Recurrent Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Gobbi PG, Ferreri AJ, Ponzoni M, Levis A. Hodgkin lymphoma. *Crit Rev Oncol Hematol.* 2013;85(2):216-237.	Review/Other-Tx	N/A	No abstract available.	No abstract available.	4
2. Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med.* 2010;363(7):640-652.	Experimental-Tx	1,370 patients	To compare 4 treatment groups consisting of a combination chemotherapy regimen of 2 different intensities followed by IFRT at 2 different dose levels.	The 2 chemotherapy regimens did not differ significantly with respect to freedom from treatment failure (P=0.39) or OS (P=0.61). At 5 years, the rates of freedom from treatment failure were 93.0% (95% CI, 90.5 to 94.8) with the 4-cycle ABVD regimen and 91.1% (95% CI, 88.3 to 93.2) with the 2-cycle regimen. When the effects of 20-Gy and 30-Gy doses of RT were compared, there were also no significant differences in freedom from treatment failure (P=1.00) or OS (P=0.61). Adverse events and acute toxic effects of treatment were most common in the patients who received 4 cycles of ABVD and 30 Gy of RT (group 1).	1
3. Josting A, Franklin J, May M, et al. New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German Hodgkin's lymphoma study group. *J Clin Oncol.* 2002;20(1):221-230.	Observational-Tx	422 patients	To evaluate salvage treatment outcome of patients with relapsed HL and to distinguish different risk groups using identified prognostic factors.	Median follow-up time after relapse was 45 months. FF2F and OS were 81% and 89% for relapse after RT, 33% and 46% for early relapse after chemotherapy, and 43% and 71% for late relapse after chemotherapy, respectively. In multivariate analysis, independent risk factors were time to relapse, clinical stage at relapse, and anemia at relapse. 4 subgroups with significantly different FF2F and OS were identified. The prognostic score was predictive for patients who relapsed after RT, chemotherapy with conventional chemotherapy salvage, and chemotherapy with HDCT/ASCT.	2

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4. Ferme C, Mounier N, Divine M, et al. Intensive salvage therapy with high-dose chemotherapy for patients with advanced Hodgkin's disease in relapse or failure after initial chemotherapy: results of the Groupe d'Etudes des Lymphomes de l'Adulte H89 Trial. *J Clin Oncol.* 2002;20(2):467-475.	Experimental-Tx	157 patients	To evaluate prospectively the feasibility and efficacy of early intensive therapy, including intensified cytoreductive chemotherapy and HDCT followed by ASCT, in patients with advanced HL who failed to respond completely or relapsed after initial treatment.	With a median follow-up of 50 months, the 5-year survival estimates were 30%, 72%, and 76% for the induction failure, partial response, and relapse groups, respectively (*P*=.0001), 71% for the 101 patients given HDCT, and 32% for the 48 patients treated without HDCT (*P*=.0001). Multivariate analysis using time-dependent Cox model indicated that B symptoms at progression, salvage without HDCT, and chemoresistant disease before HDCT were significantly associated with shorter OS.	1
5. Canioni D, Deau-Fischer B, Taupin P, et al. Prognostic significance of new immunohistochemical markers in refractory classical Hodgkin lymphoma: a study of 59 cases. *PLoS One.* 2009;4(7):e6341.	Observational-Tx	59 patients	To further evaluate the prognostic significance of new biological markers in classic HL by comparing the expression of bcl2, Ki67 and CD20 expression in H/RS cells of refractory and early relapse patients to that of responder patients; to compare the expression of TiA1 in surrounding T lymphocytes as a putative marker of an anti-tumoral immune response in both groups of patients; and, to look at the expression of c-kit to evaluate the presence of mastocytes, which might modify the behavior of classic HL.	The results showed that expression of bcl2 and CD20 in Hodgkin and Reed Sternberg cells, and expression of TiA1 in micro-environmental lymphocytes, and c-kit positive mast cells in microenvironment, were independent prognostic markers.	2

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6. 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 FF2F and OS for all patients was 17% and 26%, respectively. The 5-year FF2F 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 HL, the majority did not receive HDCT. Interestingly, salvage RT gave promising results in patients with localized progressive disease.	2
7. NCCN Clinical Practice Guidelines in Oncology. Hodgkin Lymphoma. Version 2.2015. 2015; Available at: http://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf.	Review/Other-Tx	N/A	To provide NCCN practice guidelines on HL.	N/A	4

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8. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32(27):3059-3068.	Review/Other-Dx	N/A	To modernize recommendations for evaluation, staging, and response assessment of patients with HL and non-HL.	PET/CT should be used for response assessment in FDG-avid histologies, using the 5-point scale; CT is preferred for low or variable FDG avidity. A complete metabolic response even with a persistent mass is considered a complete response. A partial response requires a decrease by more than 50% in the sum of the product of the perpendicular diameters of up to 6 representative nodes or extranodal lesions. Progressive disease by CT criteria only requires an increase in the perpendicular diameters of a single node by 50%. Surveillance scans after remission is discouraged, especially for diffuse large B-cell lymphoma and HL, although a repeat study may be considered after an equivocal finding after treatment. Judicious use of follow-up scans may be considered in indolent lymphomas with residual intra-abdominal or retroperitoneal disease.	4
9. Ha CS, Hodgson DC, Advani R, et al. ACR Appropriateness Criteria Follow-up of Hodgkin Lymphoma. *J Am Coll Radiol.* 2014;11(11):1026-1033 e1023.	Review/Other-Tx	N/A	Evidence-based guidelines to assist referring physicians and other providers in making the most appropriate imaging or treatment decision for a specific clinical condition.	N/A	4
10. Gandikota N, Hartridge-Lambert S, Migliacci JC, Yahalom J, Portlock CS, Schoder H. Very low utility of surveillance imaging in early-stage classic Hodgkin lymphoma treated with a combination of doxorubicin, bleomycin, vinblastine, and dacarbazine and radiation therapy. *Cancer.* 2015;121(12):1985-1992.	Review/Other-Dx	78 patients	To evaluate the need for surveillance imaging in early-stage classic HL after planned combined-modality therapy.	The study included 78 patients with a median follow-up of 46 months; 85% of the patients had stage II disease (32% with bulky disease). 4/77 interim PET scans were positive; none of these patients relapsed during follow-up, which ranged from 24 to 80 months. After a total of 466 follow-up imaging studies (91% with CT and 9% with PET/CT), no classic HL relapse was detected. 11 abnormal findings were noted on surveillance imaging: 9 were false-positives, and 2 were second primary malignancies. The average cumulative dose per patient from follow-up imaging was 107 mSv, which translated into an estimated lifetime excess cancer risk of 0.5%; the estimated total costs were $296,817 according to Medicare reimbursements.	4

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11. Sieniawski M, Franklin J, Nogova L, et al. Outcome of patients experiencing progression or relapse after primary treatment with two cycles of chemotherapy and radiotherapy for early-stage favorable Hodgkin's lymphoma. *J Clin Oncol.* 2007;25(15):2000-2005.	Observational-Tx	42 patients	To evaluate treatment outcome of patients with early-stage favorable HL who experience disease relapse after primary treatment with 2 cycles of chemotherapy followed by RT.	The median age was 41 years (range, 19 to 72 years); 24 patients were male, 15 patients had outfield relapse, 13 patients infield relapse, and 9 patients outfield and infield relapse. At relapse, 24 patients were treated with conventional salvage chemotherapy, 14 patients were treated with HDCT followed by ASCT, and 4 patients were treated with RT alone. At 36 months median follow-up, FF2F and OS were 52% and 67%, respectively. According to the prognostic score for relapsed HL (duration of first remission, clinical stage, and anemia at relapse), patients with 2 or 3 poor prognostic features had a significantly worse outcome compared with patients with none or 1 of these factors ($P<.05$ for FF2F and OS).	2

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12. Majhail NS, Weisdorf DJ, Defor TE, et al. Long-term results of autologous stem cell transplantation for primary refractory or relapsed Hodgkin's lymphoma. *Biol Blood Marrow Transplant.* 2006;12(10):1065-1072.	Observational-Tx	141 patients	To study long-term outcomes and evaluate factors influencing PFS in 141 patients with primary refractory or relapsed HL who underwent ASCT between 1985 and 2003.	Median age at ASCT was 30 years (range, 7–60 years); 21 patients had primary refractory, and 120 had relapsed HL. With a median follow-up of 6.3 years (range, 1–20 years), the probability of PFS at 5 and 10 years was 48% (95% CI, 39%–57%) and 45% (95% CI, 36%–54%) and that of OS was 53% (95% CI, 44%–62%) and 47% (95% CI, 37%–57%), respectively. Transplant-related mortality at 100 days was 1.4%. Among 45 5- to 20-year survivors, no late relapses of HL were observed. In multivariate analysis, 3 factors were independently predictive of poor PFS: chemoresistant disease (RR, 2.9; 95% CI, 1.7–5.0), B-symptoms at pretransplantation relapse (RR, 2.1; 95% CI, 1.3–3.4), and presence of residual disease at the time of transplantation (RR, 2.3; 95% CI, 1.1–4.8). Patients with 0 or 1 of these 3 adverse factors (low-risk disease) had a 5-year PFS of 67% (95% CI, 55%–79%) compared with 37% (95% CI, 22%–52%) in those with 2 factors (intermediate-risk group) and 9% (95% CI, 0%–20%) in those with all 3 factors (high-risk group) ($P<.001$). The rates of OS at 5 years were 71% (95% CI, 60%–82%), 49% (95% CI, 33%–65%) and 13% (95% CI, 0%–27%) in the 3 groups, respectively ($P<.001$).	2
13. Mendler JH, Friedberg JW. Salvage therapy in Hodgkin's lymphoma. *Oncologist.* 2009;14(4):425-432.	Review/Other-Tx	N/A	To discuss the evidence behind the current practice in patients with relapsed or refractory HL.	Specifically, the efficacy of various salvage chemotherapy regimens, the risk factors influencing outcome with HDCT/ASCT, and the results with alternative transplant approaches, monoclonal antibody therapies, and novel agents are addressed. We conclude by providing our approach to these patients, with the hope that this will serve as a framework for the practicing oncologist.	4

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14. Josting A, Rudolph C, Reiser M, et al. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. *Ann Oncol.* 2002;13(10):1628-1635.	Experimental-Tx	102 patients	To evaluate dexamethasone/cisplatin/cytarabine given at a median of 16-day intervals in patients with relapsed and refractory HL.	The median age of the 102 patients included was 34 years (range 21–64 years). 42% of the patients had late relapse, 29% early relapse, 12% multiple relapse and 16% primary progressive/refractory disease. The response rate after 2 cycles of dexamethasone/cisplatin/cytarabine was 89% (21% complete response, 68% partial response). The response rates for patients with late, early, multiple and progressive HL were 91%, 93%, 92% and 65%, respectively. Using the chi-square test for independence, remission status (relapsed HL vs progressive HL) and stage at relapse (stage I/II vs stage III/IV) were significant factors for response to dexamethasone/cisplatin/cytarabine. WHO grade 4 leukocytopenia and thrombocytopenia were the main toxicities occurring in 43% (mean duration 1.1 days, range 0–6) and 48% (mean duration 1.4 days, range 0–11) of all courses, respectively. Neither severe infections nor treatment-related deaths occurred. Peripheral blood stem cells were collected after the first cycle dexamethasone/cisplatin/cytarabine in 8 patients. The hematopoietic progenitors showed a very rapid increase from day 10 with a synchronous and impressive peak on day 12. A mean of 6.1 x 10(6)/kg CD34(+) cells were collected per apheresis. As originally recommended in the protocol, peripheral blood stem cells were routinely collected during sequential HDCT in the remaining patients.	1

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15. Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. *Blood.* 2001;97(3):616-623.	Experimental-Tx	65 patients	To report the results of a comprehensive 2-step protocol encompassing dose-dense and dose-intense second-line chemotherapy, followed by high-dose chemoradiotherapy and ASCT.	The EFS rate at a median follow-up of 43 months, as analyzed by intent to treat, was 58%. The response rate to ifosfamide, carboplatin, and etoposide was 88%, and the EFS rate for patients who underwent transplantation was 68%. Cox regression analysis identified 3 factors before the initiation of ifosfamide, carboplatin, and etoposide that predicted for outcome: B symptoms, extranodal disease, and complete remission duration of <1 year. EFS rates were 83% for patients with 0 to 1 adverse factors, 27% for patients with 2 factors, and 10% for patients with 3 factors (P<.001).	1
16. Bartlett NL, Niedzwiecki D, Johnson JL, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. *Ann Oncol.* 2007;18(6):1071-1079.	Experimental-Tx	91 patients	To evaluate the combination of gemcitabine, vinorelbine, and pegylated liposomal doxorubicin for relapsed HL, particularly to determine the maximum tolerated dose, toxicity, and efficacy of this combination in patients before transplant and in patients with relapsed HL following an ASCT.	The dose-limiting toxicity was mucositis for the transplant-naive patients and febrile neutropenia for post-transplant patients. The overall response rate for all patients was 70% [95% CI, 59.8, 79.7], with 19% complete remissions. The 4-year EFS and OS rates in transplant-naive patients treated with gemcitabine, vinorelbine, and pegylated liposomal doxorubicin followed by autologous transplant were 52% (95% CI, 0.34, 0.68) and 70% (95% CI, 0.49, 0.84), and in the patients in whom prior transplant failed, these were 10% (95% CI, 0.03, 0.22) and 34% (95% CI, 0.17, 0.52), respectively.	1
17. William BM, Loberiza FR, Jr., Whalen V, et al. Impact of conditioning regimen on outcome of 2-year disease-free survivors of autologous stem cell transplantation for Hodgkin lymphoma. *Clin Lymphoma Myeloma Leuk.* 2013;13(4):417-423.	Observational-Tx	225 patients alive and disease-free 2 years after ASCT	To report our single-institution experience of 225 patients with HL who were alive and disease-free at 2 years after ASCT and we aimed to compare the effect of transplant conditioning regimen (CBV vs BEAM) on long-term outcomes of these patients.	At a median follow-up of 8 (range, 2–26) years, 225 patients were alive and disease-free 2 years after ASCT. Analysis was limited to these patients. At 5 years, the PFS was 92% for BEAM and 73% for CBV (P=.002) and the OS was 95% for BEAM and 87% for CBV (P=.07). At 10 years, the PFS was 79% for BEAM and 59% for CBV (P=.01) and the OS was 84% for BEAM and 66% for CBV (P=.02).	2

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18. Kuruvilla J, Nagy T, Pintilie M, Tsang R, Keating A, Crump M. Similar response rates and superior early progression-free survival with gemcitabine, dexamethasone, and cisplatin salvage therapy compared with carmustine, etoposide, cytarabine, and melphalan salvage therapy prior to autologous stem cell transplantation for recurrent or refractory Hodgkin lymphoma. *Cancer.* 2006;106(2):353-360.	Observational-Tx	68 patients	To compare the response rates, ability to mobilize autologous hematopoietic (peripheral blood) stem cells (PBSCs), and PFS after second-line chemotherapy with GDP or mini-BEAM followed by high-dose therapy and ASCT for patients with recurrent or refractory HL.	The response rate to GDP prior to ASCT (complete responses, unconfirmed complete responses, and partial responses) was 62% (95% CI, 45%–78%) compared with 68% (95% CI, 52%–83%) for mini-BEAM (P=0.61). After mobilizing chemotherapy, the proportion of patients for whom the target (peripheral blood) stem cells number of ≥5 x 10(6) CD34-positive cells/kg was obtained was 97% after GDP and 57% after mini-BEAM (P=0.0003). More patients completed collection with a single apheresis procedure after GDP than after mini-BEAM (73% vs 36%; P=0.004), and fewer patients in the GDP group required bone marrow harvesting to proceed to ASCT. After a median follow-up of 1.8 years after ASCT, PFS was significantly better for patients who received GDP compared with patients who received mini-BEAM (74% vs 35% at 1.5 years, respectively; P=0.005). OS at 1.5 years was 91% after GDP and 82% after mini-BEAM (P=0.23).	2
19. Santoro A, Magagnoli M, Spina M, et al. Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. *Haematologica.* 2007;92(1):35-41.	Experimental-Tx	91 patients	To report results of a new induction regimen in terms of response rates, toxicity, and stem cell mobilization.	49 patients (53.8%) achieved a complete remission and 25 (27.5%) a partial response for an overall response rate of 81.3%. In the multivariate analysis response to the last chemotherapy (P<0.0001) and involvement of ≥3 sites (P<0.049) were the most important prognostic factors for response. Adequate CD34+ cell collection was achieved in 78/79 (98.7%) mobilized patients. So far, no treatment-related death has been documented. 13 (4.2%) and 27 (8.6%) out of 313 evaluated cycles had to be delayed or reduced, respectively, mainly because of neutropenia and thrombocytopenia. No grade 4 nonhematologic toxicity was observed, except for one episode of mucositis.	1

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20. Ramzi M, Rezvani A, Dehghani M. GDP versus ESHAP Regimen in Relapsed and/or Refractory Hodgkin lymphoma: A Comparison Study. *Int J Hematol Oncol Stem Cell Res.* 2015;9(1):10-14.	Experimental-Tx	44 patients	To compare the efficacy of GDP versus ESHAP.	There were 27.3% complete response, 31.8% more than 50% response, and 40.9% no response with GDP. ESHAP results were 29.5%, 24% and 45.5%, respectively.	1
21. Horning SJ, Fanale M, S. d, et al. Defining a population of Hodgkin lymphoma patients for novel therapeutics: an international effort. *Ann Oncol.* 2008;19(suppl 4):iv120-iv121.	Observational-Tx	241 patients	To evaluate OS in patients relapsed after high dose chemotherapy and autotransplantation and to define a population for trials of new agents.	Data from 3 centers are reported (n=241) and data from 2 additional centers (n=128) will be available for presentation. Selection for high dose chemotherapy and autotransplantation was center-dependent but primarily represented patient <60 years with stable or responding disease after their last therapy and prior to high dose chemotherapy and autotransplantation. Relapses after high dose chemotherapy and autotransplantation were distributed as follows: 0–3 m(23%), >3–6m(20%), >6–12m (30%) and >12m (27%) for Centers 1-3. Median OS by center (N Patients) and time to relapse after high dose chemotherapy and autotransplantation (0–3, >3–6, >6–12, >12 months) were: Center 1 (14) 4, (16) 12, (16) 7, (17) 25; Center 2 (19) 13, (18) 22, (19) 46, (10) NR; Center 3 (19) 8, (15) 15, (38) 21, (37) 48. Evaluation of overall results by time of high dose chemotherapy and autotransplantation before 1990, 1990-2000 and >2000 showed no difference in any of the Centers, indicating the relative stability of OS after relapse from high dose chemotherapy and autotransplantation during the elapsed time.	4

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22. Okeley NM, Miyamoto JB, Zhang X, et al. Intracellular activation of SGN-35, a potent anti-CD30 antibody-drug conjugate. *Clin Cancer Res.* 2010;16(3):888-897.	Experimental-Tx	N/A	To investigate the molecular basis for the activities of SGN-35 by determining the extent of targeted intracellular drug release and retention, and bystander activities.	SGN-35 treatment of CD30(+) cells leads to efficient intracellular release of chemically unmodified monomethylauristatin E, with intracellular concentrations of monomethylauristatin E in the range of 500 nmol/L. This was due to specific antibody-drug conjugate binding, uptake, monomethylauristatin E retention, and receptor recycling or resynthesis. Monomethylauristatin E accounts for the total detectable released drug from CD30(+) cells, and has a half-life of retention of 15 to 20 hours. Cytotoxicity studies with mixtures of CD30(+) and CD30(-) cell lines indicated that diffusible released monomethylauristatin E from CD30(+) cells was able to kill cocultivated CD30(-) cells.	2
23. Chen R, Palmer JM, Martin P, et al. Results of a Multicenter Phase II Trial of Brentuximab Vedotin as Second-Line Therapy before Autologous Transplantation in Relapsed/Refractory Hodgkin Lymphoma. *Biol Blood Marrow Transplant.* 2015;21(12):2136-2140.	Experimental-Tx	37 patients	To examine the activity and tolerability of brentuximab vedotin as second-line therapy in patients with HL that was relapsed or refractory after induction therapy.	Of 37 patients, the overall response rate was 68% (13 complete remission, 12 partial remission). The regimen was well tolerated with few grade 3/4 adverse events, including lymphopenia (1), neutropenia (3), rash (2), and hyperuricemia (1). 32 patients (86%) were able to proceed to autologous hematopoietic cell transplantation, with 24 patients (65%) in complete remission at time of autologous hematopoietic cell transplantation. 13 patients in complete remission, 4 in partial remission, and 1 with stable disease (49%) received autologous hematopoietic cell transplantation without salvage combination chemotherapy. CD68 expression did not correlate with response to brentuximab vedotin. The median number of stem cells mobilized was 6.0 x 10(6) (range, 2.6 to 34), and median number of days to obtain minimum collection (2 x 10(6)) was 2 (range, 1 to 6).	2

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24. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med.* 2010;363(19):1812-1821.	Experimental-Tx	42 patients	To assess the safety and clinical activity of brentuximab vedotin, we treated patients with relapsed or refractory CD30-positive hematologic cancers in a phase 1, open-label, dose-escalation trial.	The maximum tolerated dose was 1.8 mg per kilogram, administered every 3 weeks. Objective responses, including 11 complete remissions, were observed in 17 patients. Of 12 patients who received the 1.8-mg-per-kilogram dose, 6 (50%) had an objective response. The median duration of response was at least 9.7 months. Tumor regression was observed in 36/42 patients who could be evaluated (86%). The most common adverse events were fatigue, pyrexia, diarrhea, nausea, neutropenia, and peripheral neuropathy.	2
25. 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 complete response in 34% of patients. The median PFS time for all patients was 5.6 months, and the median duration of response for those in complete response 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

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26. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med.* 2015;372(4):311-319.	Experimental-Tx	23 patients	To study nivolumab in patients with relapsed or refractory hematologic cancer.	Of the 23 study patients, 78% were enrolled in the study after a relapse following ASCT and 78% after a relapse following the receipt of brentuximab vedotin. Drug-related adverse events of any grade and of grade 3 occurred in 78% and 22% of patients, respectively. An objective response was reported in 20 patients (87%), including 17% with a complete response and 70% with a partial response; the remaining 3 patients (13%) had stable disease. The rate of PFS at 24 weeks was 86%; 11 patients were continuing to participate in the study. Reasons for discontinuation included stem-cell transplantation (in 6 patients), disease progression (in 4 patients), and drug toxicity (in 2 patients). Analyses of pretreatment tumor specimens from 10 patients revealed copy-number gains in PDL1 and PDL2 and increased expression of these ligands. Reed-Sternberg cells showed nuclear positivity of phosphorylated STAT3, indicative of active JAK-STAT signaling.	2
27. Gopal AK, Ramchandren R, O'Connor OA, et al. Safety and efficacy of brentuximab vedotin for Hodgkin lymphoma recurring after allogeneic stem cell transplantation. *Blood.* 2012;120(3):560-568.	Observational-Tx	24 patients	To describe a distinct, previously unpublished cohort of 25 heavily pretreated patients with CD30 HL that relapsed after allogeneic stem cell transplantation (median of 9 treatment regimens; range, 5–19) and summarize the safety, efficacy, and potential impact of brentuximab vedotin on the unique post-allogeneic stem cell transplantation immunologic milieu.	Overall and complete response rates were 50% and 38%, respectively, among 24 evaluable patients. Median time to response was 8.1 weeks, median PFS was 7.8 months, and the median OS was not reached. Cough, fatigue, and pyrexia (52% each), nausea and peripheral sensory neuropathy (48% each), and dyspnea (40%) were the most frequent adverse events. The most common adverse events ≥grade 3 were neutropenia (24%), anemia (20%), thrombocytopenia (16%), and hyperglycemia (12%). Cytomegalovirus was detected in 5 patients (potentially clinically significant in 1).	2

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28. 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 HL.	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 2/33 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
29. Biswas T, Culakova E, Friedberg JW, et al. Involved field radiation therapy following high dose chemotherapy and autologous stem cell transplant benefits local control and survival in refractory or recurrent Hodgkin lymphoma. *Radiother Oncol.* 2012;103(3):367-372.	Observational-Tx	62 patients	To evaluate IFRT following ASCT and patterns of recurrence, OS, and disease specific survival.	Median follow-up was 2.3 years (range 0.03–11.56). Estimated 3-year OS (P=0.05) and disease specific survival (P=0.08) were 69.6% and 82.1% with IFRT and 40% and 57.6% without IFRT on univariate analysis. B-symptoms were adverse on univariate (P=0.007) and multivariate (P=0.01) analysis. HL patients who received IFRT following ASCT had improved local control in areas of previously recurrent disease (P=0.03).	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
30. Wendland MM, Asch JD, Pulsipher MA, Thomson JW, Shrieve DC, Gaffney DK. The impact of involved field radiation therapy for patients receiving high-dose chemotherapy followed by hematopoietic progenitor cell transplant for the treatment of relapsed or refractory Hodgkin disease. *Am J Clin Oncol.* 2006;29(2):189-195.	Observational-Tx	65 patients	To determine if IFRT in this setting improves patient outcomes.	38 patients were alive at the time of analysis with a median follow-up of 3.4 years in the no IFRT group and 1.8 years in the IFRT group (P=0.38). IFRT patients were more likely to have bulky disease at initial diagnosis (P=0.05). PFS was similar in the 2 groups (P=0.83). 22 patients in the no IFRT group and 5 in the IFRT group have died (P=0.06). 5-year OS rates were 55.6% for the no IFRT group and 73.3% for the IFRT group (P=0.16). There was no significant difference between the treatment groups regarding mortality in the first 100 days after hematopoietic progenitor cell transplant (P=0.41), late events (P=0.26), or failure in sites previously involved with disease (P=0.76).	2

Recurrent Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
31. Specht L, Yahalom J, Illidge T, et al. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group (ILROG). *Int J Radiat Oncol Biol Phys.* 2014;89(4):854-862.	Review/Other-Tx	N/A	To address the use of RT in HL in the modern era of combined modality therapy.	The role of reduced volumes and doses is addressed, integrating modern imaging with 3D planning and advanced techniques of treatment delivery. The previously applied extended field RT and original IFRT, which treated larger volumes based on nodal stations, have now been replaced by the use of limited volumes, based solely on detectable nodal (and extranodal extension) involvement at presentation, using contrast-enhanced CT, PET/CT, magnetic resonance imaging, or a combination of these techniques. The International Commission on Radiation Units and Measurements concepts of gross tumor volume, clinical target volume, internal target volume, and planning target volume are used for defining the targeted volumes. Newer treatment techniques, including intensity-modulated RT, breath-hold, image guided RT, and 4D imaging, should be implemented when their use is expected to decrease significantly the risk for normal tissue damage while still achieving the primary goal of local tumor control. 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 combined modality therapy. 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

Recurrent Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
32. Gentzler RD, Evens AM, Rademaker AW, et al. F-18 FDG-PET predicts outcomes for patients receiving total lymphoid irradiation and autologous blood stem-cell transplantation for relapsed and refractory Hodgkin lymphoma. *Br J Haematol.* 2014;165(6):793-800.	Observational-Tx	51 patients	To report outcomes for patients with relapsed/refractory HL who received total lymphoid irradiation followed by high-dose chemotherapy and autologous hematopoietic stem cell transplant.	Of 51 patients treated with total lymphoid irradiation and autologous hematopoietic stem cell transplant, 59% had primary refractory disease and 63% had active disease at autologous hematopoietic stem cell transplant. The 10-year PFS and OS for all patients was 56% and 54%, respectively. Patients with complete response by PET prior to autologous hematopoietic stem cell transplant had a 5-year PFS and OS of 85% and 100% compared to 52% and 48% for those without complete response (*P*=0.09 and *P*=0.007, respectively).	2
33. Brice P, Divine M, Simon D, et al. Feasibility of tandem autologous stem-cell transplantation (ASCT) in induction failure or very unfavorable (UF) relapse from Hodgkin's disease (HD). SFGM/GELA Study Group. *Ann Oncol.* 1999;10(12):1485-1488.	Experimental-Tx	43 patients	To evaluate a tandem ASCT in terms of toxicity and efficacy in unfavorable patients.	Hematologic recovery was normal after ASCT1 but delayed platelet recovery was observed after ASCT2 with busulfan in the conditioning regimen. Two grade 4 venoocclusive disease with 1 fatal occurred with busulfan at 16 mg/kg and 1 hemorrhagic cystic, no further grade 4 toxicity was observed with the reduced doses of busulfan (12 mg/kg). After ASCT2, 83% of these unfavorable patients were in remission and 20% relapsed within the first year. On an intent-to-treat analysis, 22/43 patients are in continuous complete response (including 8 patients with induction failure). For the whole population (n = 43) and for patients receiving the 2 ASCT (n = 32), the 2-year survival from the date of progression were respectively at 65% and at 74%.	1
34. Herbst C, Rehan FA, Skoetz N, et al. Chemotherapy alone versus chemotherapy plus radiotherapy for early stage Hodgkin lymphoma. *Cochrane Database Syst Rev.* 2011(2):CD007110.	Meta-analysis	1,245 patients; 5 randomized controlled trials studies	To perform a systematic review with meta-analysis of randomized controlled trials comparing chemotherapy alone with combined-modality therapy in patients with early stage HL with respect to response rate, PFS (alternatively tumor control) and OS.	5 randomized controlled trials involving 1,245 patients were included. The hazard ratio was 0.41 (95% CI, 0.25 to 0.66) for tumor control and 0.40 (95% CI, 0.27 to 0.61) for OS for patients receiving combined-modality therapy compared to chemotherapy alone. Complete response 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.	M

Recurrent Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
35. Sher DJ, Mauch PM, Van Den Abbeele A, LaCasce AS, Czerminski J, Ng AK. Prognostic significance of mid- and post-ABVD PET imaging in Hodgkin's lymphoma: the importance of involved-field radiotherapy. *Ann Oncol.* 2009;20(11):1848-1853.	Observational-Tx	73 patients	To report the failure-free outcomes of patients with and without postchemotherapy PET positivity treated with consolidative RT, and we also discuss the implications of midtreatment PET positivity in the context of routine postchemotherapy radiation treatment.	73 patients were included in this study. 20 patients (out of 46) were PET positive on interim PET, and 13 patients (out of 73) were PET positive at the conclusion of chemotherapy. At a median follow-up of 3.4 years for surviving patients, the 2-year failure-free survivals for patients PET-negative vs PET-positive disease after ABVD were 95% and 69%, respectively ($P<0.01$). On bivariable Cox regression, post-ABVD positivity (hazard ratio 4.8, $P=0.05$) was predictive of disease recurrence after controlling for bulky disease. Of the 20 patients with interim PET positivity, 3 recurred, with a 2-year failure-free survival of 85%. Among the 13 patients with interim PET positivity, but became PET negative at the completion of CT, the 2-year failure-free survival was 92%.	2
36. Aleman BM, Raemaekers JM, Tirelli U, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. *N Engl J Med.* 2003;348(24):2396-2406.	Experimental-Tx	739 patients	To determine whether RT reduces the relapse rate among patients with stage III or IV HL who have a complete remission after 6 to 8 cycles of MOPP-ABV hybrid chemotherapy (considered the standard chemotherapy at the time the trial was designed).	Of 739 patients, 421 had a complete remission; 161 of these patients were assigned to no further treatment and 172 to IFRT. The median follow-up was 79 months. The 5-year EFS rate was 84% in the group that did not receive RT and 79% in the group that received IFRT ($P=0.35$). The 5-year OS rates were 91% and 85%, respectively ($P=0.07$). Among the 250 patients in partial remission after chemotherapy, the 5-year event-free and OS rates were 79% and 87%, respectively.	1

Recurrent Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
37. 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. Freedom from treatment failure was sequentially noninferior for the 6xB(esc) and 8xB(14) groups as compared with 8xB(esc). 5-year freedom from treatment failure 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
38. Horwich A, Specht L, Ashley S. Survival analysis of patients with clinical stages I or II Hodgkin's disease who have relapsed after initial treatment with radiotherapy alone. *Eur J Cancer.* 1997;33(6):848-853.	Observational-Tx	1,364 patients; 473 relapsed	To analyze patients registered in the IDHD Database with clinical stages I or II HL who were not staged with laparotomy and whose initial treatment was with RT alone with the aim of defining the presentation variables that might indicate the probability of successful treatment of patients relapsing after initial RT.	A total of 1,364 patients with clinical stage I or II HL were treated with initial RT, of whom 473 relapsed. The probability of survival 10 years after relapse was 63%. For cause-specific survival, both multivariate and univariate analysis identified the importance of age at presentation and histological subtypes. When all causes of death were considered, the multivariate analysis identified age as the only significant factor. The length of initial disease-free interval had no influence on prognosis after relapse, but the 169 patients with nodal relapse had a higher cause-specific survival than those with an extranodal component of relapse (74% vs 51% at 10 years, $P<0.005$).	2

Recurrent Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
39. Tubiana M, Henry-Amar M, Carde P, et al. Toward comprehensive management tailored to prognostic factors of patients with clinical stages I and II in Hodgkin's disease. The EORTC Lymphoma Group controlled clinical trials: 1964-1987. *Blood.* 1989;73(1):47-56.	Observational-Tx	1,579 patients	To discuss the management strategy of the results obtained from 4 controlled trials conducted by the EORTC Lymphoma Group.	At a 4-year follow-up, no difference in survival was evidenced. In patients with unfavorable prognostic indicators, 3 MOPP-RT-3 MOPP were compared with 3 ABVD-RT-3 ABVD. From H1 to H5 trials, the proportion of patients having received chemotherapy during the course of the disease gradually decreased; the data suggest that a further reduction in the proportion of patients aggressively treated is conceptually possible. On the basis of the prognostic factors identified, one can delineate 3 subsets of patients and modulate toxic cost of the initial treatment according to the characteristics of these subsets. In the most favorable subgroup, RT alone produces high survival and chemotherapy is not justified.	2
40. Ng AK, Li S, Neuberg D, et al. Long-term results of a prospective trial of mantle irradiation alone for early-stage Hodgkin's disease. *Ann Oncol.* 2006;17(11):1693-1697.	Experimental-Tx	87 patients	To determine the long-term treatment outcome and late effects of mantle irradiation alone in selected patients with early-stage HL.	The median follow-up was 107 months (range 23–192). 13/87 patients (15%) relapsed at a median of 30 months (range 5-62). The 5- and 10-year actuarial freedom from treatment failure rates were 86% and 84.7%, respectively. All 13 patients who relapsed are alive without evidence of disease at a median of 84 months (range 30–156) post-salvage therapy. 5 patients developed a second malignancy at a median of 93 months (range 27–131). The 10-year actuarial risk of a second malignancy was 4.5%. There have been 2 deaths to date, both due to second malignancies. The 10-year OS rate was 98.2%.	1

Recurrent Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
41. Liao Z, Ha CS, Vlachaki MT, et al. Mantle irradiation alone for pathologic stage I and II Hodgkin's disease: long-term follow-up and patterns of failure. *Int J Radiat Oncol Biol Phys.* 2001;50(4):971-977.	Observational-Tx	145 patients	To determine the long-term outcome, patterns of failure, and prognostic factors for patients with pathologic stage I or II HL who were treated with mantle irradiation alone.	The median patient age was 27 years (range 10–66), with almost even male to female distribution. Every patient had splenectomy and negative laparotomy. 51 patients had stage I disease (IA-49, IB-2) and 94 stage II (IIA-89, IIB-5). The histologic subtypes were nodular sclerosing in 110, mixed cellularity in 28, lymphocyte predominance in 5, lymphocyte depleted in 1, and unclassified in 1. 12 patients with stage II disease had ≥3 sites of nodal involvement. 54 patients had a prognostic score of 0, 70 of 1, and 21 of 2. The median follow-up time for the 109 surviving patients was 146 months (range 25–381). The 10- and 20-year actuarial OS rates for the whole group were 87.6% and 65.3%, respectively. The corresponding actuarial PFS rates were 75.3% and 74.2%, respectively. 36 patients (9 stage I, 27 stage II) had relapses in a total of 41 sites. Failures by histology were 29 patients with nodular sclerosing, 6 with mixed cellularity, and 1 with lymphocyte predominance. Failures by sites were: trans-diaphragmatic, 22 (para-aortic nodes, 15; as the only site of progression in 12; visceral, 7; as the only site of progression in 5); within radiation field, 8; marginal miss, 8 (as the only site of failure in 2); and unknown, 3. The majority of the failures occurred within 5 years of diagnosis. Long-term side effects of radiation included cardiac complications in 30 patients, with 10- and 20-year actuarial cardiac complication rates of 12.6% and 35.1%, respectively; secondary solid tumors in 14, with 10- and 20-year actuarial rates of 2.3% and 25.7%, respectively; leukemia in 4; non-HL in 4, with the 10- and 20-year actuarial rates for leukemia and non-HL of 4.0% and 13.9%; and hypothyroidism in 38. Four adverse prognostic factors were identified for PFS: age ≥40 years, ≥3 sites of involvement, male sex, and constitutional symptoms.	2

Recurrent Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
42. Brice P. Managing relapsed and refractory Hodgkin lymphoma. *Br J Haematol.* 2008;141(1):3-13.	Review/Other-Tx	N/A	To identify prognostic factors at relapse and guidelines for treatment in relapsed HL.	Patients with relapsed HL should be identified according to their prognostic factors at relapse (duration of remission and extranodal disease or stage). This enables relapsing patients to be separated in to 3 different prognostic groups; primary refractory patients should be included in the unfavorable group because of their poor prognosis. All relapsed HL should receive second-line chemotherapy and the response to this chemotherapy is crucial for the outcome. Benefit of ASCT has been shown in a large randomized study and, although is often proposed in relapsed HL, it may be not necessary in the rare group of patients with stage I/II and late relapse who can receive additional RT after response to chemotherapy. Patients with intermediate and unfavorable relapse should receive HDCT and ASCT when chemosensitive; the first goal is to achieve this chemosensitivity. For patients in the unfavorable group, including refractory patients, the role of tandem HDCT or ASCT will be discussed and should be proposed for patients not in complete remission at the time of HDCT.	4
43. 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 RT 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

Recurrent Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
44. Canellos GP, Abramson JS, Fisher DC, LaCasce AS. Treatment of favorable, limited-stage Hodgkin's lymphoma with chemotherapy without consolidation by radiation therapy. *J Clin Oncol.* 2010;28(9):1611-1615.	Observational-Tx	71 patients	To examine the impact of chemotherapy alone in treatment of limited-stage, nonbulky HL, RT eliminated from primary treatment.	All patients achieved a clinical complete response or complete response unconfirmed. After a median follow-up of at least 60 months (range, at least 12 to at least 204 months), 6 patients experienced relapse at 6, 10, 11, 16, 20, and 58 months. All relapses occurred at site of presenting disease. No patients have died. Salvage therapy was successful with second-line chemotherapy/radiation and ASCT.	3
45. Josting A, Nogova L, Franklin J, et al. Salvage radiotherapy in patients with relapsed and refractory Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Lymphoma Study Group. *J Clin Oncol.* 2005;23(7):1522-1529.	Observational-Tx	100 patients	To evaluate treatment outcome and prognostic factors in patients with refractory or first relapsed HL) treated with salvage RT alone.	The volume irradiated was mantle field in 43% of patients, inverted-Y in 8%, total nodal irradiation in 12%, and involved-field in 37%. The median salvage RT dose was 40 Gy (range, 15 to 50 Gy). 77 patients achieved a complete remission and 4 patients achieved a partial remission. The 5-year freedom from treatment failure and OS rates were 28% and 51%, respectively. In multivariate analysis, significant prognostic factors for OS were B symptoms (P=.018) and stage at relapse (P=.014). For FF2F Karnofsky performance status (P=.0001) was significant. In patients with limited stage at progression/relapse, duration of first remission was significant (P=.04) for FF2F.	2

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

CBV = Cyclophosphamide, carmustine, and etoposide

CI = Confidence interval

CT = Computed tomography

DFS = Disease-free survival

EFS = Event-free survival

ESHAP = Etoposide, methyl prednisolone, cisplatin and cytarabine

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

FF2F = Freedom from second failure

GDP = Gemcitabine, dexamethasone, and cisplatin

HDCT = High-dose chemotherapy

HL = Hodgkin lymphoma

IFRT = Involved field radiation therapy

mini-BEAM = Carmustine, etoposide, cytarabine, and melphalan

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

OS = Overall survival

PFS = Progression-free survival

RR = Relative risk

RT = Radiation therapy