Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Kaplan HS. Evidence for a tumoricidal dose level in the radiotherapy of Hodgkin's disease. *Cancer Res.* 1966;26(6):1221-1224.	Review/Other-Tx	N/A	A review of the available evidence for HD.	A review of the available evidence indicates that HD tends to recur in a treated field with a frequency which is inversely related to dose and approaches zero at a dose of approximately 4000 rads, delivered at the rate of about 1000 rads/week. Such doses make the use of megavoltage X-ray beams mandatory to avoid severe skin reactions, but are otherwise well tolerated by the normal tissues. The inverse relationship of recurrence rate to radiation dose has important implications for the RT of HD, which are supported by the limited data thus far available relating radiation dose to long term survival in HD.	4
2. Rosenberg SA, Kaplan HS. Evidence for an orderly progression in the spread of Hodgkin's disease. *Cancer Res.* 1966;26(6):1225-1231.	Review/Other-Tx	100 patients	To observe patients with HD that supports the concept that it is a disease of unicentric origin that follows a predictable pattern of progression and to review the therapeutic implications.	It is apparent that areas of involvement or extension of HD are not random. Disease is found in adjacent lymphoid areas in the majority of patients. New areas of involvement were in areas immediately adjacent to the initial treatment fields in 22/26 patients. The mediastinum was the area most commonly skipped in the patients who demonstrated discontinuous involvement. These observations support the concept that HD arises in a single focus and spreads in a predictable manner along adjacent lymphoid channels.	4
3. Peters MV. A study of survivals in Hodgkin's disease treated radiologically. *American Journal of Roentgenology and Radium Therapy.* 1950;63:299-311.	Review/Other-Tx	N/A	To review the contradictory factors if HD and to estimate the efficacy of RT and to find out how new methods could be improved.	No results stated in abstract.	4

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

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4. Hoppe RT, Coleman CN, Cox RS, Rosenberg SA, Kaplan HS. The management of stage I--II Hodgkin's disease with irradiation alone or combined modality therapy: the Stanford experience. *Blood.* 1982;59(3):455-465.	Observational-Tx	230 patients	A review of the Stanford experience to identify patients whose freedom from relapse and survival could be improved by the use of adjuvant chemotherapy.	The actuarial survival at 10 years was 84% for patients in either treatment group. Freedom from relapse at 10 years was 77% among patients treated with RT alone and 84% after treatment with CMT [P(Gehan)=0.09]. Freedom from second relapse at 10 years was 89% and 94%, respectively [P(Gehan)=0.56]. Several prognostic factors were evaluated in order to identify patients at high risk for relapse or with poor ultimate survival after initial treatment with RT alone. Systemic symptoms, histologic subtype, age, and limited extranodal involvement (E-lesions) did not affect the prognosis of patients and failed to identify patients whose survival could be improved by the routine use of CMT. Patients with large mediastinal masses (mediastinal mass ratio ≥1/3) had a significantly poorer freedom from relapse when treated with RT alone than when treated initially with CMT [45% vs 81% at 10 years], (P(Gehan)=0.03). The 10-year survival of these patients, however, was not significantly different (84% vs 74%).	2
5. Bonadonna G, Zucali R, Monfardini S, De Lena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. *Cancer.* 1975;36(1):252-259.	Experimental-Tx	45 patients	To report the preliminary results of a controlled study randomizing MOPP vs a new 4-drug combination (ABVD) in advanced HD.	No patient was previously treated with chemotherapy; 20% had relapsed after primary RT. Whenever possible, complete remission was defined also through rebiopsy of known organ involvement. Complete remission occurred in 76% of patients treated with MOPP, and in 75% of those given ABVD, with no difference between the 2 regimens as far as stage (IIIB-IIIS and IV), histologic type, and prior RT was concerned. Crossover carried out for progressive disease or for relapse after initial remission showed absence of cross-resistance between MOPP and ABVD. Toxic manifestations after ABVD were in general well tolerated and reversible. The percent of optimal dose for each drug was as follows: adriamycin 87%, vinblastine 87%, bleomycin 96%, and imidazole carboxamide 96%.	2

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
6. Devita VT. Curability of Advanced Hodgkin's Disease with Chemotherapy: Long-Term Follow-up of MOPP-Treated Patients at the National Cancer Institute. *Annals of Internal Medicine.* 1980;92(5):587.	Experimental-Tx	198 patients	To analyze the results of treatment of patients with HD with MOPP.	80% attained complete remission, and 68% of patients achieving a complete remission have remained disease free beyond 10 years from the end of treatment. Results of autopsy on patients who died of other causes while in clinical complete remission did not show evidence of residual tumors except in 1 patient. Asymptomatic patients and patients with mixed-cellularity or lymphocytic-depleted HD do significantly better than symptomatic patients and those with nodular sclerosing histologic type. Advanced HD appears to be curable by chemotherapy.	2
7. Fischer JJ, Papac RJ. Theoretical considerations in combinations of localized and systemic therapy for neoplastic diseases. *J Theor Biol.* 1972;37(1):105-114.	Review/Other-Tx	N/A	To investigate the theoretical considerations of importance in combining localized and systemic treatments for neoplastic disease.	No results stated in abstract.	4
8. Ng AK, Bernardo MP, Weller E, et al. Long-term survival and competing causes of death in patients with early-stage Hodgkin's disease treated at age 50 or younger. *J Clin Oncol.* 2002;20(8):2101-2108.	Observational-Tx	1,080 patients	To analyze the long-term survival and the pattern and timing of excess mortality in patients with early-stage HD.	The median follow-up was 12 years. The 15- and 20-year Kaplan-Meier survival estimates were 84% and 78%, respectively. Cox proportional hazards models showed that number of involved sites (P=.006), mediastinal status (P=.02), and histology (P=.02) were independent predictors of death from all causes. The absolute excess risk of mortality in patients with a favorable prognosis increased over time, whereas for those with an unfavorable prognosis, the absolute excess risk peaked in the first 5 years, predominantly from HD. The relative risk of mortality from all causes, causes other than HD, second tumors, and cardiac disease remained significantly elevated more than 20 years after treatment.	2

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
9. 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 International Prognostic Score (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 complete remission and 2 patients were in partial remission. 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
10. Elconin JH, Roberts KB, Rizzieri DA, et al. Radiation dose selection in Hodgkin's disease patients with large mediastinal adenopathy treated with combined modality therapy. *Int J Radiat Oncol Biol Phys.* 2000;48(4):1097-1105.	Observational-Tx	83 patients	To determine the effective dose of consolidation radiation in HD patients with large mediastinal adenopathy treated with CMT.	OS and FFS were both 76% at 10 years. Of the 78 CR patients, 15 failed. Patterns of failure were in-field alone, 8 patients; out of field alone, 2 patients; and combined, 5 patients. Failure patterns by RT dose were: ≤20 Gy, 0/12; 20–25 Gy, 7/24; 25–30 Gy, 5/30; ≥30 Gy, 3/11. There was no apparent correlation between RT dose and subsequent failure. Post chemotherapy gallium scans were helpful in predicting for failure. Of 48 patients in whom the gallium was negative after chemotherapy, there were 6 failures, compared with 9 failures among 30 patients in whom gallium was not done after chemotherapy ($P=0.066$). Additionally, patients receiving adriamycin-based chemotherapy regimens had improved outcomes compared to those not receiving adriamycin ($P=0.03$).	2

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
11. Friedman DL, Chen L, Wolden S, et al. Dose-Intensive Response-Based Chemotherapy and Radiation Therapy for Children and Adolescents With Newly Diagnosed Intermediate-Risk Hodgkin Lymphoma: A Report From the Children's Oncology Group Study AHOD0031. *J Clin Oncol.* 2014;32(32):3651-3658.	Experimental-Tx	1,712 eligible patients	To evaluate the role of early chemotherapy response in tailoring subsequent therapy in pediatric intermediate-risk HL.	Among 1,712 eligible patients, 4-year EFS was 85.0%: 86.9% for rapid early responders and 77.4% for slow early responders (P<.001). 4-year OS was 97.8%: 98.5% for rapid early responders and 95.3% for slow early responders (P<.001). 4-year EFS was 87.9% vs 84.3% (P=.11) for rapid early responders with CR who were randomly assigned to IFRT vs no IFRT, and 86.7% vs 87.3% (P=.87) for rapid early responders with PET-negative results at response assessment. 4-year EFS was 79.3% vs 75.2% (P=.11) for slow early responders who were randomly assigned to DECA vs no DECA, and 70.7% vs 54.6% (P=.05) for slow early responders with PET-positive results at response assessment.	1
12. Faguet GB. Hodgkin's disease: basing treatment decisions on prognostic factors. *Leuk Lymphoma.* 1995;17(3-4):223-228.	Review/Other-Tx	34 publications	To review the current status of risk factor assessment in HD clinically useful for managing this disease.	Most patients with HD are curable at the outset with standard RT or chemotherapy, depending on stage and other risk factors. However, up to 40% of patients will either fail at initial induction, or experience early or late relapses. Risk factors analysis at these various times provide a solid base for selecting the therapy best suited to optimize outcome for each individual patient. Patients with truly refractory disease pose a serious challenge to clinicians and are best managed in specialized centers conducting controlled clinical trials. In conclusion it appears that although approximately 75% of newly diagnosed patients with HD can expect long-term, DFS, refractory patients exhibit a dismal survival. Improving their outcome will require innovative approaches.	4

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

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13. Gobbi PG, Broglia C, Di Giulio G, et al. The clinical value of tumor burden at diagnosis in Hodgkin lymphoma. *Cancer.* 2004;101(8):1824-1834.	Observational-Tx	351 patients	To investigate the clinical role of tumor burden in patients with HL, relating this parameter to most of the current clinical and prognostic factors and to the best predictive multifactorial models.	The mean tumor burden normalized to body surface area was 137.8 cm(3)/m(2) +/- 124.7 cm(3)/m(2) (range, 1.9-694.5 cm(3)/m(2)). In multivariate analysis, mean tumor burden normalized to body surface area was the best predictor of time to treatment failure, DFS, and complete remission; the second best predictor of OS after patient age; and largely superior to all prognostic models analyzed. For the same stage and treatment, patients who were destined to clinical failure had an initial mean tumor burden normalized to body surface area 60%–108% higher compared with the initial mean tumor burden normalized to body surface area in patients who achieved a cure, whereas differences in drug dose intensity were not significant.	2
14. Mendenhall NP, Cantor AB, Barre DM, Lynch JW, Jr., Million RR. The role of prognostic factors in treatment selection for early-stage Hodgkin's disease. *Am J Clin Oncol.* 1994;17(3):189-195.	Observational-Tx	153 patients	To identify poor prognostic factors in early-stage HD that predict a high rate of relapse after RT alone.	The only factors independently predicting a high rate of relapse were tumor dimension (>6 cm) and number of sites (>4 sites). At 10 years, in patients with and without the 2 poor prognostic factors treated with RT alone, the freedom from relapse rates were 53% and 84% (P<.0001) and the absolute survival rates were 72% and 85% (P=.004), respectively. CMT significantly improved freedom from relapse, but not absolute survival, in patients with 1 or both poor prognostic factors.	2

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

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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 HD.	The Ann Arbor staging classification remains the basis for evaluation of patients with HD. 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 HD-associated antigens and cytokines may in the future provide valuable tumor markers in HD.	4
16. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res.* 1971;31(11):1860-1861.	Review/Other-Dx	N/A	To provide a report on Hodgkin's Disease Staging Classification.	No results stated in abstract.	4

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
17. Crnkovich MJ, Leopold K, Hoppe RT, Mauch PM. Stage I to IIB Hodgkin's disease: the combined experience at Stanford University and the Joint Center for Radiation Therapy. *J Clin Oncol.* 1987;5(7):1041-1049.	Observational-Tx	180 patients	To study pretreatment characteristics of patients with pathological stage IB to IIB HD to assess their influence on survival and freedom from relapse.	The 2 most important disease characteristics predictive of relapse were the number and type of B symptoms present and the mediastinal mass ratio. Patients with both fevers and weight loss had a 7-year survival and freedom from relapse of only 57% and 48%, respectively. The poor prognosis in this group was apparent for treatment with either RT alone or CMT. Patients with night sweats only had no adverse effect of B symptoms on outcome. Patients with a mediastinal mass ratio >1/3 had a 7-year freedom from relapse of only 58% after RT, but 79% after CMT (P=.12). The 7-year survivals for these patients were 85% and 88%, respectively. CMT improved the freedom from relapse of the entire group of 180 patients when compared with RT (7-year freedom from relapse 86% and 74%, respectively, P=.02); however, survival in the 2 treatment groups was similar (88% and 89%).	2
18. Hopper KD, Diehl LF, Lynch JC, McCauslin MA. Mediastinal bulk in Hodgkin disease. Method of measurement versus prognosis. *Invest Radiol.* 1991;26(12):1101-1110.	Experimental-Dx	76 patients	To determine the best definition, and determine the role of thoracic CT vs chest radiographs in the evaluation of mediastinal bulk disease.	107 consecutive newly diagnosed adult patients with HD were evaluated using 13 commonly used definitions of mediastinal bulk. Of the 76 patients with mediastinal disease, 73 had bulk disease as defined by at least 1 definition. Of the 16 patients who had recurrence of mediastinal disease, only the presence of bulk disease according 1 definition (hilar adenopathy, ≥2 cm) was statistically significant in its prediction (P=.05). No definition based on the size of the mediastinal nodal mass reliably predicted those patients with recurrence. No differences in our data were found for differing stages or disease cell types, the presence of extension, or with differing treatment regimens.	1

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
19. Bonfante V, Santoro A, Viviani S, et al. Early stage Hodgkin's disease: ten-year results of a non-randomised study with radiotherapy alone or combined with MOPP. *Eur J Cancer.* 1992;29A(1):24-29.	Experimental-Tx	201 consecutive patients	To confirm the role of RT alone in patients with favorable presentation and to evaluate the efficacy of a combined treatment in patients with unfavorable prognosis.	The F group included 116 patients with favorable presentation: they were staged with laparotomy and treated with subtotal or total nodal RT alone. The U group included 85 cases with unfavorable presentation who were staged by laparoscopy and treated with 3MOPP-RT-3MOPP. At 10 years the F group showed a FFP of 71% with significant difference between stage I and II (85% vs 59%; *P*=0.003) and an OS of 84%. The results of the U group were: FFP 83%, OS 74%, and the findings were not influenced by stage. FFP in patients with bulky vs not bulky lymphoma was 70% vs 87% (*P*=0.04). No secondary acute non-lymphocytic leukemia developed among patients treated with RT and in continuous complete remission, while acute leukemia occurred in the F group patients who received salvage chemotherapy (4/31 cases) and in the U group (3/85 cases).	1
20. Hagemeister FB, Purugganan R, Fuller L, et al. Treatment of early stages of Hodgkin's disease with novantrone, vincristine, vinblastine, prednisone, and radiotherapy. *Semin Hematol.* 1994;31(2 Suppl 3):36-43.	Observational-Tx	129 patients	To report further results from an earlier treatment program with an early analysis of prognostic factors potentially important for relapse, and to provide a comparison with overall results previously obtained for similar patients treated with MOPP and RT after staging by laparotomy.	Novantrone, vincristine, vinblastine, prednisone, and RT is a regimen that is acutely well tolerated, although chronic toxicity issues must still be evaluated. However, FFP results appear to be similar to those observed with MOPP and RT for patients with unfavorable features, and are comparable to those reported with other regimens.	2
21. Noordijk EM, Carde P, Dupouy N, et al. Combined-modality therapy for clinical stage I or II Hodgkin's lymphoma: long-term results of the European Organisation for Research and Treatment of Cancer H7 randomized controlled trials. *J Clin Oncol.* 2006;24(19):3128-3135.	Experimental-Tx	722 patients	To reduce this toxicity using a combination of low-intensity chemotherapy and IFRT without jeopardizing disease control.	Median follow-up time of the 722 patients included was 9 years. In 333 favorable patients, the 10-year EFS rates were 88% in the EBVP arm and 78% in the subtotal nodal irradiation arm (*P*=.0113), with similar 10-year OS rates (92% vs 92%, respectively; *P*=.79). In 389 unfavorable patients, the 10-year EFS rate was 88% in the MOPP/ABV arm compared with 68% in the EBVP arm (*P*<.001), leading to 10-year OS rates of 87% and 79%, respectively (*P*=.0175).	1

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
22. Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. *J Clin Oncol.* 2010;28(27):4199-4206.	Experimental-Tx	1,395 patients	To present here in which the standard of care regimen, ABVD, was compared with the more intensive BEACOPP(baseline) regimen and to determine the best radiation dose needed in this combined-modality approach.	With a total of 1,395 patients included, the FFTF at 5 years was 85.0%, OS was 94.5%, and PFS was 86.0%. BEACOPP(baseline) was more effective than ABVD when followed by 20 Gy of IFRT (5-year FFTF difference, 5.7%; 95% CI, 0.1% to 11.3%). However, there was no difference between BEACOPP(baseline) and ABVD when followed by 30 Gy of IFRT (5-year FFTF difference, 1.6%; 95% CI, -3.6% to 6.9%). Similar results were observed for the RT question; after 4 cycles of BEACOPP(baseline), 20 Gy was not inferior to 30 Gy (5-year FFTF difference, -0.8%; 95% CI, -5.8% to 4.2%), whereas inferiority of 20 Gy cannot be excluded after 4 cycles of ABVD (5-year FFTF difference, -4.7%; 95% CI, -10.3% to 0.8%). Treatment-related toxicity occurred more often in the arms with more intensive therapy.	1
23. 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 complete remission and clinical complete remission 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-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

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24. Steidl C, Lee T, Shah SP, et al. Tumor-associated macrophages and survival in classic Hodgkin's lymphoma. *N Engl J Med.* 2010;362(10):875-885.	Observational-Tx	166 patients	To analyze frozen samples obtained from patients with classic HL during diagnostic lymph-node biopsy to determine which cellular signatures were correlated with treatment outcome by using gene-expression profiling.	Gene-expression profiling identified a gene signature of tumor-associated macrophages that was significantly associated with primary treatment failure (*P*=0.02). In an independent cohort of patients, we found that an increased number of CD68+ macrophages was correlated with a shortened PFS (*P*=0.03) and with an increased likelihood of relapse after autologous hematopoietic stem-cell transplantation (*P*=0.008), resulting in shortened disease-specific survival (*P*=0.003). In multivariate analysis, this adverse prognostic factor outperformed the IPS for disease-specific survival (*P*=0.003 vs *P*=0.03). The absence of an elevated number of CD68+ cells in patients with limited-stage disease defined a subgroup of patients with a long-term disease-specific survival of 100% with the use of current treatment strategies.	1
25. Scott DW, Chan FC, Hong F, et al. Gene expression-based model using formalin-fixed paraffin-embedded biopsies predicts overall survival in advanced-stage classical Hodgkin lymphoma. *J Clin Oncol.* 2013;31(6):692-700.	Observational-Tx	290 patients	To reliably identify patients with advanced-stage classical HL at increased risk of death by developing a robust predictor of OS using gene expression measured in routinely available formalin-fixed paraffin-embedded tissue.	A 23-gene outcome predictor was generated. The model identified a population at increased risk of death in the validation cohort. There was a 29% absolute difference in 5-year OS between the high- and low-risk groups (63% vs 92%, respectively; log-rank *P*<.001; HR, 6.7; 95% CI, 2.6 to 17.4). The predictor was superior to the IPS and CD68 immunohistochemistry in multivariate analyses.	2
26. Schwartz C, Chen L, Constine L, et al. The Childhood Hodgkin International Prognostic Score (CHIPS) for Predicting Event Free Survival in Pediatric and Adolescent Hodgkin Lymphoma. *ASH Annual Meeting Abstracts.* 2011;118(21):3649-.	Observational-Tx	770 patients	To develop a method for predicting EFS in HL using clinical factors known at diagnosis.	4 predictors (stage 4, large mediastinal adenopathy, albumen <3.5, and fever) were identified as predictive of adverse EFS. Since the HRs were similar, the CHIPS (Childhood Hodgkin IPS) score was devised that gave 1 point for each of the 4 adverse predictors. EFS based on score was found to predict an excellent outcome of nearly 90% for those with CHIPS 0 or 1 (N=589) vs 78% or 62% for those with CHIPS 2 or 3 respectively (N= 141 and 32).	1

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

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27. Yahalom J, Mauch P. The involved field is back: issues in delineating the radiation field in Hodgkin's disease. *Ann Oncol.* 2002;13 Suppl 1:79-83.	Review/Other-Tx	N/A	To review the comeback of the involved field, to address design questions and offer field borders for common disease sites.	During the last century, the role of RT in the treatment of HD has changed drastically. From a palliative treatment reserved for bulky lymph nodes of an incurable disease at the beginning of the century, to an exciting primary treatment used alone to cure most stages in the 1960s and 1970s, to the present more limited role as consolidation treatment after chemotherapy. Interestingly, the radiation field size has always influenced the evolution of treatment principles of HD. Over several decades, large or EFRT has become synonymous with the successful treatment of HD. But the critical transformation from a single-modality to a CMT, together with improvement in imaging and radiation planning techniques, mandates a reassessment of the delineation of appropriate radiation fields in HD.	4

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

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28. 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	Guidelines to provide a consensus position on the modern approach to the delivery of RT in the treatment of HL and to outline a new concept of involved site RT in which reduced treatment volumes are planned for the effective control of involved sites of disease.	The role of reduced volumes and doses is addressed, integrating modern imaging with 3D planning and advanced techniques of treatment delivery. The previously applied EFRT 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 IMRT, 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. The highly conformal INRT, recently introduced for patients for whom optimal imaging is available, is explained. 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 CMT. The use of INRT 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 INRT, 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-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

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29. Engert A, Schiller P, Josting A, et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol.* 2003;21(19):3601-3608.	Experimental-Tx	1,064 patients	To investigate whether RT can be reduced without loss of efficacy from EFRT to IFRT after 4 cycles of chemotherapy.	Of 1,204 patients randomly assigned to treatment, 1,064 patients were informative and eligible for the arm comparison (532 patients in arm A; 532 patients in arm B). The median observation time was 54 months. 5 years after random assignment, the OS for all eligible patients was 91% and FFTF was 83%. Survival rates at 5 years after start of RT revealed no differences for arms A and B, respectively, in terms of FFTF (85.8% and 84.2%) and OS at 5 years (90.8% and 92.4%). There also were no differences between arms A and B, respectively, in terms of complete remission (98.5% and 97.2%), progressive disease (0.8% and 1.9%), relapse (6.4% and 7.7%), death (8.1% and 6.4%), and secondary neoplasia (4.5% and 2.8%). In contrast, acute side effects including leukopenia, thrombocytopenia, nausea, gastrointestinal toxicity, and pharyngeal toxicity were more frequent in the EF arm.	1
30. Klimm B, Eich HT, Haverkamp H, et al. Poorer outcome of elderly patients treated with extended-field radiotherapy compared with involved-field radiotherapy after chemotherapy for Hodgkin's lymphoma: an analysis from the German Hodgkin Study Group. *Ann Oncol.* 2007;18(2):357-363.	Observational-Tx	1,064 patients	To evaluate the impact of different radiation field sizes, that is EFRT or IFRT technique when given after 4 cycles of chemotherapy.	Elderly patients had a poorer risk profile. Acute toxicity from RT was more pronounced in elderly patients receiving EFRT compared with IFRT [World Health Organization (WHO) grade 3/4: 26.5% vs 8.6%)]. FFTF (64% vs 87%) and OS (70% vs 94%) after 5 years was lower in elderly patients compared with younger patients. Importantly, elderly patients had poorer outcome when treated with EFRT compared with IFRT in terms of FFTF (58% vs 70%; P=0.034) and OS (59% vs 81%; P=0.008).	1

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
31. Sasse S, Klimm B, Gorgen H, et al. Comparing long-term toxicity and efficacy of combined modality treatment including extended- or involved-field radiotherapy in early-stage Hodgkin's lymphoma. *Ann Oncol.* 2012;23(11):2953-2959.	Experimental-Tx	1,204 patients	To evaluate long-term toxicity and efficacy of a combined modality strategy including EFRT or IFRT, the German Hodgkin Study Group carried out a follow-up analysis in patients with early unfavorable HL.	At 10 years, no arm differences were revealed with respect to FFTF (79.8% vs 79.7%), PFS (79.8% vs 80.0%), and OS (86.4% vs 87.3%). Non-inferiority of IFRT was demonstrated for the primary end point FFTF (95% CI for HR 0.72-1.25). Elderly patients had a poorer outcome when treated with EFRT. So far, 15.0% of patients in arm A and 12.2% in arm B died, mostly due to secondary malignancies (5.3% vs 3.4%) or HL (3.2% vs 3.4%). After EFRT, there were more secondary malignancies overall (58 vs 45), especially acute myeloid leukemias (11 vs 4).	1
32. Ferme C, Eghbali H, Meerwaldt JH, et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N Engl J Med.* 2007;357(19):1916-1927.	Experimental-Tx	1,538 patients	To report on the EORTC–GELA (Groupe d'Études des Lymphomes de l'Adulte) H8 trial.	The median follow-up was 92 months. In the H8-F trial, the estimated 5-year EFS rate was significantly higher after 3 cycles of MOPP-ABV plus IFRT than after subtotal nodal RT alone (98% vs 74%, $P<0.001$). The 10-year OS estimates were 97% and 92%, respectively ($P=0.001$). In the H8-U trial, the estimated 5-year EFS rates were similar in the 3 treatment groups: 84% after 7 cycles of MOPP-ABV plus IFRT, 88% after 4 cycles of MOPP-ABV plus IFRT, and 87% after 4 cycles of MOPP-ABV plus subtotal nodal RT. The 10-year OS estimates were 88%, 85%, and 84%, respectively.	1

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
33. Ferme C, Divine M, Vranovsky A, et al. Four ABVD and Involved-Field Radiotherapy in Unfavorable Supradiaphragmatic Clinical Stages (CS) I-II Hodgkin's Lymphoma (HL): Preliminary Results of the EORTC-GELA H9-U Trial. *ASH Annual Meeting Abstracts.* 2005;106(11):813-.	Experimental-Tx	808 patients	To compare 3 modalities of chemotherapy and IFRT in adult patients with supradiaphragmatic CS I-II HL with risk factors.	From October 1998 to September 2002, 808 patients were enrolled in 111 institutions from 10 European countries. The proportions of grade 3–4 chemotherapy-related hematological toxicity (mainly white blood cell) were 74%, 70% and 63%, respectively; That of grade 1–3 RT-related hematological toxicity were 10%, 12% and 17%, respectively. 10 (2+3+5, 1%) patients stopped chemotherapy because of toxicity and 8 (2+2+4, 1%) refused the treatment; 6 (2+2+2, 1%) patients stopped RT because of toxicity and 9 (3+1+5, 1%) refused the treatment. The proportions of patients in CR/CRu were 74%, 71% and 59% after 6, 4 ABVD and 4 BEACOPP, respectively. After a median follow-up of 57 months (range 33–81), 78 events (26 progressions, 37 relapses, 15 deaths) were observed.	1
34. Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. *J Clin Oncol.* 2004;22(14):2835-2841.	Experimental-Tx	136 patients	To present the final results in terms of both treatment efficacy and iatrogenic sequelae in patients with clinical stages IA, IB, and IIA disease testing 4 cycles of ABVD chemotherapy followed by subtotal nodal plus spleen irradiation vs 4 cycles of ABVD followed by IFRT.	Main patient characteristics were fairly well balanced between the 2 arms. Complete remission was achieved in 100% and in 97% of patients, respectively. The 12-year FFP rates were 93% (95% CI, 83% to 100%) after ABVD and subtotal nodal plus spleen irradiation, and 94% (95% CI, 88% to 100%) after ABVD and IFRT, whereas the figures for OS were 96% (95% CI, 91% to 100%) and 94% (95% CI, 89% to 100%), respectively. Apart from 3 patients who developed second malignancies in the subtotal nodal plus spleen irradiation arm, treatment-related morbidities were mild.	1
35. Advani RH, Hoppe RT, Baer D, et al. Efficacy of abbreviated Stanford V chemotherapy and involved-field radiotherapy in early-stage Hodgkin lymphoma: mature results of the G4 trial. *Ann Oncol.* 2013;24(4):1044-1048.	Experimental-Tx	87 patients	To assess the efficacy of an abbreviated Stanford V regimen in patients with early-stage HL.	At a median follow-up of 10 years, FFP, DSS and OS are 94%, 99% and 94%, respectively. Therapy was well tolerated with no treatment-related deaths.	2

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
36. Advani RH, Hoppe RT, Maeda LS, et al. Stage I-IIA non-bulky Hodgkin's lymphoma. Is further distinction based on prognostic factors useful? The Stanford experience. *Int J Radiat Oncol Biol Phys.* 2011;81(5):1374-1379.	Observational-Tx	101 patients	To determine the prognostic significance of these factors in patients with early-stage disease treated at Stanford University Medical Center.	At a median follow-up of 8.5 years, FFP and OS rates were 94% and 97%, respectively. From 33% to 60% of our patients were unfavorable per European criteria (i.e., GHSG, n=55%; EORTC, n=33%; and GELA, n=61%). Differences in FFP rates between favorable and unfavorable patients were significant only for GHSG criteria (*P*=0.02) with there were no differences in OS rates for any criteria. Five of 6 patients who relapsed were successfully salvaged.	2
37. Horning SJ, Hoppe RT, Breslin S, Bartlett NL, Brown BW, Rosenberg SA. Stanford V and radiotherapy for locally extensive and advanced Hodgkin's disease: mature results of a prospective clinical trial. *J Clin Oncol.* 2002;20(3):630-637.	Experimental-Tx	142 patients	To provide more mature data on the efficacy and complications of a brief, dose-intense chemotherapy regimen plus RT to bulky disease sites for locally extensive and advanced-stage HD.	With a median follow-up of 5.4 years, the 5-year FFP was 89% and the OS was 96%. No patient progressed during treatment, and there were no treatment-related deaths. FFP was significantly superior among patients with a prognostic score of 0 to 2 compared with those with a score of 3 and higher (94% vs 75%, *P*<.0001). No secondary leukemia was observed. To date, there have been 42 pregnancies after treatment. Among 16 patients who relapsed, the FF2R was 69% at 5 years.	1
38. Advani RH, Hong F, Fisher RI, et al. Randomized Phase III Trial Comparing ABVD Plus Radiotherapy With the Stanford V Regimen in Patients With Stages I or II Locally Extensive, Bulky Mediastinal Hodgkin Lymphoma: A Subset Analysis of the North American Intergroup E2496 Trial. *J Clin Oncol.* 2015;33(17):1936-1942.	Experimental-Tx	264 patients with stage I or II bulky disease	To compare ABVD with Stanford V. We report results of a planned subgroup analysis in patients with stage I or II bulky mediastinal HL.	Of 794 eligible patients, 264 had stage I or II bulky disease, 135 received ABVD, and 129 received Stanford V. Patient characteristics were matched. The overall response rate was 83% with ABVD and 88% with Stanford V. At a median follow-up of 6.5 years, the study excluded a difference of more than 21% in 5-year FFS and more than 16% in 5-year OS between ABVD and Stanford V (5-year FFS: 85% vs 79%; HR, 0.68; 95% CI, 0.37 to 1.25; *P*=.22; 5-year OS: 96% vs 92%; HR, 0.49; 95% CI, 0.16 to 1.47; *P*=.19). In-field relapses occurred in <10% of the patients in each arm.	1

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
39. Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2005;23(21):4634-4642.	Experimental-Tx	399 patients	To report results of a randomized trial comparing ABVD chemotherapy alone with treatment that includes RT in patients with limited-stage HL.	Median follow-up is 4.2 years. In comparison with ABVD alone, 5-year freedom from disease progression is superior in patients allocated to RT (*P*=.006; 93% vs 87%); no differences in EFS (*P*=.06; 88% vs 86%) or OS (*P*=.4; 94% vs 96%) were detected. In a subset analyses comparing patients stratified into the unfavorable cohort, freedom from disease progression was superior in patients allocated to combined-modality treatment (*P*=.004; 95% vs 88%); no difference in OS was detected (*P*=.3; 92% vs 95%). Of 15 deaths observed, 9 were attributed to causes other than HL or acute treatment-related toxicity.	1
40. Koontz BF, Kirkpatrick JP, Clough RW, et al. Combined-modality therapy versus radiotherapy alone for treatment of early-stage Hodgkin's disease: cure balanced against complications. *J Clin Oncol.* 2006;24(4):605-611.	Observational-Tx	181 patients	A retrospective study to compare the long-term results of subtotal nodal plus spleen irradiation with CMT using modestly reduced RT dose in the treatment of early-stage HD.	There was a trend toward improved 20-year OS with CMT (83% vs 70%; *P*=.405). No second cancers were observed in the CMT group; in the RT group the actuarial frequency of a second cancer was 16% at 20 years. There was no difference in the frequency of cardiac complications (9% vs 6%, RT vs CMT).	2

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
41. Omer B, Kadan-Lottick NS, Roberts KB, et al. Patterns of subsequent malignancies after Hodgkin lymphoma in children and adults. *Br J Haematol.* 2012;158(5):615-625.	Observational-Tx	404 patients	To evaluate the impact of reduced radiation and CMT in the treatment of HL by assessing the risk of second malignant neoplasms in patients who received EFRT only and patients who underwent CMT.	Among 404 patients treated at Yale during 1970-2004, the risk of solid second malignant neoplasms was elevated in the RT only group (n = 198, median follow-up = 21.1 years) compared to the general population, with a standardized incidence ratio of 1.85 [95% CI: 1.17–2.78]. No increase was observed in the CMT group (n = 206, median follow-up = 14.3 years), although potential differences in second malignant neoplasms risk were indicated across the age spectrum in subgroup analysis. Patients who received mustard-containing regimens had increased risks for hematological second malignant neoplasms (standardized incidence ratio = 8.74) and all second malignant neoplasms (standardized incidence ratio = 1.85). When the analysis was stratified by age at diagnosis, children (0-20 years) had a significantly higher risk of second malignant neoplasms (standardized incidence ratio = 5.24, 95% CI: 2.26–10.33), regardless of the treatment received.	2

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
42. Herbst C, Rehan FA, Brillant C, et al. Combined modality treatment improves tumor control and overall survival in patients with early stage Hodgkin's lymphoma: a systematic review. *Haematologica.* 2010;95(3):494-500.	Review/Other-Tx	1,245 patients from 10 publications	A systematic review with meta-analysis of randomized controlled trials comparing chemotherapy alone with CMT in patients with early stage HL with respect to response rate, tumor control and OS.	Medline, EMBASE and the Cochrane Library as well as conference proceedings from January 1980 to February 2009 for randomized controlled trials comparing chemotherapy alone vs the same chemotherapy regimen plus RT. PFS and similar outcomes were analyzed together as tumor control. Effect measures used were HRs for OS and tumor control as well as relative risks for CR. Meta-analyses were performed using RevMan5. 5 randomized controlled trials involving 1,245 patients were included. The HR was 0.41 (95% CI 0.25 to 0.66) for tumor control and 0.40 (95% CI 0.27 to 0.59) for OS for patients receiving CMT compared to chemotherapy alone. CR rates were similar between treatment groups. In sensitivity analyses another 6 trials were included that did not fulfill the inclusion criteria of our protocol but were considered relevant to the topic. These trials underlined the results of the main analysis.	4

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
43. Aviles A, Delgado S. A prospective clinical trial comparing chemotherapy, radiotherapy and combined therapy in the treatment of early stage Hodgkin's disease with bulky disease. *Clin Lab Haematol.* 1998;20(2):95-99.	Experimental-Tx	307 patients	To perform a randomized clinical trial to assess the usefulness and toxicity of combined therapy compared with chemotherapy and RT in the treatment of early stage HD with bulky disease as an adverse prognostic factor.	Patients were randomized to receive either RT (extended field, generally mantle, 3500 cGy), or chemotherapy (ABVD, 6 monthly) cycles or combined therapy (3 cycles of ABVD, followed by RT and 3 more cycles of chemotherapy). The median follow-up duration from start of treatment was 11.4 years. CR rates were similar in the 3 arms: 83% for RT (95% CI 67%–92%), 80% for chemotherapy (CI 69%–88%) and 87% for combined therapy (CI 74%–-94%). However, DFS and OS were better in the patients treated with combined therapy. At 12 years 76% (CI 51%–93%) of the patients treated with combined therapy remained alive in the first complete remission compared with 42% (CI 26%–61%) in patients treated with RT and 48% (CI 31%–57%) in patients who had received chemotherapy alone ($P<0.01$). Improvement in OS was also evident at 12 years: 88% (CI 59%–93%) in those who had received combined therapy, compared with 53% (CI 36%–67%) in the RT arm and 59% (CI 35%–67%) in the chemotherapy group. Acute toxicity was more frequent in patients treated with combined therapy, but no death related treatment was observed in the 3 groups. Late toxicity was similar in the 3 treatment groups.	1

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
44. Bloomfield CD, Pajak TF, Glicksman AS, et al. Chemotherapy and combined modality therapy for Hodgkin's disease: a progress report on Cancer and Leukemia Group B studies. *Cancer Treat Rep.* 1982;66(4):835-846.	Experimental-Tx	55 patients (CALGB 7751); 233 patients (CALGB 7451); 305 patients (CALGB 7551); 266 patients (CALGB 7552)	Between 1974 and 1977, the Cancer and Leukemia Group B (CALGB) initiated 4 studies to evaluate the efficacy of chemotherapy alone as compared with CMT in patients with poor-prognostic stages I and II.	Currently, both therapies produce very high complete remission rates in asymptomatic patients; the remission rate is better with CMT in symptomatic patients. Single and CMTs are compared for stage III patients in CALGB 7451. Complete remission rates have been similar, but relapse-free survival is superior for patients treated with local nodal RT followed by chemotherapy (P=0.04). In particular, stage IIIA patients with nodular sclerosis seem to benefit from the inclusion of RT in their initial treatment. In CALGB 7551, the efficacy of chemotherapy alone vs chemotherapy plus RT to areas of bulky disease is under study in patients with stages IIIB and IV. Currently, a relapse rate of less than 10% has been seen among sites irradiated, and survival is best for patients treated with RT bracketed by chemotherapy. Finally, the role of 2 alternating non-cross-resistant combination chemotherapy programs is being studied in CALGB 7552. Relapse-free and OS is better with the doxorubicin-containing regimen than with either the alternating or alternate chemotherapy program. At present, the median follow-up for each of these studies is less than 5 years.	1

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
45. Noordijk E, Thomas J, Ferme C, van't Veer M. First Results of the EORTC-GELA H9 Randomized Trials: H9-F trial (comparing 3 radiation dose levels) and H9-U trial (comparing 3 chemotherapy schemes) in Patients with Favorable or Unfavorable Early Stage Hodgkin's Lymphoma (HL). *J Clin Oncol.* 2005;23(16S):6505a.	Experimental-Tx	1,591 patients with stage I-II HL were enrolled into 2 trials	The H9-F trial compared 36 Gy IFRT vs 20 Gy IFRT vs no RT in patients in CR after 6 cycles of EBVP. The H9-U trial compared 6 cycles of ABVD vs 4 cycles of ABVD vs 4 cycles of BEACOPP baseline, followed by 30 Gy IFRT in all arms, in patients with unfavorable clinical features.	In the H9-F trial, of the 783 patients enrolled, 619 (79%) achieved a CR and were randomized. Inclusion of patients in the no-RT arm was stopped in May 2002, because stopping rules were met (ie, >20% of events). Inclusion in the other 2 arms continued until May 2004. After a median follow-up of 33 months, the 4-year EFS rates were 87% in the 36 Gy and 84% in the 20 Gy arm; it was 70% in the 0 Gy arm (P<0.001). The 4-year OS rate was 98% in all 3 arms. Until September 2002, 808 patients were randomized in the H9-U trial. The 4-year EFS rates were 94%, 89% and 91% in the 3 arms, respectively (P=0.23) and the 4-year OS rates 96%, 95% and 93% (P=0.89). Chemotherapy-related toxicity (measured by antibiotics, transfusions, hospitalization, S.A.E.) was higher with BEACOPP compared to ABVD.	1
46. Pavlovsky S, Maschio M, Santarelli MT, et al. Randomized trial of chemotherapy versus chemotherapy plus radiotherapy for stage I-II Hodgkin's disease. *J Natl Cancer Inst.* 1988;80(18):1466-1473.	Experimental-Tx	277 patients	To assess the role of RT as an adjuvant to chemotherapy in early stages of HD.	A total of 277 patients with untreated HD, clinical stages I-II, were randomized to CVPP alone for 6 monthly cycles or to CVPP plus RT, 3,000 rad to involved areas (CVPP plus RT). 1 or more of the following factors were considered as unfavorable prognosis: age >45 years, more than 2 lymph node areas involved or bulky disease. In the favorable group, DFS (77% vs 70%) or OS (92% vs 91%) at 84 months for CVPP vs RT plus CVPP was similar. Patients with unfavorable prognosis treated with RT plus CVPP had longer DFS (75% vs 34%) (P=.001) and OS (84% vs 66%) than patients treated with CVPP alone.	1

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
47. Straus DJ, Portlock CS, Qin J, et al. Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. *Blood.* 2004;104(12):3483-3489.	Experimental-Tx	152 untreated HD patients	To determine whether CMT is superior to chemotherapy alone.	Of 76 patients randomized to receive RT, 65 actually received it, and 11 did not (4 progressed, 1 had bleomycin toxicity, 6 refused). For ABVD + RT, the CR percentage was 94% and no major response, 6%. For ABVD alone, 94% achieved a CR; 1.5%, a partial response; and 4.5%, no major response. At 60 months CR duration, FFP, and OS for ABVD + RT vs ABVD alone are 91% vs 87% (*P*=.61), 86% vs 81% (*P*=.61), and 97% vs 90% (*P*=.08), respectively (log-rank). The 95% CIs for CR duration, FFP, and OS differences at 5 years were -8% to 15%, -8% to 18%, and -4% to 12%, respectively.	1
48. Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *N Engl J Med.* 2012;366(5):399-408.	Experimental-Tx	405 patients	To report the final analysis from the Hodgkin Diesease.6 (HD.6) trial, which assessed the primary outcome—the rate of 12-year OS.	The median length of follow-up was 11.3 years. At 12 years, the rate of OS was 94% among those receiving ABVD alone, as compared with 87% among those receiving subtotal nodal RT (HR for death with ABVD alone, 0.50; 95% CI, 0.25 to 0.99; *P*=0.04); the rates of freedom from disease progression were 87% and 92% in the 2 groups, respectively (HR for disease progression, 1.91; 95% CI, 0.99 to 3.69; *P*=0.05); and the rates of EFS were 85% and 80%, respectively (HR for event, 0.88; 95% CI, 0.54 to 1.43; *P*=0.60). Among the patients randomly assigned to ABVD alone, 6 patients died from HL or an early treatment complication and 6 died from another cause; among those receiving RT, 4 deaths were related to HL or early toxic effects from the treatment and 20 were related to another cause.	1
49. Laskar S, Gupta T, Vimal S, et al. Consolidation radiation after complete remission in Hodgkin's disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: is there a need? *J Clin Oncol.* 2004;22(1):62-68.	Experimental-Tx	251 patients	To evaluate the role of consolidation radiation in patients achieving a complete remission after 6 cycles of ABVD chemotherapy using EFS and OS as primary end points.	With a median follow-up of 63 months, the 8-year EFS and OS in the chemotherapy-alone arm were 76% and 89%, respectively, as compared with 88% and 100% in the chemotherapy + RT arm (*P*=.01; *P*=.002). Addition of RT improved EFS and OS in patients with age <15 years (*P*=.02; *P*=.04), B symptoms (*P*=.03; *P*=.006), advanced stage (*P*=.03; *P*=.006), and bulky disease (*P*=.04; *P*=.19).	1

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
50. Wolden SL, Chen L, Kelly KM, et al. Long-term results of CCG 5942: a randomized comparison of chemotherapy with and without radiotherapy for children with Hodgkin's lymphoma--a report from the Children's Oncology Group. *J Clin Oncol.* 2012;30(26):3174-3180.	Experimental-Tx	498 patients	To present the long-term study outcome using final data through March 2007 from the Children's Cancer Group trial for patients with HL evaluating whether low-dose IFRT improved EFS for patients achieving a CR after chemotherapy.	10-year EFS and OS rates for the entire cohort were 83.5% and 92.5%, respectively. In an as-treated analysis for randomly assigned patients, the 10-year EFS and OS rates were 91.2% and 97.1%, respectively, for IFRT and 82.9% and 95.9%, respectively, for no further therapy. For EFS and OS comparisons, *P*=.004 and *P*=.50, respectively. Bulk disease, "B" symptoms, and nodular sclerosis histology were risk factors for inferior EFS.	1
51. 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.	Experimental-Tx	829 patients	To investigate whether radiation could be omitted in patients achieving a CR to initial chemotherapy without jeopardizing the excellent outcome obtained with CMT.	The projected 3-year EFS from study entry for the entire cohort was 87% +/- 1.2%. Among patients who achieved a CR to initial chemotherapy, 92% +/- 1.9% of those randomized to receive low-dose-IFRT were alive and disease free 3 years after randomization, vs 87% +/- 2.2% for patients randomized to receive no further therapy (stratified log-rank test; *P*=.057). With an "as-treated" analysis, 3-year EFS after randomization for the radiation cohort was 93% +/- 1.7% vs 85% +/- 2.3% for patients receiving no further therapy (stratified log-rank test; *P*=.0024). 3-year survival estimates for patients treated with and without low-dose-IFRT were 98% +/- 1.1% for patients who received radiation and 99% +/- 0.5% for patients who did not receive radiation.	1

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
52. 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.	Experimental-Tx	247 patients	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 HD.	Children ≤21 years old with biopsy-proven, pathologically staged I, IIA, or IIIA1 HD were randomly assigned 6 courses of alternating nitrogen mustard, oncovin, prednisone, and procarbazine/ABVD (treatment 1) or 4 courses of alternating nitrogen mustard, oncovin, prednisone, and procarbazine/ABVD +2550 cGy IFRT (treatment 2). 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 HD, 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.	1
53. Picardi M, De Renzo A, Pane F, et al. Randomized comparison of consolidation radiation versus observation in bulky Hodgkin's lymphoma with post-chemotherapy negative positron emission tomography scans. *Leuk Lymphoma*. 2007;48(9):1721-1727.	Experimental-Dx	260 patients	To evaluate the role of consolidation radiation in a setting of HL patients, using EFS as end point.	Among 260 patients treated with induction chemotherapy for bulky HL, 160 patients achieved negative residual masses at FDG-PET scans. They were randomly divided into 2 well-matched groups to receive either 32 Gy RT to bulky area or no further therapy. At a median follow-up of 40 months, histology showed a malignancy in 14% of patients in the chemotherapy-only group (HL, 11 patients) and in 4% of patients in the chemotherapy + RT group (HL, 2 patients; carcinoma in previously irradiated area, 1 patient) (P=0.03). All the relapses in the chemotherapy-only group involved the bulky site and the contiguous nodal regions. Thus, the overall diagnostic accuracy of FDG-PET to exclude future relapses in the patients nonprotected by RT was 86% with a false-negative rate of 14%.	1

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
54. O'Dwyer PJ, Wiernik PH, Sterart MB, Slawson RG. Treatment of Early Stage Hodgkin's Disease: A Randomized Controlled Trial of Radiotherapy plus Chemotherapy versus Chemotherapy Alone. In: Cavalli F, Bonadonna G, Rozencwig M, eds. *Malignant Lymphomas and Hodgkin's Disease: Experimental and Therapeutic Advances. Proceedings of the Second International Conference on Malignant Lymphomas*. Lugano, Switzerland: Martinus Nijhoff Publishers; 1984:329-336.	Review/Other-Tx	N/A	No abstract available.	No abstract available	4
55. von Tresckow B, Plutschow A, Fuchs M, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD14 trial. *J Clin Oncol.* 2012;30(9):907-913.	Experimental-Tx	1,528 patients	To improve the results in patients with early unfavorable HL, combined modality treatment with 4 cycles of ABVD and 30 Gy IFRT results in long-term tumor control of approximately 80% by using intensive chemotherapy.	With a total of 1,528 qualified patients included, the 2 + 2 regimen demonstrated superior FFTF compared with 4 cycles of ABVD (*P*<.001; HR, 0.44; 95% CI, 0.30 to 0.66), with a difference of 7.2% at 5 years (95% CI, 3.8 to 10.5). The difference in 5-year PFS was 6.2% (95% CI, 3.0% to 9.5%). There was more acute toxicity associated with 2 + 2 than with ABVD, but there were no overall differences in treatment-related mortality or secondary malignancies.	1

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
56. Behringer K, Thielen I, Mueller H, et al. Fertility and gonadal function in female survivors after treatment of early unfavorable Hodgkin lymphoma (HL) within the German Hodgkin Study Group HD14 trial. *Ann Oncol.* 2012;23(7):1818-1825.	Observational-Tx	331 patients	To analyze gonadal function and fertility.	331 of 579 women addressed participated (57.2%) and 263 per-protocol treated patients qualified (A=ABVD: 137, B=2+2: 126, mean time after therapy 42 and 43 months, respectively). Regular menstrual cycle after treatment (A: 87%, B: 83%) and time to recovery (≤12 months) were not different. Follicle-stimulating hormone and anti-Muellerian hormone were significantly better in arm A. However, pregnancies after therapy favored arm B (A: 15%, B: 26%, *P*=0.043) and motherhood rates were equivalent to the German normal population. Multivariate analysis revealed prophylactic use of gonadotropin-releasing hormone analogues as highly significant prognostic factor for preservation of fertility (odds ratio=12.87, *P*=0.001). Severe menopausal symptoms were frequent in women ≥30 years (A: 21%, B: 25%).	1
57. 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.	Review/Other-Tx	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.	4
58. NCCN Clinical Practice Guidelines in Oncology. Hodgkin Lymphoma. Version 2.2015. 2015; Available at: http://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf. Accessed September 30, 2015.	Review/Other-Tx	N/A	To provide guidelines on HL.	No results stated in abstract.	4

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
59. Laskar S, Kumar DP, Khanna N, et al. Radiation therapy for early stage unfavorable Hodgkin lymphoma: is dose reduction feasible? *Leuk Lymphoma.* 2014;55(10):2356-2361.	Observational-Tx	151 patients	To assess patients given RT for early stage unfavorable HL.	151 patients aged between 3 and 70 years with early stage unfavorable HL were included. Patients received 4-6 cycles of ABVD chemotherapy and IFRT. The most common histology was mixed cellularity (43%). The majority had stage IIAX disease. IFRT doses were 25.2 Gy/14 fractions and 34.2 Gy/19 fractions for adults with a CR and partial response, respectively, while the doses were 19.8 Gy/11 fractions and 30.6 Gy/17 fractions, respectively, for children. After 60 months (median), the 10-year PFS and OS were 88.4% and 93.2%, respectively. On univariate analysis, prognostic factors with significant impact on PFS were age ≥18 years, nodular lymphocyte-predominant HL histology, extranodal disease and response to treatment. Extranodal disease had a significant impact on OS. On multivariate analysis, nodular lymphocyte-predominant HL histology (P=0.001) and response at 3 months (P=0.000) had a significant impact on PFS. There were no in-field relapses in patients with bulky disease receiving RT doses >25.2 Gy. Chemotherapy related acute pulmonary toxicity was documented in 21.4% and 4.8% of patients after 6 and 4 cycles of ABVD chemotherapy (P=0.041). 4 cycles of ABVD and reduced dose IFRT resulted in optimal outcomes.	2

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
60. Torok JA, Wu Y, Prosnitz LR, et al. Low-dose consolidation radiation therapy for early stage unfavorable Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys.* 2015;92(1):54-59.	Observational-Tx	90 patients	To discuss the Duke University Medical Center experience to give more than 4 cycles of chemotherapy followed by lower doses of RT in patients with early stage unfavorable HL.	A total of 90 patients met inclusion criteria for analysis. Median follow-up was 5 years. Chemotherapy consisted primarily of ABVD (88%) with a median number of 6 cycles. The median dose of consolidation RT was 23.4 Gy. Four patients had relapses, 2 of which were in-field. 10-year PFS and OS were 93% (95% CI: 0.82–0.97) and 98% (95% CI: 0.92–0.99), respectively. For the subset of patients (n=46) who received 5 to 6 cycles of chemotherapy and ≤24 Gy, the 10-year PFS and OS values were 88% (95% CI: 70%–96%) and 98% (95% CI: 85%–99%), respectively. The most common late effect was hypothyroidism (20%) with no cardiac complications. Seven secondary malignancies were diagnosed, with only 1 arising within the RT field.	2
61. Raemaekers JM, Andre MP, Federico M, et al. Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol.* 2014;32(12):1188-1194.	Experimental-Dx	1,137 patients	To evaluate whether INRT could be omitted without compromising PFS in patients attaining a negative early PET scan after two cycles of ABVD as compared with standard combined-modality treatment.	In the favorable subgroup, 85.8% had a negative early PET scan (standard arm, 1 event vs experimental arm, 9 events). In the unfavorable subgroup, 74.8% had a negative early PET scan (standard arm, 7 events vs experimental arm, 16 events). The independent data monitoring committee concluded it was unlikely that we would show noninferiority in the final results for the experimental arm and advised stopping random assignment for early PET-negative patients.	1
62. Borchmann P, Eichenauer DA, Engert A. State of the art in the treatment of Hodgkin lymphoma. *Nat Rev Clin Oncol.* 2012;9(8):450-459.	Review/Other-Tx	N/A	To provide an overview of the current treatment approaches for patients with HL.	More than 80% of patients can be cured with risk-adapted treatment that includes chemotherapy and RT. This progress is mainly due to the development of multi-agent chemotherapy and improved radiation techniques; however, severe, life-threatening treatment-related side effects occur, which include organ toxicity and secondary malignancies. Thus, the treatment approaches must be carefully balanced between optimal disease control and the risk of long-term sequelae.	4

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
63. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol.* 2014;32(27):3048-3058.	Review/Other-Dx	N/A	An imaging working group composed of representatives from major international cooperative groups was asked to review the literature, share knowledge about research in progress, and identify key areas for research pertaining to imaging and lymphoma.	A working paper was circulated for comment and presented at the Fourth International Workshop on PET in Lymphoma in Menton, France, and the 12th ICML in Lugano, Switzerland, to update the International Harmonisation Project guidance regarding PET. Recommendations were made to optimize the use of PET/CT in staging and response assessment of lymphoma, including qualitative and quantitative methods.	4
64. Biggi A, Gallamini A, Chauvie S, et al. International validation study for interim PET in ABVD-treated, advanced-stage hodgkin lymphoma: interpretation criteria and concordance rate among reviewers. *J Nucl Med.* 2013;54(5):683-690.	Observational-Dx	440 patients	To focus mainly on the interpretation criteria for interim PET to formulate a clear set of instructions for PET/CT reporters and to measure concordance rates among reviewers using the 5-PS with the defined instructions.	Complete scan datasets of acceptable diagnostic quality were available for 260/440 (59%) enrolled patients. Independent agreement among reviewers was reached on 252/260 patients (97%), for whom at least 4 reviewers agreed the findings were negative (score of 1–3) or positive (score of 4–5). After discussion, consensus was reached in all cases. There were 45/260 patients (17%) with positive interim PET findings and 215/260 patients (83%) with negative interim PET findings. 33 interim PET-positive scans were true-positive, and 12 were false-positive. 203 interim PET-negative scans were true-negative, and 12 were false-negative. Sensitivity, specificity, and accuracy were 0.73, 0.94, and 0.91, respectively. Negative predictive value and positive predictive value were 0.94 and 0.73, respectively. The 3-year FFS was 83%, 28%, and 95% for the entire population and for interim PET-positive and -negative patients, respectively (P<0.0001). The agreement between pairs of reviewers was good or very good, ranging from 0.69 to 0.84 as measured with the Cohen kappa. Overall agreement was good at 0.76 as measured with the Krippendorf alpha.	3
65. Armitage JO. Early-stage Hodgkin's lymphoma. *N Engl J Med.* 2010;363(7):653-662.	Review/Other-Tx	N/A	No abstract available.	No abstract available.	4

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
66. Kuruvilla J, Keating A, Crump M. How I treat relapsed and refractory Hodgkin lymphoma. *Blood.* 2011;117(16):4208-4217.	Review/Other-Tx	N/A	To focus on some of the difficult and controversial areas in patient management, including identification of progressive or nonresponsive disease, assessment of the role of prognostic factors and of functional imaging, and available treatments (including both SCT and nontransplantation-based strategies) and to highlight data on new treatments and novel agents currently in clinical trials.	N/A	4
67. Josting A, Rueffer U, Franklin J, Sieber M, Diehl V, Engert A. Prognostic factors and treatment outcome in primary progressive Hodgkin lymphoma: a report from the German Hodgkin Lymphoma Study Group. *Blood.* 2000;96(4):1280-1286.	Observational-Tx	239 patients	To assess whether and to which extent long-term DFS can be achieved in patients with primary progressive HL and to determine patient-, disease-, and treatment-related factors correlated with outcome.	The median age of the 206 patients available was 34 years (range, 16–71). 57 patients (28%) in intermediate stage and 149 patients (72%) in advanced stage developed progressive disease. 153 patients (74%) were treated with salvage chemotherapy, 47 patients (23%) with salvage RT, and 6 patients (3%) did not receive any therapy due to rapid progressive disease. 70 patients (34%) were treated with HDCT and ASCT. The 5-year freedom from second failure and OS for all patients was 17% and 26%, respectively. The 5-year freedom from second failure and OS for patients treated with HDCT was 31% and 43%, respectively. In multivariate analysis low Karnofsky performance score at the time of progression ($P<.0001$), age above 50 years ($P=.019$), and failure to attain a temporary remission on first-line treatment ($P=.0003$) were significant adverse prognostic factors for OS. Patients with none of these risk factors had a 5-year OS of 55% compared with 0% for patients with all 3 of these unfavorable prognostic factors. Although HDCT is a reasonable option for selected patients with primary progressive HD, the majority did not receive HDCT. Interestingly, salvage RT gave promising results in patients with localized progressive disease.	2

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
68. Van Den Neste E, Casasnovas O, Andre M, et al. Classical Hodgkin's lymphoma: the Lymphoma Study Association guidelines for relapsed and refractory adult patients eligible for transplant. *Haematologica.* 2013;98(8):1185-1195.	Review/Other-Tx	N/A	To provide hematologists with concise and clinically sound guidance on the management of these challenging situations: refractory or relapsing HL patients who are fit enough (no age limit) to be eligible for high-dose therapy.	The expert panel recommends a risk-adapted strategy (conventional treatment, or single/double transplantation and/or RT) based on 3 risk factors at progression (primary refractory disease, remission duration <1 year, stage III/IV), and an early evaluation of salvage chemosensitivity, including FDG-PET interpreted according to the Deauville scoring system. Most relapsed or refractory HL patient's chemosensitive to salvage should receive high-dose therapy and ASCT as standard. Efforts should be made to increase the proportion of chemosensitive patients by alternating non-cross-resistant chemotherapy lines or exploring the role of novel drugs.	4
69. King SC, Reiman RJ, Prosnitz LR. Prognostic importance of restaging gallium scans following induction chemotherapy for advanced Hodgkin's disease. *J Clin Oncol.* 1994;12(2):306-311.	Observational-Dx	33 patients	To assess the ability of restaging gallium scanning to distinguish between patients with residual radiographic abnormalities who still have active HD and those who are truly complete responders. Early identification of the former patients might increase the success of secondary salvage therapy.	13 of 33 patients had positive restaging gallium scans; 20 patients had negative scans. The 4-year actuarial relapse-free survival rate was 75% for patients with negative restaging gallium scans compared with 8% for those with positive restaging scans (P< .001). The 4-year actuarial OS rate was 100% for those with negative scans compared with 51% for gallium-positive patients (P= .001). 24 patients had residual chest x-ray or CT scan abnormalities. Calculated negative and positive predictive values for gallium scanning are 92% and 90%, respectively, compared with values of 48% and 83% for CT scanning.	3

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
70. 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 negative predictive value 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

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
71. Josting A, Reiser M, Rueffer U, Salzberger B, Diehl V, Engert A. Treatment of primary progressive Hodgkin's and aggressive non-Hodgkin's lymphoma: is there a chance for cure? *J Clin Oncol.* 2000;18(2):332-339.	Observational-Tx	131 patients	To determine differences in prognosis between primary progressive HD and aggressive non-HL, we retrospectively analyzed patients with progressive lymphoma who were treated with different salvage chemotherapy regimens including HDCT followed by ASCT.	The overall response rate after salvage chemotherapy for patients with primary progressive HD and non-HL was 33% and 15%, respectively. 25 HD patients (37%) received HDCT. Most patients with non-HL had progressive disease under salvage treatment, with only 6 patients (10%) receiving HDCT. Of those, only 2 patients were alive and in continuous complete remission 3 and 12 months after HDCT. No patient with non-HL survived longer than 26 months after first diagnosis. Actuarial OS after 5 years was 19% for all HD patients; 53% for HD patients receiving HDCT, and 0% for patients who did not receive HDCT. In HD patients, multivariate regression analysis identified chemosensitive disease on salvage treatment (*P*=.0001) and HDCT (*P*=.031) as significant prognostic factors for FFTF. Significant prognostic factors for OS are chemosensitive disease (*P*=.0005), HDCT (*P*=.039), and B symptoms at the time of progress (*P*=.046).	2

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
72. Spaepen K, Stroobants S, Dupont P, et al. Prognostic value of pretransplantation positron emission tomography using fluorine 18-fluorodeoxyglucose in patients with aggressive lymphoma treated with high-dose chemotherapy and stem cell transplantation. *Blood.* 2003;102(1):53-59.	Observational-Dx	60 patients	To assess the prognostic value of a pretransplantation FDG-PET scan in patients with chemosensitive lymphoma treated with salvage chemotherapy before high-dose therapy/SCT.	Presence or absence of abnormal FDG uptake was related to PFS and OS using Kaplan-Meier survival analysis. 30 patients showed a negative FDG-PET scan before high-dose therapy/SCT; 25 of those remained in complete remission, with a median follow-up of 1,510 days. 2 patients died due to a treatment-related mortality but without evidence of recurrent disease at that time (228–462 days). Only 3 patients had a relapse (median PFS, 1,083 days) after a negative FDG-PET scan. Persistent abnormal FDG uptake was seen in 30 patients and 26 progressed (median PFS, 402 days); of these 26, 16 died from progressive disease (median OS, 408 days). 4 patients are still in complete remission after a positive scan. Comparison between groups indicated a statistically significant association between FDG-PET findings and PFS (P<.000001) and OS (P<.00002).	2
73. Fung HC, Stiff P, Schriber J, et al. Tandem autologous stem cell transplantation for patients with primary refractory or poor risk recurrent Hodgkin lymphoma. *Biol Blood Marrow Transplant.* 2007;13(5):594-600.	Experimental-Tx	46 patients	To evaluate the toxicities and efficacy of a tandem transplant approach in patients with primary progressive or poor-risk recurrent HL.	After a median of 64 days (25–105), 41 patients received the second ASCT. With a median follow-up of 5.3 years (1.6–8.1), the 5-year estimate of OS, PFS, and FFP were 54% (95% CI, 40%–69%), 49% (95% CI, 34%–63%), and 55% (95% CI, 40%–70%), respectively. Our mature results from this study suggest that in patients with primary progressive or poor risk recurrent HL, this tandem ASCT program is effective and well tolerated and compares favorably with the conventional single transplant.	2

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
74. Morschhauser F, Brice P, Ferme C, et al. Risk-adapted salvage treatment with single or tandem autologous stem-cell transplantation for first relapse/refractory Hodgkin's lymphoma: results of the prospective multicenter H96 trial by the GELA/SFGM study group. *J Clin Oncol.* 2008;26(36):5980-5987.	Experimental-Tx	245 patients; 150 poor-risk and 95 intermediate-risk	To evaluate a risk-adapted salvage treatment with single or tandem ASCT for 245 HL patients who experience treatment failure with first-line therapy.	Among poor-risk patients, 105 (70%), including 30/55 with cytoreductive chemotherapy-resistant disease, received tandem ASCT, whereas 92 intermediate-risk patients (97%) received single ASCT. According to intent-to-treat analysis, the 5-year freedom from second failure and OS estimates were 73% and 85%, respectively, for the intermediate-risk group and 46% and 57%, respectively, for the poor-risk group. Outcomes were similar for primary refractory and poor-risk/relapsed HL. For patients with chemotherapy-resistant disease, the 46% 5-year OS rate achieved with tandem ASCT compares favorably with the previously reported 30%. Outcomes for partial and complete responders to cytoreduction receiving tandem ASCT did not differ significantly and were better than those previously reported for partial responders receiving single ASCT, but not superior to those reported for complete responders receiving single ASCT. Six poor-risk patients (4%) died from toxicity.	1
75. Moskowitz CH, Matasar MJ, Zelenetz AD, et al. Normalization of pre-ASCT, FDG-PET imaging with second-line, non-cross-resistant, chemotherapy programs improves event-free survival in patients with Hodgkin lymphoma. *Blood.* 2012;119(7):1665-1670.	Experimental-Dx	97 patients	To determine whether the incorporation of non-cross-resistant chemotherapy followed by a tailored radiation-based transplant conditioning regimen could improve EFS in patients with 0 to 2 risk factors who failed or had a suboptimal response (FDG-PET-positive) to ICE-based chemotherapy before high-dose therapy/ASCT.	At a median follow-up of 51 months, EFS analyzed by intent to treat as well as for transplanted patients is 70% and 79%, respectively. Patients transplanted with negative FDG-PET, pre-high-dose therapy/ASCT after 1 or 2 salvage chemotherapy programs, had an EFS of >80%, vs 28.6% for patients with a positive scan (P<.001).	1
76. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol.* 2012;30(18):2183-2189.	Experimental-Tx	102 patients	To evaluate brentuximab vedotin in a larger homogenous population of patients with HL who had relapsed or refractory disease after ASCT.	The objective response rate was 75% with CR in 34% of patients. The median PFS time for all patients was 5.6 months, and the median duration of response for those in CR was 20.5 months. After a median observation time of more than 1.5 years, 31 patients were alive and free of documented progressive disease. The most common treatment-related adverse events were peripheral sensory neuropathy, nausea, fatigue, neutropenia, and diarrhea.	2

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
77. Younes A, Connors JM, Park SI, et al. Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study. *Lancet Oncol.* 2013;14(13):1348-1356.	Experimental-Tx	51 patients	To assess the safety and early clinical efficacy of brentuximab vedotin as first-line treatment in combination with standard or modified-standard treatment in patients with previously untreated HL.	Between Jan 29, 2010, and Sept 17, 2012, 51 patients were enrolled and received at least 1 dose of brentuximab vedotin. The maximum tolerated dose of brentuximab vedotin when combined with ABVD or AVD was not exceeded at 1.2 mg/kg. 21 (95%) of 22 patients given brentuximab vedotin and ABVD achieved CR, as did 24 (96%) of 25 patients given brentuximab vedotin and AVD. Adverse events were generally grade 1 or 2; however, an unacceptable number of patients in the brentuximab vedotin and ABVD groups had pulmonary toxic effects (11 [44%] of 25), which exceeded the historical incidence for ABVD alone. No patients experienced pulmonary toxic effects when treated with brentuximab vedotin plus AVD. The most common grade 3 or worse events were neutropenia (20 [80%] of 25 patients in the brentuximab vedotin and ABVD group vs 20 [77%] of 26 patients in the brentuximab vedotin and AVD group), anemia (5 [20%] vs 3 [12%]), febrile neutropenia (5 [20%] vs 2 [8%]), pulmonary toxic effects (6 [24%] vs 0), syncope (3 [12%] vs 2 [8%]), dyspnoea (3 [12%] vs 1 [4%]), pulmonary embolism (3 [12%] vs 0), fatigue (1 [4%] each), and leucopenia (1 [4%] each). Serious events occurred in 41% of all patients (14 [56%] in the brentuximab vedotin and ABVD group and 7 [27%] in the brentuximab vedotin and AVD group). Serious events occurring in 10% of patients or more overall were febrile neutropenia (4 [16%] in the brentuximab vedotin and ABVD group vs 2 [8%] in the brentuximab vedotin and AVD group), and, in the brentuximab vedotin and ABVD group only, pulmonary toxic effects (6 [24%]).	1

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
78. Kahn S, Flowers C, Xu Z, Esiashvili N. Does the addition of involved field radiotherapy to high-dose chemotherapy and stem cell transplantation improve outcomes for patients with relapsed/refractory Hodgkin lymphoma? *Int J Radiat Oncol Biol Phys.* 2011;81(1):175-180.	Observational-Tx	92 patients	To evaluate the value of adding IFRT to patients with relapsed/refractory HL undergoing HDCT and SCT.	There was a trend for better disease control in patients receiving IFRT. Specifically, 10/46 IFRT patients (22%) relapsed/progressed after SCT compared with 17/46 control patients (37%). Of the failures after IFRT, 70% were inside the radiation field, all in sites of bulky disease. In patients with nonbulky disease, IFRT also resulted in significantly improved outcomes (failure rate 6% vs 33%, respectively). When stratified by disease bulk, the use of IFRT was found to significantly improve DFS (P=0.032), but did not affect OS. In addition, IFRT and nonbulky disease were found to be positive prognostic indicators for DFS with HRs of 0.357 (P=0.032) and 0.383 (P=0.034), respectively. Grade IV/V toxicities were significantly higher in the IFRT vs non-IFRT group (28% vs 2%; P<0.001), observed only in patients receiving a busulfan-based conditioning regimen.	1
79. Mundt AJ, Sibley G, Williams S, Hallahan D, Nautiyal J, Weichselbaum RR. Patterns of failure following high-dose chemotherapy and autologous bone marrow transplantation with involved field radiotherapy for relapsed/refractory Hodgkin's disease. *Int J Radiat Oncol Biol Phys.* 1995;33(2):261-270.	Experimental-Tx	54 patients	To evaluate the patterns of failure and outcome of patients undergoing HDCT and ABMT for relapsed/refractory HD with emphasis on the impact of IFRT.	25 of the 54 patients (46.3%) relapsed. 17 (68.0%) relapsed in sites of disease present prior to HDCT. Patients treated with IFRT had a lower rate of relapse in sites of prior disease involvement (26.3 vs 42.8%) (P< 0.05) than those not treated with RT. 21 patients had disease persistence following HDCT, of which 10 received IFRT and were converted to a CR. Patients with disease persistence who received IFRT had a better PFS (40.0 vs 12.1%) (P= 0.04) than those who did not. Moreover, the patients converted to a CR had similar progression-free and cause-specific survival as those patients achieving a CR with HDCT alone. Of the initial 147 sites, 142 (97.3%) were amenable to IFRT. The addition of IFRT improved the 5-year local control of all sites (P= 0.008), nodal sites (P= 0.01), and sites of disease persistence (P= 0.0009).	2

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
80. Poen JC, Hoppe RT, Horning SJ. High-dose therapy and autologous bone marrow transplantation for relapsed/refractory Hodgkin's disease: the impact of involved field radiotherapy on patterns of failure and survival. *Int J Radiat Oncol Biol Phys*. 1996;36(1):3-12.	Experimental-Tx	100 patients	To assess the efficacy and toxicity of IFRT in conjunction with high-dose therapy and ABMT in relapsed or refractory HD.	With a median follow-up of 40 months (range: 18–88 months), 3-year actuarial rates of freedom from relapse, survival, and EFS were 66%, 64%, and 57%, respectively. 33 patients (33%) relapsed at a median of 8 months after ABMT. Only 2 of 33 relapses (6%) occurred beyond 18 months. By multivariate analyses, factors associated with recurrence were pleural disease (*P*=0.02), multiple pulmonary nodules (*P*=0.03), and a poor response to cytoreductive therapy (*P*=0.001). A median IFRT dose of 30 Gy (range: 12.5–45 Gy) was given to 67 sites in the 24 patients. Local failure occurred within 4 irradiated sites (6%) in 2 patients (8%). In patients with relapse Stage I-III disease (n = 62), the use of IFRT was associated with an improved 3-year freedom from relapse (100% vs 67%, *P*=0.04) and a trend toward improved survival (85% vs 60%, *P*=0.16). Among patients not previously irradiated (n = 39), IFRT was associated with an improved freedom from relapse (85% vs 57%, *P*=0.07) and survival (93% vs 55%, *P*=0.02). Crude rates of treatment-related Grade 5 complications (including late events and second malignancies) were similar with or without IFRT (17% vs 14%).	1

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
81. Mundt AJ, Connell PP, Mansur DB. What is the optimal treatment volume in Hodgkin's disease patients undergoing high-dose chemotherapy and adjuvant radiation therapy? *Radiat Oncol Investig.* 1999;7(6):353-359.	Observational-Tx	56 adult patients	To determine the optimal treatment volume in HD patients undergoing HDCT and RT.	21 (38%) received IFRT before or after HDCT encompassing sites of prior disease. Failure sites were designated as previously involved (old) or uninvolved (new) sites. 7 patients (12%) died in the immediate post-HDCT period, leaving 49 evaluable (median follow-up, 41 months). 25 patients (51%) relapsed (14 HDCT, 11 HDCT + IFRT): 7 (28%) in old, 9 (32%) in new, and 10 (40%) in old and new sites. 6 of the 7 who relapsed in old sites received HDCT alone, whereas 7 of the 8 who relapsed in new sites received IFRT. Relapse in old sites was particularly common in patients failing to achieve a CR. The most common new failure site was nodal, occurring in 11 patients and was primarily (10/11) adjacent to an old site. Although it controls prior disease, IFRT is insufficient in HD patients undergoing HDCT. Relapse is common in new nodal sites and is primarily adjacent to prior sites. These results suggest that EFRT encompassing old and adjacent uninvolved nodal sites may be the optimal treatment volume in these patients.	2

Hodgkin Lymphoma-Unfavorable Clinical Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
82. Tsang RW, Gospodarowicz MK, Sutcliffe SB, Crump M, Keating A. Thoracic radiation therapy before autologous bone marrow transplantation in relapsed or refractory Hodgkin's disease. PMH Lymphoma Group, and the Toronto Autologous BMT Group. *Eur J Cancer*. 1999;35(1):73-78.	Observational-Tx	59 patients	To assess the relationship between RT and treatment-related mortality in patients receiving HDCT and ABMT) for recurrent/refractory HD.	With a median follow-up of 4.6 years (range 1.2–7.4 years), the actuarial OS was 41% +/- 14% at 5 years. We observed 37 deaths, and 10 of these were treatment-related deaths. Among the 24 patients who received thoracic RT before ABMT, there were 8 treatment-related deaths, 3 of these solely attributable to radiation pneumonitis. The remaining 5 treatment-related deaths all had respiratory failure with complicating sepsis as a major medical problem. The interval from RT to ABMT was shorter for 8 patients dying of treatment-related death (mean 37 days; range 0–103 days), than for the 16 survivors (mean 105 days; range 0–263 days) (*P*=0.026). Among 9 patients with ABMT within 50 days of thoracic RT, 6 had treatment-related death. In contrast, among the 35 patients without thoracic RT (26 no RT, 9 nonthoracic RT), there were only 2 treatment-related deaths. The 4 patients treated with mantle RT post-ABMT had no serious pulmonary complications. The use of thoracic RT before HDCT and ABMT was associated with a high post-transplant mortality rate. It was most evident in patients who received thoracic RT within 50 days prior to ABMT, or when the target volume included large volume of lung.	2
83. Yahalom J, Rimner A, Tsang R. Salvage Therapy for Relapsed and Refractory Hodgkin Lymphoma. In: Specht L, Yahalom J, eds. *Radiotherapy for Hodgkin Lymphoma*: Springer Berlin Heidelberg; 2011:31-44.	Review/Other-Tx	N/A	Book.	N/A	4

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

ABMT = Autologous bone marrow transplantation
ABVD = Doxorubicin, bleomycin, vinblastine, and dacarbazine
ASCT = Autologous stem-cell transplantation
BEACOPP = Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
CI = Confidence interval
CMT = Combined modality therapy
CR = Complete response
CT = Computed tomography
CVPP = Cyclophosphamide, vinblastine, procarbazine, and prednisone
DECA = Dexamethasone, etoposide, cisplatin and cytarabine
DFS = Disease-free survival
EBVP = Epirubicin, bleomycin, vinblastine, and prednisone
EFRT = Extended-field radiation therapy
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
HD = Hodgkin disease
HDCT = High-dose chemotherapy
HL = Hodgkin lymphoma
HR = Hazard ratio
IFRT = Involved-field radiotherapy
INRT = Involved-node radiotherapy
MOPP = Mechlorethamine, vincristine, procarbazine, and prednisone
MOPP/ABV = Mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine
OS = Overall survival
PFS = Progression-free survival
RT = Radiation therapy
SCT = Stem cell transplantation
Stanford V = Mechlorethamine, doxorubicin, vincristine, bleomycin, vinblastine, etoposide, and prednisone