater CR frequency than those receiving mechlorethamine (*P*=.006). Significant risk factors favoring longer duration of remission were age <40 (*P*=.005), the absence of splenic involvement (*P*=.007), and the use of nitrosourea-containing programs (*P*=.015). The advantage for nitrosourea-containing programs was seen only in patients <40 years of age.	2
14. Somers R, Carde P, Henry-Amar M, et al. A randomized study in stage IIIB and IV Hodgkin's disease comparing eight courses of MOPP versus an alteration of MOPP with ABVD: a European Organization for Research and Treatment of Cancer Lymphoma Cooperative Group and Groupe Pierre-et-Marie-Curie controlled clinical trial. *J Clin Oncol.* 1994;12(2):279-287.	Experimental-Tx	192 patients	To study the influence of time of remission on clinical outcome.	The CR rate at the end of chemotherapy (CR8) was similar in both arms (57% vs 59%). However, there were more progressions in the MOPP arm compared with the MOPP/ABVD arm (23% vs 8%, *P*=.014). A significantly higher FFS rate was found in the MOPP/ABVD arm (60% vs 43% at 6 years, *P*=.025). There was no difference in the RFS or survival rate. Of patients not in CR4, only 28% still reached a CR8. RFS at 6 years of patients with CR4 (69%) was not different from that of patients with CR8 (68%); patients with a CR(chemotherapy + RT)) had a lower RFS rate (48%). CR4 (*P*<.001) predicted strongly for final remission at the end of chemotherapy. Cox analysis showed that age >50 years, 6 or more involved lymph node areas, no CR by the fourth cycle, chemotherapy with MOPP alone, and no RT were unfavorable factors for survival.	1

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15. Specht L. Prognostic Factors in Hodgkin's Disease. *Semin Radiat Oncol.* 1996;6(3):146-161.	Review/Other-Tx	N/A	To review prognostic factors in HL.	The Ann Arbor staging classification remains the basis for evaluation of patients with HL. However, subgroups of patients with differing prognoses exist within the individual stages. In pathological stages I and II, the number of involved regions and the tumor mass in each region are important, and an estimate of the total tumor burden has proved significant. B symptoms, histological subtype, age, and gender are also generally significant but less important. 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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16. Yelle L, Bergsagel D, Basco V, et al. Combined modality therapy of Hodgkin's disease: 10-year results of National Cancer Institute of Canada Clinical Trials Group multicenter clinical trial. *J Clin Oncol.* 1991;9(11):1983-1993.	Experimental-Tx	226 patients	To compare 4 methods of treatment for stage III-IV HL.	The survival of AX3 patients was somewhat better than for the A group, but the difference was not significant (*P*=.0565). However, there was a significant interaction (*P*=.0029) between age and treatment, so that among patients >30 years of age, the survival of the A group was better, whereas for older patients, treatment with AX3 resulted in improved survival. Age itself remained a significant prognostic factor for survival after controlling for the amount of RT delivered to the abdomen and the dose intensity of vincristine for the first 3 courses of chemotherapy. The addition of RT to MOPP significantly reduced the frequency of nodal relapses.	1
17. Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. *J Clin Oncol.* 2007;25(24):3746-3752.	Experimental-Dx	260 patients	To evaluate the prognostic role of an early interim FDG-PET scan and the IPS in advanced HL treated with conventional ABVD therapy.	After a median follow-up of 2.19 years (range, 0.32 to 5.18 years), 205 patients were in continued CR and 2 patients were in PR. 43 patients progressed during therapy or immediately after, whereas 10 patients relapsed. The 2-year PFS for patients with positive PET-2 results was 12.8% and for patients with negative PET-2 results was 95.0% (*P*<.0001). In univariate analysis, the treatment outcome was significantly associated with PET-2 (*P*<.0001), stage IV (*P*<.0001), white blood cell more than 15,000 (*P*<.0001), lymphopenia (*P*<.001), IPS as a continuous variable (*P*<.0001), extranodal involvement (*P*<.0001), and bulky disease (*P*=.012). In multivariate analyses, only PET-2 turned out to be significant (*P*<.0001).	1
18. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007;25(5):579-586.	Review/Other-Dx	N/A	Guidelines to help improved therapies for patients with lymphoma.	No results stated in abstract.	4

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19. Horning SJ, Juweid ME, Schoder H, et al. Interim positron emission tomography scans in diffuse large B-cell lymphoma: an independent expert nuclear medicine evaluation of the Eastern Cooperative Oncology Group E3404 study. *Blood.* 2010;115(4):775-777; quiz 918.	Observational-Dx	38 cases; 3 reviewers	To determine the reproducibility of interim PET interpretation, an expert panel of 3 external nuclear medicine physicians visually scored baseline and interim PET scans.	The binary ECOG study criteria were based on modifications of the Harmonization Criteria; the London criteria were also applied. Of 38 interim scans, agreement was complete in 68% and 71% by ECOG and London criteria, respectively. The range of PET(+) interim scans was 16% to 34% (*P*=not significant) by reviewer. Moderate consistency of reviews was observed: kappa statistic = 0.445 using ECOG criteria, and kappa statistic = 0.502 using London criteria. These data, showing only moderate reproducibility among nuclear medicine experts, indicate the need to standardize PET interpretation in research and practice.	4
20. Meignan M, Gallamini A, Haioun C, Polliack A. Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8-9 April 2010. *Leuk Lymphoma.* 2010;51(12):2171-2180.	Review/Other-Tx	N/A	To report on the presentation from the second international workshop on interim PET in lymphoma.	No results stated in abstract.	4
21. NCCN Clinical Practice Guidelines in Oncology. Hodgkin Lymphoma. Version 2.2015. 2015; Available at: http://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf.	Review/Other-Tx	N/A	To provide NCCN practice guidelines on HL.	N/A	4

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22. Borchmann P, Haverkamp H, Diehl V, et al. Eight cycles of escalated-dose BEACOPP compared with four cycles of escalated-dose BEACOPP followed by four cycles of baseline-dose BEACOPP with or without radiotherapy in patients with advanced-stage hodgkin's lymphoma: final analysis of the HD12 trial of the German Hodgkin Study Group. *J Clin Oncol.* 2011;29(32):4234-4242.	Experimental-Tx	1,574 patients	To compare 8 cycles of BEACOPP(escalated) with 4 cycles of BEACOPP(escalated) followed by 4 cycles of the baseline dose of BEACOPP (BEACOPP[baseline]; (4 + 4 arm) as well as consolidation RT to initial bulk and residual disease with no additional RT to these locations in a 22 factorial design.	Between January 1999 and January 2003, 1,670 patients age 16 to 65 years were enrolled onto the HD12 study. At 5 years, FFTF was 86.4% in the BEACOPP(escalated) arm and 84.8% in the 4 + 4 arm (difference, -1.6%; 95% CI, -5.2% to 1.9%), and OS was 92% vs 90.3% (difference, -1.7%; 95% CI, -4.6% to 1.1%). Deaths related to acute toxicity of chemotherapy were observed in 2.9% of patients (BEACOPP(escalated), n = 19; 4 + 4, n = 27). FFTF was inferior without RT (90.4% vs 87%; difference, -3.4%; 95% CI, -6.6% to -0.1%), particularly in patients who had residual disease after chemotherapy (difference, -5.8%; 95% CI, -10.7% to -1.0%), but not in patients with bulk in complete response after chemotherapy (difference, -1.1%; 95% CI, -6.2% to 4%).	1
23. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet.* 2012;379(9828):1791-1799.	Experimental-Tx	2,182 patients	To show noninferiority of tumor control for the experimental groups and to assess if RT given only to patients with a persistent mass measuring 2.5 cm or more, and positive on PET scan after chemotherapy, was adequate.	Of the 2,182 patients enrolled in the study, 2,126 patients were included in the intention-to-treat analysis set, 705 in the 8xB(esc) group, 711 in the 6xB(esc) group, and 710 in the 8xB(14) group. FFTF was sequentially noninferior for the 6xB(esc) and 8xB(14) groups as compared with 8xB(esc). 5-year FFTF rates were 84.4% (97.5% CI, 81.0–87.7) for the 8xB(esc) group, 89.3% (86.5–92.1) for 6xB(esc) group, and 85.4% (82.1–88.7) for the 8xB(14) group (97.5% CI for difference between 6xB(esc) and 8xB(esc) was 0.5–9.3). OS in the 3 groups was 91.9%, 95.3%, and 94.5% respectively, and was significantly better with 6xB(esc) than with 8xB(esc) (97.5% CI, 0.2–6.5). The 8xB(esc) group showed a higher mortality (7.5%) than the 6xB(esc) (4.6%) and 8xB(14) (5.2%) groups, mainly due to differences in treatment-related events (2.1%, 0.8%, and 0.8%, respectively) and secondary malignancies (1.8%, 0.7%, and 1.1%, respectively). The NPV for PET at 12 months was 94.1% (95% CI, 92.1–96.1); and 225 (11%) of 2,126 patients received additional RT.	1

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24. Zinzani PL, Rigacci L, Stefoni V, et al. Early interim 18F-FDG PET in Hodgkin's lymphoma: evaluation on 304 patients. *Eur J Nucl Med Mol Imaging.* 2012;39(1):4-12.	Observational-Dx	304 patients	To assess the early prognostic value of PET after 2 cycles of treatment, evaluating visual data.	Of the 304 patients, 53 showed a positive interim PET scan and of these only 13 (24.5%) achieved continuous CR, whereas 251 patients showed a negative PET scan and of these 231 (92%) achieved continuous CR. Comparison between interim PET-positive and interim PET-negative patients indicated a significant association between PET findings and 9-year PFS and 9-year OS, with a median follow-up of 31 months. Among the early-stage patients, 19 had a positive interim PET scan and only 4 (21%) achieved continuous CR; among the 128 patients with a negative interim PET scan, 122 (97.6%) achieved continuous CR. Among the advanced-stage patients, 34 showed a persistently positive PET scan with only 9 (26.4%) achieving continuous CR, whereas 123 showed a negative interim PET scan with 109 (88.6%) achieving continuous CR.	4
25. Tseng D, Rachakonda LP, Su Z, et al. Interim-treatment quantitative PET parameters predict progression and death among patients with Hodgkin's disease. *Radiat Oncol.* 2012;7:5.	Observational-Dx	30 patients	To assess if quantitative PET parameters have predictive value beyond that of traditional clinical factors such as the IPS among HL patients.	Median follow-up of the study group was 50 months. 6/30 patients progressed clinically. Absolute value PET parameters from pretreatment scans were not significant. Absolute value SUV max from interim-treatment scans was associated with OS as determined by univariate analysis ($P<0.01$). All 4 calculated PET parameters (interim/pretreatment values) were associated with OS: metabolic tumor volume int/pre ($P<0.01$), SUV mean int/pre ($P<0.05$), SUV max int/pre ($P=0.01$), and integrated SUV int/pre ($P<0.01$). Absolute value SUV max from interim-treatment scans was associated with PFS ($P=0.01$). Three calculated PET parameters (int/pretreatment values) were associated with PFS: metabolic tumor volume int/pre ($P=0.01$), SUV max int/pre ($P=0.02$) and integrated SUV int/pre ($P=0.01$). IPS was associated with PFS ($P<0.05$) and OS ($P<0.01$).	4

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26. Devita VT, Jr., Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann Intern Med.* 1970;73(6):881-895.	Experimental-Tx	43 patients	To report the results of a study to increase the CR rate and study the duration of unmaintained remission.	The limiting toxicity was primarily bone marrow suppression and, although occasionally severe, was generally tolerable. Other toxicity such as alopecia and neurotoxicity were troublesome but reversible. The response rate was superior to that previously reported with the use of single drugs with 35 of 43, or 81% of the patients achieving a CR, defined as the complete disappearance of all tumor and return to normal performance status. The duration of these responses after all therapy was discontinued was gratifyingly long, with a median of not less than 29 and not more than 42 months. 17 of 35 patients continue free of their disease, and 28 of these 35 are still alive. The median survival of the responding group is greater than 42 months, and life table analysis of the results indicates that of those complete responders at risk for 4 years, 77% remain alive and 47% are continuously free of their disease. The surviving fraction of the entire group at risk 4 years is 63%.	3
27. 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.	Experimental-Tx	232 patients	To analyze fully the 7-year comparative treatment and toxicologic results of a prospective randomized study testing MOPP vs ABVD within a combined modality approach for the intermediate stages of 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 FFP (80.8% vs 62.8%; $P<.002$), RFS (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 2 two treatment groups.	1

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28. Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. *J Clin Oncol.* 2003;21(4):607-614.	Experimental-Tx	852 patients	To compare both the therapeutic benefit and toxicity of the MOPP/AVB hybrid regimen with that of ABVD alone.	The rates of CR (76% vs 80%, *P*=.16), FFS at 5 years (63% vs 66%, *P*=.42), and OS at 5 years (82% vs 81%, *P*=.82) were similar for ABVD and MOPP/ABV, respectively. Clinically significant acute pulmonary and hematologic toxicity were more common with MOPP/ABV (*P*=.060 and.001, respectively). There was no difference in cardiac toxicity. There were 24 deaths attributed to initial treatment: 9 with ABVD and 15 with MOPP/ABV (*P*=.057). There have been 18 second malignancies associated with ABVD and 28 associated with MOPP/ABV (*P*=.13). 13 patients have developed myelodysplastic syndromes or acute leukemia: 11 were initially treated with MOPP/ABV, and 2 were initially treated with ABVD but subsequently received MOPP-containing regimens and RT before developing leukemia (*P*=.011).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
29. Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *N Engl J Med.* 2003;348(24):2386-2395.	Experimental-Tx	1,195 patients	To assess the efficacy and toxicity of standard and increased-dose BEACOPP.	For the final analysis, 1195/1201 patients could be evaluated: 260 in the COPP-ABVD group, 469 in the BEACOPP group, and 466 in the increased-dose BEACOPP group; the median follow-up was 72, 54, and 51 months, respectively. The rate of FFTF at 5 years was 69% in the COPP-ABVD group, 76% in the BEACOPP group, and 87% in the increased-dose BEACOPP group (P=0.04 for the comparison of the COPP-ABVD group with the BEACOPP group and P<0.001 for the comparison of the increased-dose BEACOPP group with the COPP-ABVD group and with the BEACOPP group), and the 5-year rates of OS were 83%, 88%, and 91%, respectively (P=0.16 for the comparison of the COPP-ABVD group with the BEACOPP group, P=0.06 for the comparison of the BEACOPP group with the increased-dose BEACOPP group, and P=0.002 for the comparison of the COPP-ABVD group with the increased-dose BEACOPP group). Rates of early progression were significantly lower with increased-dose BEACOPP than with COPP-ABVD or standard BEACOPP.	1
30. Engert A, Diehl V, Franklin J, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. *J Clin Oncol.* 2009;27(27):4548-4554.	Experimental-Tx	1,196 patients	To report the 10-year follow-up of the HD9 trial of the German Hodgkin Study Group that compared 2 different doses (baseline and escalated) of the BEACOPP chemotherapy regimen.	Median follow-up was 111 months. At 10 years, FFTF was 64%, 70%, and 82% with OS rates of 75%, 80%, and 86% for patients treated with COPP/ABVD (arm A), BEACOPP baseline (arm B), and BEACOPP escalated (arm C), respectively (P<.001). BEACOPP escalated was significantly better than BEACOPP baseline in terms of FFTF (P<.0001) and OS (P=.0053). A total of 74 second malignancies (6.2%) were documented, including acute myeloid leukemia (0.4%, 1.5%, and 3.0%), NHL (2.7%, 1.7%, and 1.0%), and solid tumors (2.7%, 3.4%, and 1.9%). The corresponding overall secondary malignancy rates were 5.7%, 6.6%, and 6.0%, respectively.	1

Hodgkin Lymphoma-Stage III and IV
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
31. Kobe C, Dietlein M, Franklin J, et al. Positron emission tomography has a high negative predictive value for progression or early relapse for patients with residual disease after first-line chemotherapy in advanced-stage Hodgkin lymphoma. *Blood.* 2008;112(10):3989-3994.	Experimental-Dx	275 patients	To present the results of HD15-PET demonstrating a NPV of 94% after 6 to 8 cycles of BEACOPP for PET-negative patients.	The PFS was 96% for PET(-) patients (95% CI, 94%–99%) and 86% for PET(+) patients (95% CI, 78%–95%, *P*=.011). The NPV for PET in this analysis was 94% (95% CI, 91%–97%).	1
32. Sieber M, Bredenfeld H, Josting A, et al. 14-day variant of the bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone regimen in advanced-stage Hodgkin's lymphoma: results of a pilot study of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol.* 2003;21(9):1734-1739.	Experimental-Tx	94 patients	To assess the feasibility and efficacy of a time-intensified BEACOPP regimen given in 14-day intervals (BEACOPP-14) with granulocyte colony-stimulating factor support in advanced HL.	All patients were assessable for toxicity and treatment outcome. 86 patients received the planned 8 cycles of BEACOPP-14. Consolidation RT was given in 66 patients. Chemotherapy could generally be administered on schedule. Dose reductions varied among drugs but were generally low. Acute toxicity was moderate, with World Health Organization grade 3/4 leukopenia in 75%, thrombocytopenia in 23%, anemia in 65%, and infection in 12% of patients. A total of 88 patients (94%) achieved a CR. 4 patients had progressive disease. At a median observation time of 34 months, 5 patients have relapsed, 1 patient developed a secondary NHL, and 3 deaths were documented. The OS and FFTF rates at 34 months were 97% (95% CI, 93% to 100%) and 90% (95% CI, 84% to 97%), respectively.	2

Hodgkin Lymphoma-Stage III and IV
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
33. Federico M, Luminari S, Iannitto E, et al. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. *J Clin Oncol.* 2009;27(5):805-811.	Experimental-Tx	305 patients	To compare ABVD vs BEACOPP vs COPPEBVCAD; CEC for advanced HL.	After a median follow-up of 41 months, BEACOPP resulted in a superior PFS, with a significant reduction in risk of progression (HR = 0.50) compared with ABVD. No differences between BEACOPP and CEC, or CEC and ABVD were observed. The 5-year PFS was 68% (95% CI, 56% to 78%), 81% (95% CI, 70% to 89%), and 78% (95% CI, 68% to 86%), for ABVD, BEACOPP, and CEC, respectively (BEACOPP vs ABVD, *P*=.038; CEC vs ABVD and BEACOPP vs CEC, *P*=not significant). The 5-year OS was 84% (95% CI, 69% to 92%), 92% (95% CI, 84% to 96%), and 91% (95% CI, 81% to 96%) for ABVD, BEACOPP, and CEC, respectively (*P*=not significant). BEACOPP and CEC resulted in higher rates of grade 3-4 neutropenia than ABVD (*P*=.016); BEACOPP was associated with higher rates of severe infections than ABVD and CEC (*P*=.003).	1

Hodgkin Lymphoma-Stage III and IV
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
34. Merli F, Luminari S, Mammi C, et al. Long-Term Follow-up Analysis of HD2000 Trial Comparing ABVD Versus BEACOPP Versus Copp/EBV/CAD in Patients with Newly Diagnosed Advanced-Stage Hodgkin's Lymphoma: A Study from the Fondazione Italiana Linfomi. *Blood.* 2014;124(21):499-499.	Experimental-Tx	305 patients	To report the analysis of long-term outcome and toxicity from the HD2000 trial which compared ABVD vs BEACOPP vs MOPPEBVCAD in 305 eligible patients with advanced-stage HL.	At time of current analysis the median follow-up was 119 months (range 1–169) with 92% of patients with a last contact later than January 2012. In the prolonged observation period 23 additional failures (cumulative=82) were recorded, including 17 new relapses/progression (cum=71) and 6 deaths not related to lymphoma progression (cum=11). Additional relapses and progressions were observed in 5, 7 and 5 patients treated with ABVD (cum=31), BEACOPP (cum=17), and CEC (cum=23), respectively. No death unrelated to lymphoma progression was recorded among patients treated with ABVD, while 8 (+4) and 3 (+2) events were documented among patients treated with BEACOPP or CEC, respectively. The 10-year PFS was 69%, 74% and 74% in the ABVD, BEACOPP and CEC arm, respectively (*P*=0.639). Using ABVD as reference, HR for PFS for BEACOPP and CEC was 0.73 (CI 95%, 0.43–1.25) and 0.80 (0.47–1.36); this result was adjusted by IPS. Overall 42 patients died (+19), 13 (+5) in the ABVD arm, 15 (+7) in the BEACOPP arm and 14 (+7) in the CEC arm. The 10-year OS rates were 84%, 84% and 86% for ABVD, BEACOPP and CEC, respectively (*P*=0.883). A total of 11 second malignancies were documented including 2 MDS/AML (1 BEACOPP and 1 CEC), 2 non-HL (1 BEACOPP and 1 CEC), and 7 solid cancers: 2 lung cancer (BEACOPP), 2 bladder cancer (2 CEC), 1 sarcoma (BEACOPP), 1 Kaposi sarcoma (BEACOPP) and 1 thyroid cancer (ABVD). The risk of second malignancy at 10-year was 6.7, 4.4 and 0.9 for BEACOPP, CEC and ABVD, respectively; the difference between BEACOPP and ABVD was statistically significant (*P*=0.027).	1

Hodgkin Lymphoma-Stage III and IV
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
35. Viviani S, Zinzani PL, Rambaldi A, et al. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. *N Engl J Med.* 2011;365(3):203-212.	Experimental-Tx	331 patients	To assess the long-term clinical outcome after initial therapy with BEACOPP as compared with ABVD in patients with advanced stage HL.	The 7-year rate of freedom from first progression was 85% among patients who had received initial treatment with BEACOPP and 73% among those who had received initial treatment with ABVD (P=0.004), and the 7-year rate of EFS was 78% and 71%, respectively (P=0.15). A total of 65 patients (20 in the BEACOPP group, and 45 in the ABVD group) went on to receive the intended high-dose salvage regimen. As of the cutoff date, 3/20 patients in the BEACOPP group and 15/45 in the ABVD group who had had progressive disease or relapse after the initial therapy were alive and free of disease. After completion of the overall planned treatment, including salvage therapy, the 7-year rate of freedom from a second progression was 88% in the BEACOPP group and 82% in the ABVD group (P=0.12), and the 7-year rate of OS was 89% and 84%, respectively (P=0.39). Severe adverse events occurred more frequently in the BEACOPP group than in the ABVD group.	1

Hodgkin Lymphoma-Stage III and IV
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
36. Carde P, Karrasch M, Fortpied C, et al. ABVD (8 cycles) versus BEACOPP (4 escalated cycles => 4 baseline) in stage III-IV high-risk Hodgkin lymphoma (HL): First results of EORTC 20012 Intergroup randomized phase III clinical trial. *J Clin Oncol.* 2012;30(suppl):abstr 8002.	Experimental-Tx	549 patients	To confirm OS superiority of escalated BEACOPP over ABVD.	From 2002-2010, 549 patients were randomized (ABVD 275, BEACOPP 274): stage IV 74%, PS 0, 1, 2: 34%, 48% and 17%, B-symptoms 81%, median age 35.2 years, males 75%. IPS was 4 or higher for 59% of patients. Histology reviewed no HL in 4 cases. CR was 83% in both arms. With a median follow-up of 3.8 years, EFS at 4 years was 63.7% vs 69.3% (HR = 0.86, 95% CI = 0.64 to 1.15, *P*=0.312). PFS at 4 years was 72.8% vs 83.4% (HR = 0.58, 95% CI = 0.39 to 0.85, *P*=0.005). OS at 4 years was 86.7 vs 90.3 (HR = 0.71, 95% CI = 0.42 to 1.21, *P*=0.208). Toxic deaths occurred in 6 and 5 patients, with early discontinuation (prior to cycle 5) in 12 and 26 patients, respectively. There were 5 crossovers to BEACOPP and 10 to ABVD. Second malignancies occurred in 8 ABVD and 10 BEACOPP patients (myelodysplasia/leukemia 2 and 4, lung 2 and 1, NHL 3 and 2, other 1 and 3); cumulative incidence curves did not differ significantly.	1

Hodgkin Lymphoma-Stage III and IV
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
37. Koontz MZ, Horning SJ, Balise R, et al. Risk of therapy-related secondary leukemia in Hodgkin lymphoma: the Stanford University experience over three generations of clinical trials. *J Clin Oncol.* 2013;31(5):592-598.	Observational-Tx	754 patients	To assess therapy-related acute myeloid leukemia/myelodysplastic syndrome risk in patients treated for HL on successive generations of Stanford clinical trials.	754 patients treated from 1974 to 2003 were identified. Therapy varied across studies. RT evolved from extended fields (S and C studies) to involved fields (G studies). Primary chemotherapy was MOPP or procarbazine, mechlorethamine, and vinblastine in S studies; MOPP, procarbazine, mechlorethamine, and vinblastine, and vinblastine, bleomycin, and methotrexate, or ABVD in C studies; and vinblastine, bleomycin, and methotrexate (reduced dose of bleomycin compared with vinblastine, bleomycin, and methotrexate) or Stanford V in G studies. Cumulative exposure to alkylating agent was notably lower in the G studies compared with the S and C studies, with a 75% to 83% lower dose of nitrogen mustard in addition to omission of procarbazine and melphalan. 24 (3.2%) of 754 patients developed therapy-related acute myeloid leukemia/myelodysplastic syndrome, 15 after primary chemotherapy and nine after salvage chemotherapy for relapsed HL. The incidence of therapy-related acute myeloid leukemia/myelodysplastic syndrome was significantly lower in the G studies (0.3%) compared with the S (5.7%) or C (5.2%) studies ($P<.001$). Additionally, in the G studies, no therapy-related acute myeloid leukemia/myelodysplastic syndrome was noted after primary therapy, and the only patient who developed therapy-related acute myeloid leukemia/myelodysplastic syndrome did so after second-line therapy.	2

Hodgkin Lymphoma-Stage III and IV
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
38. Gobbi PG, Levis A, Chisesi T, et al. ABVD versus modified stanford V versus MOPPEBVCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi. *J Clin Oncol.* 2005;23(36):9198-9207.	Experimental-Tx	334 patients	To compare the efficacy and toxicity of 2 chemotherapy regimens, Stanford V and MOPPEBVCAD, with ABVD as standard therapy to select which regimen would best support a reduced RT program.	The complete response rates for ABVD, Stanford V, and MOPPEBVCAD were 89%, 76% and 94%, respectively; 5-year FFS and PFS rates were 78%, 54%, 81% and 85%, 73%, and 94%, respectively ($P<.01$ for comparison of Stanford V with the other 2 regimens). Corresponding 5-year OS rates were 90%, 82%, and 89% for ABVD, Stanford V, and MOPPEBVCAD, respectively. Stanford V was more myelotoxic than ABVD but less myelotoxic than MOPPEBVCAD, which had larger reductions in the prescribed drug doses.	1
39. Hoskin PJ, Lowry L, Horwich A, et al. Randomized comparison of the stanford V regimen and ABVD in the treatment of advanced Hodgkin's Lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. *J Clin Oncol.* 2009;27(32):5390-5396.	Experimental-Tx	520 patients	To compare the efficacy and toxicity of 2 chemotherapy regimens in advanced HL: the weekly alternating Stanford V and the standard, twice-weekly regimen of ABVD.	The overall response rates after completion of all treatment were 91% for Stanford V and 92% for ABVD. During a median follow-up of 4.3 years, there was no evidence of a difference in projected 5-year PFS and OS rates (76% and 90%, respectively, for ABVD; 74% and 92%, respectively, for Stanford V). More pulmonary toxicity was reported for ABVD, whereas other toxicities were more frequent with Stanford V.	1
40. Gordon LI, Hong F, Fisher RI, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). *J Clin Oncol.* 2013;31(6):684-691.	Experimental-Tx	854 patients	To determine if FFS was superior in patients treated with the Stanford V regimen compared with ABVD.	There was no significant difference in the overall response rate between the 2 arms, with CR and clinical CR rates of 73% for ABVD and 69% for Stanford V. At a median follow-up of 6.4 years, there was no difference in FFS: 74% for ABVD and 71% for Stanford V at 5 years ($P=.32$).	1

Hodgkin Lymphoma-Stage III and IV
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
41. Younes A, Thieblemont C, Morschhauser F, et al. Combination of ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for treatment-naive patients with CD20-positive B-cell non-Hodgkin lymphoma: a non-randomised, phase 1b study. *Lancet Oncol.* 2014;15(9):1019-1026.	Experimental-Tx	33 patients	To investigate the safety and efficacy of ibrutinib in combination with R-CHOP for patients with previously untreated CD20-positive B-cell non-HL.	From June 22, 2012, to March 25, 2013, 33 patients were enrolled (part 1: 17; part 2: 16) and 32 received ibrutinib plus R-CHOP treatment (1 patient in the part 2 cohort withdrew). The maximum tolerated dose was not reached and the recommended phase 2 dose for ibrutinib was 560 mg per day. The most common grade 3 or greater adverse events included neutropenia (73% [24/33 patients]), thrombocytopenia (21% [7 patients]), and febrile neutropenia and anemia (18% each [6 patients]). The most frequently reported serious adverse events were febrile neutropenia (18% [6 patients]) and hypotension (6% [2 patients]). 30 (94%) of 32 patients who received 1 or more doses of combination treatment achieved an overall response. All 18 patients with diffuse large B-cell lymphoma who received the recommended phase 2 dose had an overall response. For those subtyped and treated at the recommended phase 2 dose, 5 (71%) of 7 patients with the germinal center B-cell-like subtype and 2 (100%) patients with the non-germinal center B-cell-like subtype had a complete response. R-CHOP did not affect pharmacokinetics of ibrutinib, and ibrutinib did not alter the pharmacokinetics of vincristine. Pharmacodynamic data showed Bruton's tyrosine kinase was fully occupied (>90% occupancy) at the recommended phase 2 dose.	2

Hodgkin Lymphoma-Stage III and IV
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
42. Ferme C, Mounier N, Casasnovas O, et al. Long-term results and competing risk analysis of the H89 trial in patients with advanced-stage Hodgkin lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte (GELA). *Blood.* 2006;107(12):4636-4642.	Experimental-Tx	533 patients	To report the long term results with special emphasis on late toxicities and causes of death of the H89 trial.	A better survival probability was observed after ABVPP alone: the 10-year OS estimates were 90% for ABVPP x 8, 78% for MOPP/ABV x 8, 82% for MOPP/ABV with RT, and 77% for ABVPP x 6 with RT (*P*=.03); and the 10-year disease-free survival estimates were 70%, 76%, 79%, and 76%, respectively (*P*=.09). The 10-year disease-free survival estimates for patients treated with consolidation chemotherapy or RT were 73% and 78% (*P*=.07), and OS estimates were 84% and 79%, respectively (*P*=.29).	1
43. Aleman BM, Raemaekers JM, Tirelli U, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. *N Engl J Med.* 2003;348(24):2396-2406.	Experimental-Tx	739 patients	To determine whether RT reduces the relapse rate among patients with stage III or IV HL who have a CR after 6 to 8 cycles of MOPP-ABV hybrid chemotherapy (considered the standard chemotherapy at the time the trial was designed).	Of 739 patients, 421 had a CR; 161 of these patients were assigned to no further treatment, and 172 to IFRT. The median follow-up was 79 months. The 5-year EFS rate was 84% in the group that did not receive RT and 79% in the group that received IFRT (*P*=0.35). The 5-year OS rates were 91% and 85%, respectively (*P*=0.07). Among the 250 patients in PR after chemotherapy, the 5-year EFS and OS rates were 79% and 87%, respectively.	1
44. Aleman BM, Raemaekers JM, Tomisic R, et al. Involved-field radiotherapy for patients in partial remission after chemotherapy for advanced Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys.* 2007;67(1):19-30.	Experimental-Tx	739 patients	To describe the role of RT in patients with advanced HL who were in PR after chemotherapy.	Of 739 enrolled patients, 57% were in CR and 33% in PR after chemotherapy. The median follow-up was 7.8 years. Patients in PR had bulky mediastinal involvement significantly more often than did those in CR after chemotherapy. The 8-year EFS and OS rate for the 227 patients in PR who received IFRT was 76% and 84%, respectively. These rates were not significantly different from those for CR patients who received IFRT (73% and 78%) or for those in CR who did not receive IFRT (77% and 85%). The incidence of second malignancies in patients in PR who were treated with IFRT was similar to that in nonirradiated patients.	1

Hodgkin Lymphoma-Stage III and IV
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
45. Johnson PW, Sydes MR, Hancock BW, Cullen M, Radford JA, Stenning SP. Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: survival data from the UKLG LY09 randomized controlled trial (ISRCTN97144519). *J Clin Oncol.* 2010;28(20):3352-3359.	Experimental-Tx	807 patients	To analyze the outcomes of nonrandomized consolidation RT given after chemotherapy in the initial treatment of advanced HL.	Among 807 patients randomly assigned, 702 achieved objective response. Postchemotherapy RT for consolidation was reported in 300 (43%). With median follow-up of 6.9 years, 161 PFS events and 83 deaths were reported. Baseline characteristics showed more patients with bulk disease having RT (190 [63%] vs 111 [28%]) and only partial response after chemotherapy (150 [50%] vs 36 [9%]). Other baseline characteristics were similar. PFS was superior for patients having RT (HR, 0.43; 95% CI, 0.30 to 0.60) with 5-year PFS 71% without RT, 86% with RT. A similar advantage was seen for OS (HR, 0.47; 95% CI, 0.29 to 0.77). There was no evidence of heterogeneity of treatment effect across subgroups.	1
46. Press O, LeBlanc M, Rimsza LM, et al. A phase II trial of response-adapted therapy of stage III-IV Hodgkin lymphoma using early interim FDG-PET imaging: U.S. Intergroup S0816. *Hematol Oncol.* 2013;31(suppl 1):Abstract 124.	Experimental-Tx	357 patients	To examine a response-adapted approach in an attempt to increase efficacy while limiting treatment-related morbidity.	Between 7/1/2009 and 12/2/2012, 371 patients with stage III–IV HL were enrolled, of whom 357 were eligible and evaluable. The median age was 32 (18– 61), with 57% males, 80% white, 49% IPS 0–2, 51% IPS 3–7, and 4% HIV positive (13 patients). Of 357 patients with an interim PET2 scan evaluated by central review, 292 (82%) were PET and 65 were PET+ (18%). 349 patients registered to continued therapy based on the interim PET result, 291 on continued ABVD and 58 on the BEACOPP arm. 7 of 65 PET+ patients (10%) did not receive BEACOPP due to patient or physician refusal. The Kaplan–Meier estimate for 1-year OS in HIV-negative patients is 98% (95% CI: 95%, 99%) and for 1-year PFS is 84% (95% CI: 79%, 89%). The landmark of 1-year PFS of PET2 patients planned to receive ABVD is 85% (95% CI: 79%, 90%) and for PET2+ patients `planned to receive BEACOPP is 72% (95% CI: 55%, 84%), which appears promising compared with the 15%–30% 2-year PFS expected in PET2+ patients. 3 deaths occurred among 306 patients evaluable for toxicity, (1/259 [0.3%] on ABVD and 2/47 [4.2%] on BEACOPP).	2

Hodgkin Lymphoma-Stage III and IV
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
47. National Cancer Institute (NCI). Response-Based Therapy Assessed By PET Scan in Treating Patients With Bulky Stage I and Stage II Classical Hodgkin Lymphoma. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). September 16, 2015. Available from: https://clinicaltrials.gov/ct2/show/NCT01118026?term=NCT01118026. NLM Identifier: NCT01118026.	Review/Other-Dx	Ongoing	To improve treatment outcomes in patients diagnosed with bulky, early stage HL and to reduce the side effects that are associated with use of radiation used in current treatments.	This trial is still recruiting study subjects and results are not available yet.	4

Hodgkin Lymphoma-Stage III and IV
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
48. Borchmann P, Haverkamp H, Lohri A, et al. Addition of Rituximab to BEACOPPescalated to Improve the Outcome of Early Interim PET Positive Advanced Stage Hodgkin Lymphoma Patients: Second Planned Interim Analysis of the HD18 Study. *Blood.* 2014;124(21):500-500.	Experimental-Tx	440 PET-2 positive patients	To report the results of the second planned interim analysis for the PET-2 positive patient cohort in the HD18 study.	Between May 2008 and May 2011, 1,100 patients were enrolled into the HD18 trial, of whom 440 were PET-2 positive and randomized (BEACOPP n=220; R-BEACOPP n=220), corresponding to 43% of all randomized patients. 1 patient in the BEACOPPesc group was excluded from intention-to-treat analysis because HL was not confirmed by reference histology. Median age was 30 years (range 18–60), 177 were female (40%). 1 patient had stage IIA disease, 103 patients (23%) had Ann Arbor stage IIB disease with the risk factors large mediastinal mass or extranodal involvement, the remaining patients had stage III/IV disease. IPS risk groups were distributed as follows: 120 patients 0-1 (28%), 241 2-3 (55%), and 75 4-6 (17%). Overall, grade 4 toxicity occurred in 197/218 (90.4%) and 206/220 (93.6%) of the documented patients in the BEACOPP and R-BEACOPP group, respectively. Grade 4 leukopenia was documented in 193 (88.5%) and 201 (91.4%) patients, grade 4 thrombocytopenia in 112 (51.4%) and 123 (55.9%) patients, anemia in 27 (12.4%) and 31 (14.1%) patients, and grade 4 infections in 9 (4.1%) and 13 (5.9%) patients. Other grade 4 toxicities had a frequency of <2%. Treatment related mortality occurred in 1 (0.5%) and 3 patients (1.4%), respectively. Overall, 16 patients died, 6 in the BEACOPPesc group and 10 in the R-BEACOPPesc group. With a median follow-up of 35 months, Kaplan-Meier PFS estimates were largely overlapping (log rank *P*=0.99) with an estimated 3 year PFS of 91.4% for BEACOPP (95% CI: 87.0% – 95.7%) and 93% for R-BEACOPP (95% CI: 89.4% – 96.6%). Accordingly, overall survival was not different (96.5% vs 94.4% at 3 years for BEACOPP vs R-BEACOPP, *P*=0.31).	1

Hodgkin Lymphoma-Stage III and IV
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
49. Specht L, Yahalom J, Illidge T, et al. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group (ILROG). *Int J Radiat Oncol Biol Phys.* 2014;89(4):854-862.	Review/Other-Tx	N/A	To address the use of RT in HL in the modern era of combined modality therapy.	The role of reduced volumes and doses is addressed, integrating modern imaging with 3D planning and advanced techniques of treatment delivery. The previously applied extended field RT and original IFRT, which treated larger volumes based on nodal stations, have now been replaced by the use of limited volumes, based solely on detectable nodal (and extranodal extension) involvement at presentation, using contrast-enhanced CT, PET/CT, MRI, or a combination of these techniques. The International Commission on Radiation Units and Measurements concepts of gross tumor volume, clinical target volume, internal target volume, and planning target volume are used for defining the targeted volumes. Newer treatment techniques, including intensity modulated RT, breath-hold, image guided RT, and 4D imaging, should be implemented when their use is expected to decrease significantly the risk for normal tissue damage while still achieving the primary goal of local tumor control. A new concept, involved site RT, is introduced as the standard conformal therapy for the scenario, commonly encountered, wherein optimal imaging is not available. There is increasing evidence that RT doses used in the past are higher than necessary for disease control in this era of combined modality therapy. The use of involved node RT and of lower doses in early-stage HL is supported by available data. Although the use of involved site RT has not yet been validated in a formal study, it is more conservative than involved node RT, accounting for suboptimal information and appropriately designed for safe local disease control. The goal of modern smaller field RT is to reduce both treatment volume and treatment dose while maintaining efficacy and minimizing acute and late sequelae.	4

Hodgkin Lymphoma-Stage III and IV
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
50. Fabian CJ, Mansfield CM, Dahlberg S, et al. Low-dose involved field radiation after chemotherapy in advanced Hodgkin disease. A Southwest Oncology Group randomized study. *Ann Intern Med.* 1994;120(11):903-912.	Experimental-Tx	278 patients	To determine if low-dose IFRT after CR induction with chemotherapy is effective in preventing relapse and improving survival in patients with stage III or IV HL.	Remission duration, RFS, and OS were similar for the 2 groups (P=0.09, P>0.2, and P=0.14, respectively). Factors that predicted shorter remission duration in a multivariate analysis were nodular sclerosis histology, bulky disease, and receipt of <85% of planned chemotherapy. Low-dose radiation improved remission duration in the subgroups of patients with nodular sclerosis and bulky disease. For the 169 patients with nodular sclerosis, the 5-year remission-duration estimate was 82% for the low-dose radiation group and 60% for the no further treatment group (P=0.002). For all patients with bulky disease, the 5-year remission-duration estimate was 75% for the low-dose radiation group and 57% for the no further treatment group (P=0.05). No difference in OS was noted between low-dose radiation and no further treatment in all patients or major subgroups. The 5-year survival was 86% for all patients who had a complete response as well as for patients in the nodular sclerosis subgroup.	1
51. Eich HT, Gossmann A, Engert A, et al. A Contribution to solve the problem of the need for consolidative radiotherapy after intensive chemotherapy in advanced stages of Hodgkin's lymphoma--analysis of a quality control program initiated by the radiotherapy reference center of the German Hodgkin Study Group (GHSG). *Int J Radiat Oncol Biol Phys.* 2007;69(4):1187-1192.	Experimental-Tx	1,449 patients	To test whether consolidative RT in the region of initial bulky disease and of residual disease is necessary after effective chemotherapy.	In the fifth interim analysis, 1449 patients were eligible for the arm comparison with regard to RT. After a median observation time of 48 months the FFTF rate was 86% and the OS 92%. The FFTF was 95% in the RT arms A+C and 88% in the non-RT arms B+D: no sequential significant difference. 1084 patients were evaluated by the panel. The panel defined initial bulky disease in 800 patients and residual disease in 600 patients. The panel recommended continuation of therapy according to the randomization for 934/1084 patients and additive RT independently from the randomization arm for 145/1084 patients.	1

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
  a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  c) the study is an expert opinion or consensus document.
- M = Meta-analysis

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

ABVD = Adriamycin, bleomycin, vincristine, and dacarbazine

ABVPP = Doxorubicin, bleomycin, vinblastine, procarbazine, and prednisone

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

CI = Confidence interval

COPP = Cyclophosphamide, vincristin, procarbazine, prednisone

COPPEBVCAD; CEC = Cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxirubicin, vincristine, procarbazine, vinblastine, and bleomycin

CR = Complete remission

CT = Computed tomography

EFS = Event-free survival

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

FFP = Freedom from progression

FFS = Failure-free survival

FFTF = Freedom from treatment failure

FF2R = Freedom from second relapse

HL = Hodgkin lymphoma

HR = Hazard ratio

IFRT = Involved-field radiotherapy

IPS = International Prognostic Score

MOPP = Mechlorethamine, vincristine, procarbazine, and prednisone

MOPP/ABV = Mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine

MOPPEBVCAD = Mechlorethamine, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine

NHL = Non-Hodgkin lymphoma

NPV = Negative predictive value

OS = Overall survival

PFS = Progression-free survival

PR = Partial remission

RFS = Relapse-free survival

RT = Radiation therapy

Stanford V = Doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone

SUV = Standardized uptake value