Hodgkin Lymphoma-Favorable Prognosis Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. 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
2. Cosset JM, Henry-Amar M, Meerwaldt JH, et al. The EORTC trials for limited stage Hodgkin's disease. The EORTC Lymphoma Cooperative Group. *Eur J Cancer.* 1992;28A(11):1847-1850.	Review/Other-Tx	4 studies	To review the results of 4 controlled studies conducted by the Lymphoma Group of the EORTC (European Organisation for Research and Treatment of Cancer) from 1964 to 1988 for stages I and II HD. The authors also presented in detail the designs of the on-going H7 randomized trials for these same subsets of HD patients.	Long-term survival rates, superior or close to 90%, are at hand for most of the patients presenting with clinical stage I-II supradiaphragmatic HD.	4
3. 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 from 27 hospitals	To discuss the management strategy in the light 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, 1 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

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
4. Farah R, Ultmann J, Griem M, et al. Extended mantle radiation therapy for pathologic stage I and II Hodgkin's disease. *J Clin Oncol.* 1988;6(6):1047-1052.	Observational-Tx	135 patients	To analyze the relapse-free and OS, to study the acute and late complications, and to compare these data with survival and complications from other centers.	Actuarial OS was 96% and 83% at 5 and 10 years, respectively. Acute complications were evaluated in 112 patients available for analysis. Severe nausea and vomiting occurred in 13%, weight loss of >10% of body weight in 19%, and acute hematologic toxicity in 4% of patients. Bone marrow suppression was transient and did not interfere with subsequent delivery of salvage treatment with either chemotherapy or RT in 22 patients who relapsed. The cost of extended mantle RT is 40% lower than the cost of treatment with mantle and para-aorta fields. The median treatment time was 38 days, 33% less than the 56 days for mantle and para-aorta fields assuming no interruptions.	2
5. 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 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 greater than or equal to 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

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
6. Mauch P, Tarbell N, Weinstein H, et al. Stage IA and IIA supradiaphragmatic Hodgkin's disease: prognostic factors in surgically staged patients treated with mantle and paraaortic irradiation. *J Clin Oncol.* 1988;6(10):1576-1583.	Observational-Tx	315 patients	To evaluate patients with surgically staged IA and IIA HD treated with mantle and para-aortic RT.	The 14-year actuarial freedom-from-first relapse and survival were 82% and 93%, respectively, with a median follow-up time of 9 years. Mediastinal size was the only factor that predicted for a lower freedom-from-first relapse, $P<0.001$. 49 patients have developed recurrent HD. 36 patients are disease-free following retreatment and only 13 patients have died of HD. Patients with mixed cellularity histology were more likely to relapse below the diaphragm (11%) as compared with patients with nodular sclerosis (5.1%) or lymphocyte predominant (3.6%) histology. These relapses were often associated with bulky pelvic nodal adenopathy and salvage treatment with chemotherapy alone often failed to control recurrent disease. Alternative diagnostic and therapeutic recommendations are presented for these patients. Thyroid abnormalities represented the most common long-term complication with an actuarial risk at 16 years of 37%.	2
7. Abrahamsen JF, Andersen A, Hannisdal E, et al. Second malignancies after treatment of Hodgkin's disease: the influence of treatment, follow-up time, and age. *J Clin Oncol.* 1993;11(2):255-261.	Observational-Tx	1,152 patients	To evaluate the data concerning HD and SC from Norwegian Radium Hospital and compare the findings with those of other centers.	68 patients had developed a SC, including 9 acute nonlymphocytic leukemia's, 8 non-HLs, and 51 solid tumors, including 11 lung cancers. The RR of SC and leukemia was 1.86 (95% CI, 1.4 to 2.4) and 24.3 (95% CI, 11.1 to 46.2), respectively. The RR of SC was highest in younger patients (<41 years, RR = 3.8). No significant association between splenectomy and development of acute nonlymphocytic leukemia was found. The influence of treatment and follow-up time on the development of SC agrees with data from other large cancer institutions.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
8. De Bruin ML, Dorresteijn LD, van't Veer MB, et al. Increased risk of stroke and transient ischemic attack in 5-year survivors of Hodgkin lymphoma. *J Natl Cancer Inst.* 2009;101(13):928-937.	Observational-Tx	2,201 patients	Retrospective cohort study to quantify the long-term risk of cerebrovascular disease associated with the use of RT and chemotherapy in survivors of HL.	After a median follow-up of 17.5 years, 96 patients developed cerebrovascular disease (55 strokes, 31 transient ischemic attacks, and 10 with both transient ischemic attack and stroke; median age = 52 years). Most ischemic events were from large-artery atherosclerosis (36%) or cardioembolisms (24%). The standardized incidence ratio for stroke was 2.2 (95% CI = 1.7 to 2.8), and for transient ischemic attack, it was 3.1 (95% CI = 2.2 to 4.2). The risks remained elevated, compared with those in the general population, after prolonged follow-up. The cumulative incidence of ischemic stroke or transient ischemic attack 30 years after HL treatment was 7% (95% CI = 5% to 8%). Radiation to the neck and mediastinum was an independent risk factor for ischemic cerebrovascular disease (HR = 2.5, 95% CI = 1.1 to 5.6 vs without RT). Treatment with chemotherapy was not associated with an increased risk. Hypertension, diabetes mellitus, and hypercholesterolemia were associated with the occurrence of ischemic cerebrovascular disease, whereas smoking and overweight were not.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
9. Dores GM, Metayer C, Curtis RE, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. *J Clin Oncol.* 2002;20(16):3484-3494.	Observational-Tx	32,591 HD patients	To quantify the relative and absolute excess risks of site-specific SC, in particular solid tumors, among long-term survivors of HD and to assess risks according to age at HD diagnosis, attained age, and time since initial treatment.	2,153 SC (observed-to-expected ratio = 2.3; 95% CI, 2.2 to 2.4), including 1,726 solid tumors (observed-to-expected ratio = 2.0; 95% CI, 1.9 to 2.0) were reported. Cancers of the lung (observed = 377; observed-to-expected ratio = 2.9), digestive tract (observed = 376; observed-to-expected ratio = 1.7), and female breast (observed = 234; observed-to-expected ratio = 2.0) accounted for the largest number of subsequent malignancies. 25-years after HD diagnosis, the actuarial risk of developing a solid tumor was 21.9%. The RR of solid neoplasms decreased with increasing age at HD diagnosis, however, patients aged 51 to 60 years at HD diagnosis sustained the highest cancer burden (absolute excess risks = 79.2/10,000 patients/year). After a progressive rise in RR and absolute excess risks of all solid tumors over time, there was an apparent downturn in risk at 25 years. Temporal trends and treatment group distribution for cancers of the esophagus, stomach, rectum, female breast, bladder, thyroid, and bone/connective tissue were suggestive of a radiogenic effect.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
10. Mauch PM, Kalish LA, Marcus KC, et al. Long-term survival in Hodgkin's disease relative impact of mortality, second tumors, infection, and cardiovascular disease. *Cancer J Sci Am.* 1995;1(1):33-42.	Observational-Tx	794 patients	To determine the causes of death in a group of patients with pathologically staged and intensively treated HD who were followed for long intervals.	Of 124 patients who died, 56 died of HD, 36 of second malignant neoplasms, 15 of cardiac causes, 9 of infection, and 8 of miscellaneous causes. The 20-year actuarial survival rate for all patients in this study is 73%. Age 40 years or older, mixed cellularity/lymphocyte-depleted histologic type, and stage-III disease were adverse independent predictors of survival. The largest differences were seen by age. The 20-year actuarial rates of survival were 78%, 78%, and 46%, respectively, for patients aged 16 or less, 17 to 39, and 40 years or older at diagnosis. HD diagnosed at age 40 or older was a significant risk factor for all causes of death. The use of combined chemotherapy/RT was a significant risk factor for second tumor and infection-related mortality. The excess risk of death from all causes, including HD, remained constant with time from treatment and was approximately 1.2% per year over the first 20 years. Deaths from HD decreased with time from treatment, with no patients dying after 15 years. This decrease, combined with an increased excess mortality risk with time from other causes, especially second tumors, accounted for the constant excess mortality with time after HD.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
11. 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 RR of mortality from all causes other than HD, second tumors, and cardiac disease remained significantly elevated more than 20 years after treatment.	2
12. Ng AK, Bernardo MV, Weller E, et al. Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: long-term risks and risk factors. *Blood.* 2002;100(6):1989-1996.	Observational-Tx	1,319 patients	To determine the risk of second malignancy after HL treated with RT with or without chemotherapy.	Among 1,319 patients with clinical stage I-IV HD, 181 second malignancies and 18 third malignancies were observed. With a median follow-up of 12 years, the RR and absolute excess risk of second malignancy were 4.6 and 89.3/10,000 person-years. The RR was significantly higher with combined chemotherapy and RT (6.1) than with RT alone (4.0, P=.015). The risk increased with increasing radiation field size (P=.03) in patients who received CMT, and with time after HD. After 15 and 20 years, there was a 2.3% and 4.0% excess risk of second malignancy per person per year. The 5-year survival after development of a second malignancy was 38.1%, with the worst prognosis seen after acute leukemia and lung cancer. The excess risk of second malignancy after HD continues to be increased after 15 to 20 years, and there does not appear to be a plateau.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
13. Swerdlow AJ, Barber JA, Hudson GV, et al. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. *J Clin Oncol.* 2000;18(3):498-509.	Observational-Tx	5,519 patients	To assess the long-term risk of second malignancy after HL therapy and risk factors for individual malignancies.	322 second malignancies occurred. RRs of gastrointestinal, lung, breast, and bone and soft tissue cancers, and of leukemia, increased significantly with younger age at first treatment. Absolute excess risks and cumulative risks of solid cancers and leukemia, however, were greater at older ages than at younger ages. Gastrointestinal cancer risk was greatest after mixed-modality treatment (RR = 3.3; 95% CI, 2.1 to 4.8); lung cancer risks were significantly increased after chemotherapy (RR = 3. 3; 95% CI, 2.4 to 4.7), mixed-modality treatment (RR = 4.3; 95% CI, 2.9 to 6.2), and RT (RR = 2.9; 95% CI, 1.9 to 4.1); breast cancer risk was increased only after RT without chemotherapy (RR = 2.5; 95% CI, 1.4 to 4.0); and leukemia risk was significantly increased after chemotherapy (RR = 31.6; 95% CI, 19.7 to 47.6) and mixed-modality treatment (RR = 38.1; 95% CI, 24.6 to 55. 9). These risks were generally greater after treatment at younger ages: for patients treated at ages younger than 25 years, there were RRs of 18.7 (95% CI, 5.8 to 43.5) for gastrointestinal cancer after mixed-modality treatment, 14.4 (95% CI, 5.7 to 29.3) for breast cancer after RT, and 85.2 (95% CI, 45.3 to 145.7) for leukemia after chemotherapy (with or without RT).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
14. Swerdlow AJ, Higgins CD, Smith P, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. *J Natl Cancer Inst.* 2007;99(3):206-214.	Observational-Tx	7,033 HD patients	A cohort of HD patients who were treated in Britain from November 1, 1967, through September 30, 2000, were followed and their risk of myocardial infarction mortality was compared with that in the general population of England and Wales.	A total of 166 deaths from myocardial infarction occurred in the cohort, statistically significantly more than expected (SMR = 2.5, 95% CI = 2.1 to 2.9), with an absolute excess risk of 125.8 per 100,000 person-years. SMRs decreased sharply with older age at first treatment, but absolute excess risks of death from myocardial infarction increased with older age up to age 65 years at first treatment. The statistically significantly increased risk of myocardial infarction mortality persisted through to 25 years after first treatment. Risks were increased statistically significantly and independently for patients who had been treated with supradiaphragmatic RT, anthracyclines, or vincristine. Risk was particularly high for patients treated with the ABVD regimen (SMR = 9.5, 95% CI = 3.5 to 20.6). Risk at 20 or more years after first treatment was particularly great for patients who had received supradiaphragmatic RT and vincristine without anthracyclines (SMR = 14.8, 95% CI = 4.8 to 34.5).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
15. van Leeuwen FE, Klokman WJ, Veer MB, et al. Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. *J Clin Oncol.* 2000;18(3):487-497.	Observational-Tx	1,253 patients	To quantify the long-term risk of SCs in patients diagnosed with HD during adolescence or young adulthood.	In all, 137 patients developed SCs, compared with 19.4 cases expected on the basis of incidence rates in the general population (RR = 7.0; 95% CI, 5.9 to 8.3). The 25-year actuarial risk of SC overall was 27.7%. The RR of solid tumors increased greatly with younger age at the first treatment of HD, not only for breast cancer but also for all other solid tumors, with RRs of 4.9, 6.9, and 12.7 for patients first treated at ages 31 to 39 years, 21 to 30 years, and ≤20 years, respectively. Among patients first treated at the age of 20 years or younger, the RR of developing a solid tumor before the age of 40 years was significantly greater than the RR of solid tumor development at ages 40 to 49 years (RR = 27.9 vs RR = 4.2; *P*=.0001). Patients who received salvage chemotherapy had significantly greater risk of solid cancers other than breast cancer than did patients whose treatment was restricted to initial RT or initial CMT (RR = 9.4 and 4.7, respectively; *P*=.004).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
16. Engert A, Franklin J, Eich HT, et al. Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: final results of the GHSG HD7 trial. *J Clin Oncol.* 2007;25(23):3495-3502.	Experimental-Tx	650 patients	To investigate whether CMT with 2 cycles of ABVD followed by EFRT is superior to EFRT alone in patients with early favorable HL.	At a median observation time of 87 months, there was no difference between treatment arms in terms of complete response rate (arm A, 95%; arm B, 94%) and OS (at 7 years: arm A, 92%; arm B, 94%; P=.43). However, FFTF was significantly different, with 7-year rates of 67% in arm A (95% CI, 61% to 73%) and 88% in arm B (95% CI, 84% to 92%; P≤.0001). This was due mainly to significantly more relapses after EFRT only (arm A, 22%; arm B, 3%). No patient treated with CMT experienced relapse before year 3. Relapses were treated mainly with BEACOPP, or with the combination COPP/ABVD; treatment of relapse was significantly more successful in arm A than in arm B (P=.017). In total, there were 39 second malignancies, with 21 in arm A and 18 in arm B, respectively. The incidence was approximately 0.8% per year during years 2 to 9 and was highest in older patients (P<.0001) and those with "B" symptoms (P=.012).	1
17. Press OW, LeBlanc M, Lichter AS, et al. Phase III randomized intergroup trial of subtotal lymphoid irradiation versus doxorubicin, vinblastine, and subtotal lymphoid irradiation for stage IA to IIA Hodgkin's disease. *J Clin Oncol.* 2001;19(22):4238-4244.	Experimental-Tx	348 patients	To evaluate whether staging laparotomy could be safely avoided in early-stage HD and whether chemotherapy should be a part of the treatment of nonlaparotomy staged patients, a phase III intergroup trial was performed.	The study was closed at the second, planned, interim analysis because of a markedly superior failure-free survival rate for patients on the CMT arm (94%) compared with the STLI arm (81%). With a median follow-up of 3.3 years, 10 patients have experienced relapse or died on the chemoradiotherapy arm, compared with 34 on the RT arm (P<.001). Few deaths have occurred on either arm (3 deaths on CMT and 7 deaths on STLI). Treatment was well tolerated, with only 1 death on each arm attributed to treatment.	1

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18. 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 STNI 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
19. 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 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 STNI 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 6 cycles of MOPP/ABV plus IFRT, 88% after 4 cycles of MOPP/ABV plus IFRT, and 87% after 4 cycles of MOPP/ABV plus STNI. The 10-year OS estimates were 88%, 85%, and 84%, respectively.	1

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20. Carde P, Hagenbeek A, Hayat M, et al. Clinical staging versus laparotomy and combined modality with MOPP versus ABVD in early-stage Hodgkin's disease: the H6 twin randomized trials from the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Group. *J Clin Oncol.* 1993;11(11):2258-2272.	Experimental-Tx	H6F trial (n = 262); H6U trial (n = 316)	To compare (1) clinical staging and irradiation alone vs staging laparotomy and treatment adaptation in patients with a favorable prognosis (H6F); (2) two combined modalities in patients with an unfavorable prognosis (H6U).	In the H6F trial, 6-year FFP rates (78% vs 83%; *P*=.27) were similar in clinical and laparotomy staging's, respectively. Survival rates were 93% and 89%, due to laparotomy-related deaths. In the H6U trial, the ABVD arm had superior results (6-year FFP rate, 88% vs 76%; *P*=.01), but they were not significant for survival (91% vs 85%; *P*=.22). Chemotherapy discontinuation due to hematologic intolerance occurred more often with MOPP (14.5% vs 7.3%). Decrease of the pulmonary vital capacity (<70% of the theoretic value) was observed more frequently after ABVD than after MOPP (12% vs 2%; *P*=.08), with 2 lethal pulmonary insufficiencies occurring in the ABVD arm. No modification of the isotopic left ventricular ejection fraction occurred. Gonadal toxicity was less in the ABVD arm.	1
21. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med.* 1992;327(21):1478-1484.	Experimental-Tx	361 patients; 123 received MOPP, 123 received MOPP alternating with ABVD, and 115 received ABVD alone	To compare 3 regimens of primary systemic therapy for newly diagnosed advanced HD in stages IIIA2, IIIB, and IVA or IVB: (1) MOPP alone given for 6 to 8 cycles, (2) MOPP alternating with ABVD for 12 cycles, and (3) ABVD alone for 6 to 8 cycles.	The overall response rate was 93%, with complete responses in 77%: 67% in the MOPP group, 82% in the ABVD group, and 83% in the MOPP/ABVD group (*P*= 0.006 for the comparison of MOPP with the other 2 regimens, both of which contained doxorubicin). The rates of failure-free survival at 5 years were 50% for MOPP, 61% for ABVD, and 65% for MOPP/ABVD. Age, stage (III vs IV), and regimen influenced failure-free survival significantly. OS at 5 years was 66% for MOPP, 73% for ABVD, and 75% for MOPP/ABVD (*P*=0.28 for the comparison of MOPP with the doxorubicin regimens). MOPP had more severe toxic effects on bone marrow than ABVD and was associated with greater reductions in the prescribed dose.	1

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22. 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 freedom from second relapse was 69% at 5 years.	1
23. 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
24. 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.	Meta-analysis	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 RRs for complete response. 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. 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

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25. 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 STNI 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 STNI, 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 STNI arm, treatment-related morbidities were mild.	1
26. Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. *JAMA.* 2003;290(21):2831-2837.	Observational-Tx	415 consecutive patients	Retrospective study to identify and quantify the incidence of and factors contributing to long-term cardiovascular complications after RT for HL. Patients treated from 1962 to 1998 were compared with a matched general population.	42 patients (10.4%) developed coronary artery disease at a median of 9 years after treatment, 30 patients (7.4%) developed carotid and/or subclavian artery disease at a median of 17 years after treatment, and 25 patients (6.2%) developed clinically significant valvular dysfunction at a median of 22 years. The most common valve lesion was aortic stenosis, which occurred in 14 valves. The observed-to-expected ratio for valve surgery was 8.42 (95% CI, 3.20–13.65) and the observed-to-expected ratio for coronary artery bypass graft surgery or percutaneous coronary intervention was 1.63 (95% CI, 0.98–2.28). At least 1 cardiac risk factor was present in all patients who developed coronary artery disease. The only treatment-related factor associated with the development of coronary artery disease was utilization of a radiation technique that resulted in a higher total dose to a portion of the heart (RR, 7.8; 95% CI, 1.1–53.2; P=.04). No specific treatment-related factor was associated with carotid or subclavian artery disease or valvular dysfunction. Freedom from any cardiovascular morbidity was 88% at 15 years and 84% at 20 years.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
27. Inskip PD, Robison LL, Stovall M, et al. Radiation dose and breast cancer risk in the childhood cancer survivor study. *J Clin Oncol.* 2009;27(24):3901-3907.	Observational-Tx	120 patients and 464 controls	Case-control study in a cohort of 6,647 women was conducted to quantify the risk of breast cancer in relation to radiation dose and chemotherapy among survivors of childhood cancer.	The OR for breast cancer increased linearly with radiation dose, and it reached 11-fold for local breast doses of approximately 40 Gy relative to no radiation (P<.0001). Risk associated with breast irradiation was sharply reduced among women who received 5 Gy or more to the ovaries (P=.002). The excess OR per Gy was 0.36 for those who received ovarian doses <5 Gy and was 0.06 for those who received higher doses. Radiation-related risk did not vary significantly by age at exposure. Borderline significantly elevated risks were seen for doxorubicin, dactinomycin, dacarbazine, and carmustine.	2
28. Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. *J Natl Cancer Inst.* 2002;94(3):182-192.	Observational-Tx	222 patients and 444 controls	A population-based study to assess the risk of lung cancer after HL in relationship to treatment exposure and tobacco history.	Treatment with alkylating agents without RT was associated with increased lung cancer risk (RR = 4.2; 95% CI = 2.1 to 8.8), as was radiation dose of 5 Gy or more without alkylating agents (RR = 5.9; 95% CI = 2.7 to 13.5). Risk increased with both increasing number of cycles of alkylating agents and increasing radiation dose (P<.001). Among patients treated with MOPP, risk increased with cumulative amounts of mechlorethamine and procarbazine (P<.001) when evaluated separately. Statistically significantly elevated risks of lung cancer were apparent within 1–4 years after treatment with alkylating agents, whereas excess risk after RT began 5 years after treatment and persisted for more than 20 years. Risk after treatment with alkylating agents and RT together was as expected if individual excess risks were summed. Tobacco use increased lung cancer risk more than 20-fold; risks from smoking appeared to multiply risks from treatment.	2

Hodgkin Lymphoma-Favorable Prognosis Stage I and II
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
29. Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA.* 2003;290(4):465-475.	Observational-Tx	105 patients; 266 controls	Matched case-control study within a cohort of 3,817 females, 1-year survivors of HL diagnosed at age 30 years or younger. Purpose of study is to determine the long-term risk of breast cancer associated with use of RT and chemotherapy to treat young women with HL.	A radiation dose of 4 Gy or more delivered to the breast was associated with a 3.2-fold (95% CI, 1.4–8.2) increased risk, compared with the risk in patients who received lower doses and no alkylating agents. Risk increased to 8-fold (95% CI, 2.6–26.4) with a dose of more than 40 Gy (P<.001 for trend). Radiation risk did not vary appreciably by age at exposure or reproductive history. Increased risks persisted for 25 or more years following RT (RR 2.3; 95% CI, 0.5–16.5; P=.03 for trend with dose). Treatment with alkylating agents alone resulted in a reduced risk (RR, 0.6; 95% CI, 0.2–2.0) of breast cancer, and combined alkylating agents and RT in a 1.4-fold (95% CI, 0.6–3.5) increased risk. Risk of breast cancer decreased with increasing number of alkylating agent cycles (P=.003 for trend). Risk also was low (RR 0.4; 95% CI, 0.1–1.1) among women who received 5 Gy or more delivered to ovaries compared with those who received lower doses.	2
30. van den Belt-Dusebout AW, Aleman BM, Besseling G, et al. Roles of radiation dose and chemotherapy in the etiology of stomach cancer as a second malignancy. *Int J Radiat Oncol Biol Phys.* 2009;75(5):1420-1429.	Observational-Tx	42 patients with stomach cancer and 126 matched controls	To evaluate the roles of radiation dose, chemotherapy, and other factors in the etiology of stomach cancer in long-term survivors of testicular cancer or HL.	The risk of stomach cancer was 3.4-fold increase compared with the general population. The risk increased with increasing mean stomach dose (P<0.001 for trend), at an ERR of 0.84 per Gy (95% CI, 0.12–15.6). Mean stomach doses of more than 20 Gy were associated with a RR of 9.9 (95% CI, 3.2–31.2) compared with doses below 11 Gy. The risk was 1.8-fold (95% CI, 0.8–4.4) increased after chemotherapy and 5.4-fold (95% CI, 1.2–23.9) increased after high doses of procarbazine (≥13,000 mg) vs <10,000 mg. The RR of smoking more than 10 cigarettes per day vs no smoking was 1.6 (95% CI, 0.6–4.2).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
31. van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. *J Natl Cancer Inst.* 2003;95(13):971-980.	Observational-Tx	48 patients and 175 controls	Case-control study in The Netherlands in a cohort of 770 female patients who had been diagnosed with HL before age 41. Purpose of study is to investigate the effects of radiation dose, chemotherapy and reproductive factors on breast cancer risk after HL.	The risk of breast cancer increased statistically significantly with radiation dose (*P*=.01 for trend); patients who received 38.5 Gy or more had an RR of 4.5 (95% CI = 1.3 to 16) times that of patients who received less than 4 Gy. Patients who received both chemotherapy and RT had a statistically significantly lower risk than those treated with RT alone (RR = 0.45, 95% CI = 0.22 to 0.91). Breast cancer risk increased with increasing radiation dose among patients who received RT only (RR = 12.7, 95% CI = 1.8 to 86, for patients receiving ≥38.5 Gy) but not among patients treated with chemotherapy and RT. 69% of control subjects treated with RT and more than 6 cycles of chemotherapy, but only 9% of those who received RT alone, reached menopause before age 41. Reaching menopause before age 36 was associated with a strongly reduced risk of breast cancer (RR = 0.06, 95% CI = 0.01 to 0.45).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
32. Franklin J, Pluetschow A, Paus M, et al. Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trials. *Ann Oncol.* 2006;17(12):1749-1760.	Meta-analysis	RT vs combined chemotherapy (15 trials - 3,343 patients); chemotherapy vs combined chemotherapy (16 trials - 2,861 patients); IFRT vs EFRT (10 trials, 3,221 patients)	Meta-analysis of randomized trials comparing RT alone vs combined chemotherapy, chemotherapy alone vs combined chemotherapy, RT alone vs chemotherapy alone or IFRT vs EFRT alone for untreated HL.	Data for between 53% and 69% of patients were obtained for the 4 comparisons. (i) RT vs chemoradiotherapy (15 trials, 3,343 patients): SMR were lower with chemoradiotherapy than with RT as initial treatment (OR = 0.78, 95% CI = 0.62–0.98 and *P*=0.03). (ii) CT vs chemoradiotherapy (16 trials, 2,861 patients): SMRs were marginally higher with chemoradiotherapy than with chemotherapy as initial treatment (OR = 1.38, CI 1.00–1.89 and *P*=0.05). (iii) IFRT vs EFRT (19 trials, 3,221 patients): no significant difference in SMR (*P*=0.28) although more breast cancers occurred with EFRT (*P*=0.04 and OR = 3.25). Administration of chemotherapy alone in addition to RT alone as initial therapy for HL decreases overall second malignancy risks by reducing relapse and need for salvage therapy. Administration of RT alone additional to chemotherapy alone, marginally increases overall second malignancy risks in advanced stages. Breast cancer risk (but not second malignancy risks in general) was substantially higher after EFRT.	M
33. Hodgson DC, Pintilie M, Gitterman L, et al. Fertility among female hodgkin lymphoma survivors attempting pregnancy following ABVD chemotherapy. *Hematol Oncol.* 2007;25(1):11-15.	Observational-Tx	36 HL survivors; 29 controls	To determine the pregnancy rate among female HL survivors attempting pregnancy following ABVD chemotherapy. Cox proportional hazards models were constructed to compare the pregnancy rate among HL survivors to that reported by friend or sibling controls.	The median time to pregnancy among both HL survivors and controls was 2.0 months. The 12-month pregnancy rates were 70% and 75%, respectively. The fertility ratio for HL survivors vs controls was 0.94 (95%; CI = 0.53–1.66; *P*=0.84) after adjusting for age and frequency of intercourse. Female HL patients who had survived without recurrence ≥3 years and who had attempted pregnancy after ABVD did not experience significant sub-fertility.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
34. Koontz MZ, Horning SJ, Balise R, et al. Risk of therapy-related secondary leukemia in Hodgkin lymphoma: the Stanford University experience over three generations of clinical trials. *J Clin Oncol.* 2013;31(5):592-598.	Observational-Tx	754 patients	To assess therapy-related acute myeloid leukemia/myelodysplastic syndromerisk in patients treated for HL on successive generations of Stanford clinical trials.	754 patients treated from 1974 to 2003 were identified. Therapy varied across studies. RT evolved from extended fields (S and C studies) to involved fields (G studies). Primary chemotherapy was MOPP or procarbazine, mechlorethamine, and vinblastine in S studies; MOPP, procarbazine, mechlorethamine, and vinblastine, vinblastine, bleomycin, and methotrexate, or ABVD in C studies; and vinblastine, bleomycin, and methotrexate (reduced dose of bleomycin compared with vinblastine, bleomycin, and methotrexate) or mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, and prednisone in G studies. Cumulative exposure to alkylating agent was notably lower in the G studies compared with the S and C studies, with a 75% to 83% lower dose of nitrogen mustard in addition to omission of procarbazine and melphalan. 24 (3.2%) of 754 patients developed therapy-related acute myeloid leukemia/myelodysplastic syndrome, 15 after primary chemotherapy and 9 after salvage chemotherapy for relapsed HL. The incidence of therapy-related acute myeloid leukemia/myelodysplastic syndrome was significantly lower in the G studies (0.3%) compared with the S (5.7%) or C (5.2%) studies ($P<.001$). Additionally, in the G studies, no therapy-related acute myeloid leukemia/myelodysplastic syndrome was noted after primary therapy, and the only patient who developed therapy-related acute myeloid leukemia/myelodysplastic syndrome did so after second-line therapy.	2

Hodgkin Lymphoma-Favorable Prognosis Stage I and II
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
35. 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 FFTF (*P*=0.39) or OS (*P*=0.61). At 5 years, the rates of FFTF 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 FFTF (*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
36. Behringer K, Goergen H, Hitz F, et al. Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin's lymphoma (GHSG HD13): an open-label, randomised, non-inferiority trial. *Lancet.* 2015;385(9976):1418-1427.	Experimental-Tx	1,502 patients	To investigate whether omission of either bleomycin or dacarbazine, or both, from ABVD reduced the efficacy of this regimen in treatment of HL.	Of 1,502 qualified patients, 566, 198, 571, and 167 were randomly assigned to receive ABVD, ABV, AVD, or AV, respectively. 5 year FFTF was 93.1%, 81.4%, 89.2%, and 77.1% with ABVD, ABV, AVD, and AV, respectively. Compared with ABVD, inferiority of the dacarbazine-deleted variants was detected with 5 year differences of -11.5% (95% CI, -18.3 to -4.7; HR 2.06 [1.21 to 3.52]) for ABV and -15.2% (-23.0 to -7.4; HR 2.57 [1.51 to 4.40]) for AV. Noninferiority of AVD compared with ABVD could also not be detected (5 year difference -3.9%, -7.7 to -0.1; HR 1.50, 1.00 to 2.26). 178 (33%) of 544 patients given ABVD had WHO grade III or IV toxicity, compared with 53 (28%) of 187 given ABV, 142 (26%) of 539 given AVD, and 40 (26%) of 151 given AV. Leucopenia was the most common event, and highest in the groups given bleomycin.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
37. Advani R, Horning SJ, Jonathan E, et al. Abbreviated 8-week chemotherapy (CT) plus involved node radiotherapy (INRT) for nonbulky stage I-II Hodgkin lymphoma: Preliminary results of the Stanford G5 Study. *ASCO Meeting Abstracts.* 2011;29(15_suppl):8064.	Experimental-Tx	43 patients	To test brief chemotherapy (Stanford V–C x 8 weeks) + 20 Gy INRT (G5 study) in order to further limit treatment risk in patients with non-bulky stage I-II HL.	At median follow-up of 4.8 years (0.8–9.6), the overall PFS and OS are 94.6% and 100%, respectively. For patients with unfavorable risk factors the PFS and OS are 88.5% and 100%, respectively. Therapy failed in 2 patients considered "unfavorable" by GHSG criteria with >2 nodal sites. The mean time to relapse was 23 months (16–30). One patient failed in RT field and the second in-field and distant. Both were salvaged with secondary therapy and stem cell support. No bleomycin lung toxicity or radiation pneumonitis have been noted and to date there have been no second malignancies, AML or cardiac events.	2
38. Noordijk EM, Thomas J, Ferme C, et al. First results of the EORTC-GELA H9 randomized trials: the 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). *ASCO Meeting Abstracts.* 2005;23(16S):561S.	Experimental-Tx	1,591 patients	Patients with stage I-II HL were enrolled into 2 trials based on 4 prognostic factors. The H9-F trial compared 36 Gy IFRT vs 20 Gy IFRT vs no RT in patients in complete remission 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 complete remission 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

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
39. 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 EFRT arm.	1
40. 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
41. Campbell BA, Voss N, Pickles T, et al. Involved-nodal radiation therapy as a component of combination therapy for limited-stage Hodgkin's lymphoma: a question of field size. *J Clin Oncol.* 2008;26(32):5170-5174.	Observational-Tx	325 patients	To determine the influence of field size on incidence and patterns of relapse in limited-stage HL treated with CMT and, in particular, to determine if further reduction in field size beyond IFRT, can be safely accomplished without risking an increase in marginal recurrences.	At diagnosis, median age was 35 years; 52% male; stage IA 29%; stage IIA 71%. 95% of patients received 2 chemotherapy cycles. The 3 RT groups were: EFRT, 39%; IFRT, 30%; and INRT ≤5 cm, 31%. Median follow-up of living patients was 80 months. Median time to relapse was 37 months. 12 relapses occurred: 4 after EFRT (3%); 5 after IFRT (5%); and 3 after INRT ≤5 cm (3%; P=.9). No marginal recurrences occurred after INRT ≤5 cm. Locoregional relapse occurred in 5 patients: 3 after EFRT; 2 with IFRT; and none with INRT ≤5 cm. At 5 years, PFS was 97%, and OS was 95%. At 10 years, PFS and OS were 95% and 90%, respectively.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
42. Maraldo MV, Aznar MC, Vogelius IR, Petersen PM, Specht L. Involved node radiation therapy: an effective alternative in early-stage hodgkin lymphoma. *Int J Radiat Oncol Biol Phys.* 2013;85(4):1057-1065.	Observational-Tx	97 patients	To present treatment outcome in a retrospective analysis using the INRT strategy in a cohort of clinical stage I-II HL patients.	The 4-year freedom from disease progression was 96.4% (95% CI: 92.4%–100.4%), median follow-up of 50 months (range: 4–71 months). Three relapses occurred: 2 within the previous radiation field and 1 in a previously uninvolved region. The 4-year OS was 94% (95% CI: 88.8%–99.1%), median follow-up of 58 months (range: 4–91 months). Early RT toxicity was limited to grade 1 (23.4%) and grade 2 (13.8%). During follow-up, 8 patients died, none from HL, 7 malignancies were diagnosed, and 5 patients developed heart disease.	2
43. Eich HT, Muller RP, Engenhart-Cabillic R, et al. Involved-node radiotherapy in early-stage Hodgkin's lymphoma. Definition and guidelines of the German Hodgkin Study Group (GHSG). *Strahlenther Onkol.* 2008;184(8):406-410.	Review/Other-Tx	N/A	Definition and guidelines on INRT in early-stage HL by the GHSG.	The clinical target volume encompasses the initial volume of the lymph node(s) before chemotherapy and incorporates the initial location and extent of the disease taking the displacement of the normal tissues into account. The margin of the planning target volume should be 2 cm in axial and 3 cm in craniocaudal direction. If necessary, it can be reduced to 1–1.5 cm. To minimize lung and cardiac toxicity, the target definition in the mediastinum is different.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
44. 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 CMT.	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

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
45. Fiandra C, Filippi AR, Catuzzo P, et al. Different IMRT solutions vs. 3D-conformal radiotherapy in early stage Hodgkin's Lymphoma: dosimetric comparison and clinical considerations. *Radiat Oncol.* 2012;7:186.	Observational-Tx	10 patients	To investigate the most appropriate planning solution, in terms of plan quality (target coverage and organs-at-risk sparing) and treatment efficiency.	Planning treatment volume coverage was reached for all plans (V95% ≥95%); highest mean conformity number was obtained with helical tomotherapy (0.77) and VMAT (0.76). B-VMAT showed intermediate conformity number mean values (0.67), while the lowest conformity number were obtained with tomodirect (0.30) and 3D-CRT techniques (0.30). A trend of inverse correlation between higher conformity number and larger healthy tissues volumes receiving low radiation doses was shown for lungs and breasts. For thyroid gland and heart/coronary ostia, helical tomotherapy, VMAT and B-VMAT techniques allowed a better sparing in terms of both Dmean and volumes receiving intermediate-high doses compared to 3D-CRT and tomodirect.	2
46. Filippi AR, Ciammella P, Piva C, et al. Involved-site image-guided intensity modulated versus 3D conformal radiation therapy in early stage supradiaphragmatic Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys.* 2014;89(2):370-375.	Observational-Tx	90 stage IIA HL patients	To compare involved-site IG-IMRT with involved-site 3D-CRT in the treatment of early stage HL involving the mediastinum, with efficacy and toxicity as primary clinical endpoints.	49 patients were treated with 3D-CRT (54.4%) and 41 with IG-IMRT (45.6%). Median follow-up time was 54.2 months for 3D-CRT and 24.1 months for IG-IMRT. No differences in relapse-free survival were observed between the 2 groups, with 1 relapse each. 3-year relapse-free survival was 98.7% for 3D-CRT and 100% for IG-IMRT. Grade 2 toxicity events, mainly mucositis, were recorded in 32.7% of 3D-CRT patients (16/49) and in 9.8% of IG-IMRT patients (4/41). IG-IMRT was significantly associated with a lower incidence of grade 2 acute toxicity (P=.043).	2
47. Hoppe BS, Flampouri S, Su Z, et al. Effective dose reduction to cardiac structures using protons compared with 3DCRT and IMRT in mediastinal Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys.* 2012;84(2):449-455.	Experimental-Tx	13 patients	To investigate the dosimetric impact of proton therapy on various cardiac subunits in patients with HL.	The mean heart doses were 21 Gy, 12 Gy, and 8 Gy (relative biologic effectiveness) with 3D-CRT, IMRT, and proton therapy, respectively. Compared with 3D-CRT and IMRT, proton therapy reduced the mean doses to the left and right atria; the left and right ventricles; the aortic, mitral, and tricuspid valves; and the left anterior descending, left circumflex, and right circumflex coronary arteries.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
48. Hoppe BS, Flampouri S, Zaiden R, et al. Involved-node proton therapy in combined modality therapy for Hodgkin lymphoma: results of a phase 2 study. *Int J Radiat Oncol Biol Phys.* 2014;89(5):1053-1059.	Experimental-Tx	20 patients	To describe the early clinical outcomes of a prospective phase 2 study of consolidative involved-node proton therapy as a component of combined-mode therapy in patients with stages I to III HL with mediastinal involvement.	The median follow-up was 37 months (range, 26–55). 2 events occurred during follow-up: 1 relapse (inside and outside the targeted field) and 1 transformation into a primary mediastinal large B cell lymphoma. The 3-year relapse-free survival rate was 93%, and the 3-year EFS rate was 87%. No acute or late grade 3 nonhematologic toxicities were observed.	2
49. Paumier A, Ghalibafian M, Beaudre A, et al. Involved-node radiotherapy and modern radiation treatment techniques in patients with Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys.* 2011;80(1):199-205.	Experimental-Tx	50 HL patients (48 patients with primary HL, 1 patient with recurrent disease, and 1 patient with refractory disease)	To assess the clinical outcome of the INRT concept using modern radiation treatments (IMRT or deep-inspiration breath-hold RT) in patients with localized supradiaphragmatic HL.	Median follow-up was 53.4 months (range, 19.1–93 months). The 5-year PFS and OS rates for the whole population were 92% (95% CI, 80%–97%) and 94% (95% CI, 75%–98%), respectively. Recurrences occurred in 4 patients: 2 patients had in-field relapses, and 2 patients had visceral recurrences. Grade 3 acute lung toxicity (transient pneumonitis) occurred in 1 case.	2
50. 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 complete remission percentage was 94% and no major response, 6%. For ABVD alone, 94% achieved a complete remission; 1.5%, a partial response; and 4.5%, no major response. At 60 months complete remission 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 complete remission duration, FFP, and OS differences at 5 years were -8% to 15%, -8% to 18%, and -4% to 12%, respectively.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
51. 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 HD6 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 STNI (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
52. 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-Favorable Prognosis Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
53. 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 complete response 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 complete response 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
54. Olszewski AJ, Shrestha R, Castillo JJ. Treatment selection and outcomes in early-stage classical Hodgkin lymphoma: analysis of the national cancer data base. *J Clin Oncol.* 2015;33(6):625-633.	Observational-Tx	20,600 patients	To define factors affecting treatment selection and resulting survival outcomes in the United States.	Only 49.5% of patients received CMT, and this proportion steadily declined between 2003 (59.4%) and 2011 (45.2%), particularly in younger patients. Apart from classical prognostic factors (age, stage, tumor location, histology, comorbidities), treatment selection was significantly influenced by sex, black race, distance to facility, and type of insurance. Uninsured patients had the lowest odds of receiving CMT. A significant random effect related to facility-specific treatment preference was also evident. Estimated 5-year OS was 89.6% and relative survival was 94.3%. After adjustment for guarantee-time and indication biases, CMT was associated with better OS (HR, 0.61; 95% CI, 0.53 to 0.70) and relative survival (excess HR, 0.42; 95% CI, 0.33 to 0.54) than chemotherapy alone. This effect was without significant heterogeneity in subset analysis and was not sensitive to unobserved confounding.	2

Hodgkin Lymphoma-Favorable Prognosis Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
55. 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 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 ($P<.001$), International Prognostic Score 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
56. Hutchings M, Loft A, Hansen M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. *Blood.* 2006;107(1):52-59.	Experimental-Dx	77 patients	To prospectively assess the value of FDG-PET after 2 cycles of chemotherapy for prediction of PFS and OS in HL.	Median follow-up was 23 months. After 2 cycles of chemotherapy, 61 patients had negative FDG-PET scans and 16 patients had positive scans. 11/16 FDG-PET-positive patients progressed and 2 died. 3/61 FDG-PET-negative patients progressed; all were alive at latest follow-up. Survival analyses showed strong associations between early FDG-PET after 2 cycles and PFS ($P<.001$) and OS ($P<.01$). For prediction of PFS, interim FDG-PET was as accurate after 2 cycles as later during treatment and superior to computerized tomography at all times. In regression analyses, early interim FDG-PET was stronger than established prognostic factors.	1

Hodgkin Lymphoma-Favorable Prognosis Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
57. Hutchings M, Mikhaeel NG, Fields PA, Nunan T, Timothy AR. Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma. *Ann Oncol.* 2005;16(7):1160-1168.	Experimental-Dx	85 patients	To assess the value of FDG-PET after 2 or 3 cycles of chemotherapy for prediction of PFS and OS.	After 2 or 3 cycles of chemotherapy, 63 patients had negative FDG-PET scans, 9 patients had minimal residual uptake and 13 patients had positive scans. 3 PET-negative patients and 1 patient from the minimal residual uptake group relapsed. In the PET-positive group, 9 patients progressed and 2 died. Survival analyses showed highly significant associations between early interim FDG-PET and PFS ($P<0.0001$) and OS ($P<0.03$). All advanced-stage patients with positive interim FDG-PET relapsed within 2 years.	1
58. Zinzani PL, Tani M, Fanti S, et al. Early positron emission tomography (PET) restaging: a predictive final response in Hodgkin's disease patients. *Ann Oncol.* 2006;17(8):1296-1300.	Experimental-Dx	40 patients	To examine the predictive value of early evaluation for the clinical response rate and DFS in HD patients.	After 2 cycles (PET-2), the PET was negative in 28/40 (70%), positive in 8/40 (20%), and minimal residual uptake was present in the remaining 4 (10%) patients. After treatment, among 8 patients who were PET-2+, 7 showed refractory disease and 1 had relapse after 3 months. All 4 patients with minimal residual uptake at the PET-2 became PET- during the further 4 cycles and, after treatment, 3 were in complete response and 1 relapsed after 5 months. All 28 PET negative patients at the PET-2 remained PET negative and all of them were in complete response after treatment.	2

Hodgkin Lymphoma-Favorable Prognosis Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
59. 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
60. 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 2 cycles of ABVD as compared with standard CMT.	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

Hodgkin Lymphoma-Favorable Prognosis Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
61. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med.* 2015;372(17):1598-1607.	Experimental-Dx	420 patients	To determine whether patients with clinical stage IA or stage IIA HL and negative PET findings after 3 cycles of ABVD chemotherapy require consolidation RT to areas of previous involvement to delay or prevent disease progression.	A total of 602 patients (53.3% male; median age, 34 years) were recruited, and 571 patients underwent PET scanning. The PET findings were negative in 426 of these patients (74.6%), 420 of whom were randomly assigned to a study group (209 to the RT group and 211 to no further therapy). At a median of 60 months of follow-up, there had been 8 instances of disease progression in the RT group, and 8 patients had died (3 with disease progression, 1 of whom died from HL); there had been 20 instances of disease progression in the group with no further therapy, and 4 patients had died (2 with disease progression and none from HL). In the RT group, 5 of the deaths occurred in patients who received no RT. The 3-year PFS rate was 94.6% (95% CI, 91.5 to 97.7) in the RT group and 90.8% (95% CI, 86.9 to 94.8) in the group that received no further therapy, with an absolute risk difference of -3.8 percentage points (95% CI, -8.8 to 1.3).	1

Hodgkin Lymphoma-Favorable Prognosis Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
62. Diehl V, Sextro M, Franklin J, et al. Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's disease and lymphocyte-rich classical Hodgkin's disease: report from the European Task Force on Lymphoma Project on Lymphocyte-Predominant Hodgkin's Disease. *J Clin Oncol.* 1999;17(3):776-783.	Observational-Tx	426 assessable cases	To investigate the clinical characteristics and course of LPHL patients and lymphocyte-rich classical HL patients classified according to morphologic and immunophenotypic criteria.	The 426 assessable cases were reclassified as LPHL (51%), lymphocyte-rich classical HL (27%), classical HL (5%), non-HL (3%), and reactive lesion (3%); 11% of cases were not assessable. Patients with LPHL and lymphocyte-rich classical HL were predominantly male, with early-stage disease and few risk factors. Patients with lymphocyte-rich classical HL were significantly older. Survival and failure-free survival rates with adequate therapy were similar for patients with LPHL and lymphocyte-rich classical HL, and were stage-dependent and not significantly better than stage-comparable results for classical HL (German trial data). 27% of relapsing LPHL patients had multiple relapses, which is significantly more than the 5% of relapsing lymphocyte-rich classical HL patients who had multiple relapses. LPHL patients had significantly superior survival after relapse compared with lymphocyte-rich classical HL or classical HL patients; however, this was partly due to the younger average age of LPHL patients.	2
63. Nogova L, Reineke T, Brillant C, et al. Lymphocyte-predominant and classical Hodgkin's lymphoma: a comprehensive analysis from the German Hodgkin Study Group. *J Clin Oncol.* 2008;26(3):434-439.	Observational-Tx	8,298 HL patients	To shed more light on the prognosis and outcome of LPHL, the authors reviewed all LPHL patients registered in the GHSG database, comparing patient characteristics and treatment outcome with cHL patients.	Complete remission and unconfirmed complete remission after first-line treatment was achieved in 91.6% vs 85.9% of patients in early favorable stages, 85.7% vs 83.3% of patients in early unfavorable stages, and 76.8% vs 77.8% of patients in advanced stages of LPHL compared with classical HL, respectively. Tumor control (FFTF) for LPHL and classical HL patients at a median observation of 50 months was 88% and 82% (P=.0093) and OS was 96% and 92%, respectively (P=.0166). In LPHL patients, negative prognostic factors were advanced stage (P=.0092), Hb <10.5 g/dL (P=.0171), and lymphopenia (P=.010) for FFTF. Age ≥45 years (P=.0125), advanced stage (P=.0153), and Hb <10.5 g/dL (P=.0014) were negative prognostic factors for OS.	2

Hodgkin Lymphoma-Favorable Prognosis Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
64. Eichenauer DA, Plutschow A, Fuchs M, et al. Long-Term Course of Patients With Stage IA Nodular Lymphocyte-Predominant Hodgkin Lymphoma: A Report From the German Hodgkin Study Group. *J Clin Oncol.* 2015;33(26):2857-2862.	Observational-Tx	256 patients	To evaluate the long-term outcome of patients treated within prospective GHSG clinical trials.	The median age at nodular lymphocyte-predominant hodgkin lymphoma diagnosis was 39 years (range, 16 to 75 years). Most patients were male (76%). The whole patient group had a median follow-up of 91 months (CMT: 95 months; EFRT: 110 months; IFRT: 87 months; rituximab: 49 months). At 8 years, PFS and OS rates were 88.5% and 98.6% for CMT, 84.3% and 95.7% for EFRT, and 91.9% and 99.0% for IFRT, respectively. Patients treated with rituximab had 4-year PFS and OS rates of 81.0% and 100%, respectively. A second malignancy during the course of follow-up was diagnosed in 17 (6.6%) of 256 patients. A total of 12 deaths occurred. However, only 1 patient died from nodular lymphocyte-predominant hodgkin lymphoma.	2
65. Chen RC, Chin MS, Ng AK, et al. Early-stage, lymphocyte-predominant Hodgkin's lymphoma: patient outcomes from a large, single-institution series with long follow-up. *J Clin Oncol.* 2010;28(1):136-141.	Observational-Tx	113 patients	To present the long-term outcome of patients treated at a single institution.	Median follow-up was 136 months. 10-year PFS rates were 85% (stage I) and 61% (stage II); OS rates were 94% and 97% for stages I and II, respectively. PFS and OS did not differ among patients who received limited-field, regional-field, or EFRT. In contrast, 6 of 7 patients who received chemotherapy alone without RT developed early disease progression and required salvage treatment. Multivariable analysis adjusting for extent of RT, clinical stage, sex, and use of chemotherapy confirmed that the extent of RT was not significantly associated with PFS (P=.67) or OS (P=.99). The addition of chemotherapy to RT did not improve PFS or OS compared with RT alone.	2
66. Eichenauer DA, Fuchs M, Pluetschow A, et al. Phase 2 study of rituximab in newly diagnosed stage IA nodular lymphocyte-predominant Hodgkin lymphoma: a report from the German Hodgkin Study Group. *Blood.* 2011;118(16):4363-4365.	Experimental-Tx	28 patients	To evaluate efficacy and safety of rituximab in patients with newly diagnosed stage IA nodular LPHL.	Among the 28 evaluable patients, overall response rate was 100%, 24 patients (85.7%) achieved complete remission, and 4 (14.3%) achieved partial remission. At a median follow-up of 43 months, OS was 100%; PFS at 12, 24, and 36 months was 96.4%, 85.3%, and 81.4%, respectively. No grade 3 or 4 toxicity was observed.	2

Hodgkin Lymphoma-Favorable Prognosis Stage I and II
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
67. Advani RH, Horning SJ, Hoppe RT, et al. Mature results of a phase II study of rituximab therapy for nodular lymphocyte-predominant Hodgkin lymphoma. *J Clin Oncol.* 2014;32(9):912-918.	Experimental-Tx	39 patients	To evaluate rituximab as a therapeutic option in nodular LPHL.	A total of 39 patients were enrolled (R, n = 23; R + MR, n = 16). After 4 once-per-week treatments, overall response rate was 100% (complete response, 67%; partial response, 33%). At median follow-ups of 9.8 years for R and 5 years for R + MR, median PFS were 3 and 5.6 years (*P*=.26), respectively; median OS was not reached. Estimated 5-year PFS and OS for patients treated with R vs R + MR were 39.1% (95% CI, 23.5 to 65.1) and 95.7% (95% CI, 87.7 to 100) vs 58.9% (95% CI, 38.0 to 91.2) and 85.7% (95% CI, 69.2 to 100), respectively. 9 of 23 patients experiencing relapse had evidence of transformation to aggressive B-cell lymphoma; 6 of these patients had infradiaphragmatic involvement at study entry.	1

Evidence Table Key

Study Quality Category Definitions

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

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

3D-CRT = 3D-conformal radiation therapy
ABV = Doxorubicin, bleomycin, and vinblastine
ABVD = Doxorubicin, bleomycin, vinblastine, and dacarbazine
BEACOPP= Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone
CI = Confidence interval
CMT = Combined-modality treatment
COPP= Cyclophosphamide, vincristine, procarbazine, and prednisone
CVPP= Cyclophosphamide, vinblastine, procarbazine, and prednisone
DFS = Disease-free survival
EBVP= Epirubicin, bleomycin, vinblastine, and prednisone
EFRT = Extended-field radiation therapy
EFS = Event-free survival
ERR = Excess relative risk
FDG-PET = Fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography
FFP= Freedom from progression
FFTF = Freedom from treatment failure
HD = Hodgkin disease
HL = Hodgkin lymphoma
HR = Hazard ratio
IFRT = Involved-field radiation therapy
IG-IMRT = Image-guided intensity modulated radiation therapy
INRT = Involved-node radiation therapy
LPHL = Lymphocyte-predominant Hodgkin lymphoma
MOPP= Mechlorethamine, vincristine, procarbazine, and prednisone
OR = Odds ratio
OS = Overall survival
PFS = Progression-free survival
RR = Relative risk
RT = Radiation therapy
SC = Second cancers
SMR = Standardized mortality ratio
STLI = Subtotal lymphoid irradiation
STNI = Subtotal nodal irradiation