

**Hodgkin's Lymphoma—Favorable Prognosis Stage I and II  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
1. Mauch PM. Controversies in the management of early stage Hodgkin's disease. <i>Blood</i> 1994; 83(2):318-329.	7	N/A	Discussion of the controversies in the staging and treatment of early stage Hodgkin's disease (HD), including the role of radiation field size, use of chemotherapy (CT), the influence of prognostic factors on treatment, indications for staging laparotomy, factors for development of lat complications, and current clinical trials.	In the U.S. aggressive staging by means of laparotomy and splenectomy is accepted as a means to minimize future treatment. But patients with certain indicators such as LMA or extensive B symptoms or high-risk for abdominal involvement should not undergo staging laparotomy. And there are other circumstances such as in pediatric patients when combined CT and RT would be preferred to laparotomy. The majority of patients will be cured with RT alone.	4
2. 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. <i>Blood</i> 1982; 59(3):455-465.	3A	230	To compare the overall and disease-free (DFS) survival for stage I-II HD patients between: A. RT alone; or B. radiation and 6 cycles of adjuvant combination CT. Also to determine prognostic factors identify patients as being at a higher risk of failure.	<ul style="list-style-type: none"> <li>• 10-year overall survival (OS) = 84% in both A and B.</li> <li>• 10-year DFS was A=77%, B=84%.</li> <li>• Systemic symptoms, histologic subtype, age and limited extranodal involvement did not affect prognosis.</li> <li>• Large mediastinal masses were good indicators of a higher rate of relapse when treated with RT alone compared to CMT (45% 10-year freedom from relapse vs 81%), but survival rates are much closer (74% vs 84%).</li> </ul>	2
3. 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. <i>J Clin Oncol</i> 1988; 6(10):1576-1583.	4	315	To evaluate relapse rates, survival rates, prognostic factors and long-term complications in patients with early stage FP HD treated with mantle and para-aortic irradiation.	<ul style="list-style-type: none"> <li>• 14-year: DFS = 82% and OS = 93%.</li> <li>• Mediastinal size was the only factor that predicted lower freedom-from-first relapse (FFR).</li> <li>• Patients with mixed cellularity (MC) histology were more likely to relapse below the diaphragm than patients with nodular sclerosis (NS) or lymphocyte predominant (LP) histology.</li> <li>• Thyroid abnormalities were the most common long-term complication, affecting 37% of patients after 16 years.</li> <li>• Mantle and para-aortic irradiation should remain standard treatment for early-stage HD.</li> </ul>	3

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4. Specht L, Nordentoft AM, Cold S, Clausen NT, Nissen NI. Tumor burden as the most important prognostic factor in early stage Hodgkin's disease. Relations to other prognostic factors and implications for choice of treatment. <i>Cancer</i> 1988; 61(8):1719-1727.	1	290	To compare the results of treatment by RT alone with RT combined with adjuvant combination CT, and to determine the most significant prognostic indicators for early stage HD.	Tumor burden was by far the most important prognostic factor for DFS for patients who received RT alone and for those who received RT + CT. For survival, only tumor burden and age were independently significant factors. A combination of tumor burden, histologic subtype, and sex identified patients with a high relapse rate, and a low survival rate, after both RT alone and after RT + CT.	2
5. Gospodarowicz MK, Sutcliffe SB, Clark RM, et al. Analysis of supradiaphragmatic clinical stage I and II Hodgkin's disease treated with radiation alone. <i>Int J Radiat Oncol Biol Phys</i> 1992; 22(5):859-865.	4	250	To determine the impact of patient selection and extended field radiation (EF-RT) on outcome for HD patients with supradiaphragmatic disease.	<ul style="list-style-type: none"> <li>• 8-year actuarial survival = 83.3%.</li> <li>• Cause-specific survival = 90.1%.</li> <li>• Relapse-free survival (RFS) = 71.6%.</li> <li>• Local tumor control = 94.6%.</li> <li>• Extent of radiation significantly affects risk of relapse, particularly out-of-field.</li> <li>• Prognostic factors include age, histology, ERS.</li> </ul>	2
6. Pavlovsky S, Maschio M, Santarelli MT, et al. Randomized trial of chemotherapy versus chemotherapy plus radiotherapy for stage I-II Hodgkin's disease. <i>J Natl Cancer Inst</i> 1988; 80(18):1466-1473.	1	277	RCT in which stage I-II favorable or unfavorable prognosis HD patients were randomized to receive either 6-cycles of cyclophosphamide, vinblastine, procarbazine and prednisone (CVPP), or CVPP followed by involved field radiotherapy (IFRT).	Patients in the CMT arm had a significantly higher rate of DFS compared to the CT alone arm (71% vs 62% at 84 months, P=0.01). However, subgroup analysis showed that there was no significant difference in DFS rate (77% vs 70%) or OS rate (92% vs 91%) between the two arms for favorable prognosis patients.	1
7. 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. <i>Blood</i> 1989; 73(1):47-56.	1	494	To determine if mantle irradiation alone is sufficient therapy in laparotomy staged favorable prognosis stage I-II HD. A. Mantle RT alone, B. Mantle and para-aortic RT.	<ul style="list-style-type: none"> <li>• 9-year DFS: A=69%, B=70%, P=NS.</li> <li>• 9-year OS: A=94%, B=91%, P=NS.</li> <li>• Mantle irradiation alone is sufficient therapy in FR CS I-II HD.</li> </ul>	1
8. Cosset JM, Henry-Amar M, Meerwaldt JH, et al. The EORTC trials for limited stage Hodgkin's disease. The EORTC Lymphoma Cooperative Group. <i>Eur J Cancer</i> 1992; 28A(11):1847-1850.	1	168  165	A. EBVP X 6 + IFRT (36 Gy).  B. B. subtotal lymphoid irradiation (STLI) (S).	<ul style="list-style-type: none"> <li>• 6-year RFS: A=92%, B=81%, P=0.004.</li> <li>• 6-year survival: A=98%, B=96%, P=0.156.</li> <li>• Modified CT and limited RT has a better RFS compared to EF-RT in favorable prognosis CS I-II HD.</li> </ul>	1

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9. Sutcliffe SB, Gospodarowicz MK, Bergsagel DE, et al. Prognostic groups for management of localized Hodgkin's disease. <i>J Clin Oncol</i> 1985; 3(3):393-401.	3a	252 (RT only) 67 (chemo + RT)	To retrospectively assess the factors effecting prognosis among patients being treated with: A) radical irradiation or B).CT + RT.	<ul style="list-style-type: none"> <li>• 10-year OS was: A=78%, B=78%, and DFS was: A=61%, B=63%.</li> <li>• Independent prognostic factors for survival and relapse: age, stage, histology.</li> <li>• Relapse prognostic factors: disease bulk, intrathoracic failure rate was higher in patients with large mediastinal masses, especially those with isolated upper cervical stage IA disease, younger patients with localized early stage disease with favorable histologic type, and older patients with extensive or symptomatic stages I and II disease with less favorable histology.</li> <li>• Younger patients with localized stage I and II disease and favorable histology could be treated effectively with upper abdominal radiation and achieve the same results as those achieved with full RT for surgically staged patients.</li> </ul>	3
10. Specht L, Gray RG, Clarke MJ, Peto R. Influence of more extensive radiotherapy and adjuvant chemotherapy on long-term outcome of early-stage Hodgkin's disease: a meta-analysis of 23 randomized trials involving 3,888 patients. International Hodgkin's Disease Collaborative Group. <i>J Clin Oncol</i> 1998; 16(3):830-843.	7	3,888	Meta analysis to determine outcomes in early-stage HD patients of more vs less extensive RT; and of RT + CT vs RT alone.	<ul style="list-style-type: none"> <li>• More extensive RT reduced risk of treatment failure at 10 years from 43.4% to 31.3%; P&lt;.00001, but there was no improvement in OS (77.0% vs 77.1%).</li> <li>• CT + RT reduced 10-year risk of failure from 32.7% to 15.8% (P&lt;.00001) but had a non-significant improvement in survival (76.5% to 79.4%).</li> <li>• More extensive RT fields or the addition of CT to RT in the initial treatment of early-stage HD had a large effect on disease control, but only a small effect on OS.</li> </ul>	2
11. Duhmke E, Franklin J, Pfreundschuh M, et al. Low-dose radiation is sufficient for the noninvolved extended-field treatment in favorable early-stage Hodgkin's disease: long-term results of a randomized trial of radiotherapy alone. <i>J Clin Oncol</i> 2001; 19(11):2905-2914.	1	382 recruited 376 eligible	To show that RT dose to the noninvolved extended field can be reduced without loss of efficacy in patients with early-stage HD.	<ul style="list-style-type: none"> <li>• With a median follow-up of 86 months, 7-year RFS rates were 78% (arm A) and 83% (arm B) (P=.093).</li> <li>• The upper 95% confidence limit for the possible inferiority of arm B in RFS was 4%.</li> <li>• Corresponding OS rates were 91% (arm A) and 96% (arm B) (P=.16).</li> </ul>	1

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12. Farah R, Ultmann J, Griem M, et al. Extended mantle radiation therapy for pathologic stage I and II Hodgkin's disease. <i>J Clin Oncol</i> 1988; 6(6):1047-1052.	4	135	To examine outcome for stage I and II HD patients treated with extended mantle radiation technique (EMRT).	5- and 10-year DFS was 82.5%. OS was 96% at 5 years and 83% at 10 years. In light of reduced cost and lower morbidity for EMRT, the results support its use.	3
13. Cosset JM, Henry-Amar M, Meerwaldt JH. Long-term toxicity of early stages of Hodgkin's disease therapy: the EORTC experience. EORTC Lymphoma Cooperative Group. <i>Ann Oncol</i> 1991; 2 Suppl 2:77-82.	7	1,660	To report on non-malignant late complications and second cancers (SC). Report based on the analysis of the late effects of treatment which were prospectively recorded in 4 trials conducted in early stage HD.	In EORTC cohort, there was steadily increasing mortality due to SC, intercurrent diseases and cardiac failure. After 20 years, data showed main causes of death were SC (9.3%), intercurrent diseases (7.6%) and cardiac failures (5.7%).	1
14. Hancock SL, Hoppe RT, Horning SJ, Rosenberg SA. Intercurrent death after Hodgkin disease therapy in radiotherapy and adjuvant MOPP trials. <i>Ann Intern Med</i> 1988; 109(3):183-189.	1	326	To assess differential mortality among favorable prognosis HD patients with either: A. RT alone or, B. RT + 6 cycles MOPP.	After median follow-up of >14 years, there were no significant differences between A and B for actuarial survival, intercurrent disease, or HD mortality, though the MOPP improved freedom from relapse.	1
15. Henry-Amar M, Hayat M, Meerwaldt JH, et al. Causes of death after therapy for early stage Hodgkin's disease entered on EORTC protocols. EORTC Lymphoma Cooperative Group. <i>Int J Radiat Oncol Biol Phys</i> 1990; 19(5):1155-1157.	1	1,449	To quantify the risk of dying after treatment for early-stage HD.	15-year survival rate was 69%. Although probably cured from HD, patients are at higher risk for death than expected, a risk that might be a consequence of therapy.	1
16. 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. <i>Cancer J Sci Am</i> 1995; 1(1):33-42.	5	794	To quantify causes of death in patients with intensively treated HD comparing patients who received: A. RT alone; or B. RT + CT.	Of 124 patients who died, 56 died of HD, 36 of second malignant neoplasms, 15 of cardiac causes, 9 of infection and 8 from other causes. 20-year survival rate: 70%. Patients in group B had a significantly higher risk of a second tumor or infection-related mortality.	2
17. 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. <i>J Clin Oncol</i> 2002; 20(8):2101-2108.	3	1,080	To analyze the long-term survival and the pattern and timing of excess mortality in patients with early-stage HD.	The 15- and 20-year Kaplan-Meier survival estimates were 84% and 78%, respectively. The absolute excess risk of mortality in patients with a favorable prognosis increased over time, whereas for those with an unfavorable prognosis, the absolute excess risk peaked in the first 5 years, predominantly from HD. The relative risk (RR) of mortality from all causes other than HD, second tumors, and cardiac disease remained significantly elevated more than 20 years after treatment.	2

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18. 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. <i>J Clin Oncol</i> 1993; 11(2):255-261.	3	1,152	To evaluate patients with HD for development of SC.	68 patients had developed a SC, including nine acute nonlymphocytic leukemia's, eight non-Hodgkin's lymphomas, and 51 solid tumors, including 11 lung cancers. The RR of SC and leukemia was 1.86 and 24.3, respectively. The RR of SC was highest in younger patients (<41 years, RR=3.8).	2
19. 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. <i>J Clin Oncol</i> 2002; 20(16):3484-3494.	3	32,591	To quantify the relative and absolute excess risks of site-specific SC, in particular solid tumors, among long-term survivors of HD.	Cancers of the lung, digestive tract, and female accounted for the largest number of subsequent malignancies. Twenty-five 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.	2
20. 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. <i>Blood</i> 2002; 100(6):1989-1996.	3	1,319	To analyze the long-term risks and temporal trends, identify patient-related and treatment-related risk factors, and determine the prognosis of patients who develop a second malignancy after radiation treatment with or without CT for HD.	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 CT 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.	2
21. 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. <i>J Clin Oncol</i> 2000; 18(3):498-509.	3	5,519	To assess long-term site-specific risks of second malignancy after HD in relation to age at treatment and other factors.	Relative risks 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.	2
22. 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. <i>J Clin Oncol</i> 2000; 18(3):487-497.	3	1,253	To quantify the long-term risk of second primary cancers in patients diagnosed with HD during adolescence or young adulthood.	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 RR of 4.9, 6.9, and 12.7 for patients first treated at ages 31-39 years, 21-30 years, and ≤20 years, respectively.	2

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23. Swerdlow AJ, Higgins CD, Smith P, et al. Myocardial infarction mortality risk after treatment for Hodgkin disease: a collaborative British cohort study. <i>J Natl Cancer Inst</i> 2007; 99(3):206-214.	3	7033	To evaluate patients with HD for development of myocardial infarction.	A total of 166 deaths from myocardial infarction occurred in the cohort, statistically significantly more than expected, with an absolute excess risk of 125.8 per 100,000 person-years. 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.	2
24. Hodgson DC, Koh ES, Tran TH, et al. Individualized estimates of second cancer risks after contemporary radiation therapy for Hodgkin lymphoma. <i>Cancer</i> 2007.	3b	37	Construct 3 RT plans (mantle, IFRT) for HD patients to estimate the excess relative risk (ERR) and cumulative incidence of radiation-induced SC.	Contemporary IFRT is predicted to substantially reduce risk of secondary breast and lung cancer compared with mantle RT, with considerable variation in risk among individuals.	3
25. Koh ES, Tran TH, Heydarian M, et al. A comparison of mantle versus involved-field radiotherapy for Hodgkin's lymphoma: reduction in normal tissue dose and second cancer risk. <i>Radiation oncology (London, England)</i> 2007; 2:13.	3b	41	Compare mantle and IFRT to determine reduction in normal tissue doses and SC risks.	Dose reductions resulted in corresponding reductions in predicted ERR for SC induction. Moving from 35 Gy mantle RT to 35 Gy IFRT reduces predicted ERR for female breast and lung cancer by approximately 65%, and for male lung cancer by approximately 35%; moving from 35 Gy IFRT to 20 Gy IFRT reduces predicted ERR approximately 40% more.	3
26. Eich H, Mueller R, A. E, et al. Comparison of 30 Gy versus 20 Gy involved field radiotherapy after two versus four cycles ABVD in early stage Hodgkin's lymphoma: Interim analysis of the German Hodgkin Study Group trial HD10. <i>Int J Rad Oncol Biol Phys</i> 2005; 63(2S1):S1 (Abstract 2).	1	1131	RCT in which patients were randomized to one of four arms: 4 cycles of ABVD followed by 30 Gy IFRT, 4 cycles of ABVD followed by 20 Gy IFRT, 2 cycles of ABVD followed by 30 Gy IFRT, and 2 cycles of ABVD followed by 20 Gy IFRT.	Preliminary results show no significant difference in freedom from treatment failure or OS between patients treated with 2 cycles of ABVD and those treated with 4 cycles of ABVD. Preliminary results show no significant difference in freedom from treatment failure or OS between patients treated with 20 Gy or 30 Gy of IFRT.	2
27. Girinsky T, van der Maazen R, Specht L, et al. Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: conceptpatients and guidelines. <i>Radiother Oncol</i> 2006; 79(3):270-277.	7	n/a	To describe new conceptpatients for radiation fields in patients with early stage HD treated with a combined modality.	Concept of involved-node radiotherapy (INRT) is the first attempt to reduce the size of radiation fields compared to the classic involved fields used in adult patients. Proper implementation of INRT requires adequate training and an efficient prospective or early retrospective quality assurance program.	4

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28. Hodgson DC, Pintilie M, Gitterman L, et al. Fertility among female hodgkin lymphoma survivors attempting pregnancy following ABVD chemotherapy. <i>Hematol Oncol</i> 2007; 25(1):11-15.	3	36	To determine the pregnancy rate among survivors who had received ABVD and to determine the time to pregnancy in those who had attempted and become pregnant, in comparison with friend or sibling controls.	The median time-to-pregnancy among both HD survivors and controls was 2.0 months. The 12-month pregnancy rates were 70% and 75%, respectively. The fertility ratio (FR) for HD survivors. The differences between survivors and controls were not significantly different. Age at treatment and the number of cycles of CT were not associated with pregnancy rate among survivors.	3
29. Carde P, Burgers JM, Henry-Amar M, et al. Clinical stages I and II Hodgkin's disease: a specifically tailored therapy according to prognostic factors. <i>J Clin Oncol</i> 1988; 6(2):239-252.	1	198  296	Two studies: 1) To compare the outcomes for patients with favorable prognoses and negative laparotomy treated with either: A. mantle (M) irradiation B. extended field mantle plus para-aortic (M+PA) irradiation. 2) To compare outcomes for patients with positive laparotomy (but favorable initial disease prognoses) or unfavorable initial prognoses treated with either: C. TNI/STNI, D. MOPP, M irradiation, MOPP (3M).	1) CR = 99% 6-year RFS: A = 74%, B = 72%. OS: A = 96%, B = 89%.  2) RFS rate for positive laparotomy group: C = 53%, D = 100% (P<.002). RFS rate for unfavorable prognosis group: C = 77%, D = 91% (P=.02). Similar 6-year survival rates: 92% overall OS rate: C = 82%, D = 89% (P=.05). Similar TS in patients under 40 years of age.	1
30. Ganesan TS, Wrigley PF, Murray PA, et al. Radiotherapy for stage I Hodgkin's disease: 20 years experience at St Bartholomew's Hospital. <i>Br J Cancer</i> 1990; 62(2):314-318.	5	90	To assess the efficacy of primary therapy for patients treated with early stage HD over the course of 12 years at a single hospital.	<ul style="list-style-type: none"> <li>• 15-year proportion in remission 75%.</li> <li>• 15-year survival rate 75%.</li> <li>• 10-year rate of survival of second remission 40%.</li> <li>• Factors predictive of a prolonged remission were pathological staging vs clinical staging (P=0.02) and lymph node size &lt;3 cm (P=0.04).</li> </ul>	3

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31. Mandelli F, Anselmo AP, Cartoni C, Cimino G, Maurizi Enrico R, Biagini C. Evaluation of therapeutic modalities in the control of Hodgkin's disease. <i>Int J Radiat Oncol Biol Phys</i> 1986; 12(9):1617-1620.	1	58  42  218	Three studies: 1. Determine the outcomes of mantle field irradiation.  2. Compare outcomes of MOPP treatment and EF-RT.  3. Compare MOPP and ABVD.	1. Complete remission rate 98%. Survival rate 90% (median 80 months).  2. CR: MOPP = 68%, RT = 95% (P<0.05). Survival: MOPP = 82%, RT = 100%. No relapses in patients treated with MOPP.  3. 60-month CR rate: MOPP = 77%, ABVD = 75%. 60-month RFS rate: MOPP = 68%, ABVD = 77%. 60-month survival rate: MOPP = 76%, ABVD = 80%.	1
32. Mauch PM, Canellos GP, Shulman LN, et al. Mantle irradiation alone for selected patients with laparotomy-staged IA to IIA Hodgkin's disease: preliminary results of a prospective trial. <i>J Clin Oncol</i> 1995; 13(4):947-952.	1	46	To determine the feasibility of omitting prophylactic para-aortic irradiation in selected patients with PS IA to IIA HD. Two groups: A. Group with NS or LP histology, no B-symptoms, negative laparotomy and disease limited above the carina receiving mantle radiation alone, B. B. Retrospective group of 23 patients receiving mantle irradiation alone.	A. 4-year RFS: 83% 4-year OS: 100%  B. 10-year RFS: 83% 10-year survival: 89%  These early results support the use of mantle irradiation alone in selected PS IA to IIA patients with NS or LP histology. Relapses, although rare, have occurred predominantly below the diaphragm. This suggests the need for continued long-term surveillance of abdominal and pelvic nodes in this group of treated patients.	2
33. Wirth A, Byram D, Chao M, et al. Long term results of mantle irradiation(MRT) alone in 261 patients with clinical stage I-II supradiaphragmatic Hodgkin's disease. <i>Int J Radiat Oncol Biol Phys</i> 1997; 39(2):174.	5	261	To evaluate mantle radiotherapy (MRT) alone as the initial therapy of patients with clinical stage I-II HD, and to determine prognostic factors for progression-free survival (PFS).	10-year survival = 73%. Age was the only significant prognostic factor. 10-year PFS = 58%. Prognostic factors: clinical stage, B symptoms, histology, number of sites, and tumor bulk. Results support the use of MRT alone in patients with favorable CS I HD and CS I-II HD with lymphocyte-predominant histology. Other patients with CS I-II HD require more intensive treatment.	2

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34. Noordijk EM, Carde P, Hagenbeek A, et al. Combination of radiotherapy and chemotherapy is advisable in all patients with clinical stage I-II Hodgkin's disease. Six-year results of the EORTC-GPMC controlled clinical trials 'H7-VF', 'H7-F' and 'H7-U'. <i>Int J Radiat Oncol Biol Phys</i> 1997; 39(2):173.	1	40	To determine if MRT alone is sufficient treatment for very favorable prognosis clinical stage IA HD.	<ul style="list-style-type: none"> <li>6-year RFS of 73% and 6-year cause specific and OS of 96% caused this trial to close early due to the high recurrence rates.</li> <li>Mantle irradiation alone is not sufficient treatment for very favorable prognosis clinical stage IA HD.</li> </ul>	2
35. 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. <i>J Clin Oncol</i> 2007; 25(23):3495-3502.	1	650	To investigate whether CMT with two cycles of ABVD followed by extended-field radiotherapy (EF-RT) is superior to EF-RT alone in patients with early favorable HD.	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, freedom from treatment failure was significantly different, with 7-year rates of 67% in arm A (95% CI, 61%-73%) and 88% in arm B (95% CI, 84%-92%; P<.0001). This was due mainly to significantly more relapses after EF-RT only (arm A, 22%; arm B, 3%).	1
36. 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. <i>J Clin Oncol</i> 2001; 19(22):4238-4244.	1	348	RCT in which patients with clinical stage IA to IIA supradiaphragmatic HD were randomized without staging laparotomy to treatment with either STLI or combined-modality therapy (CMT) consisting of three cycles of doxorubicin and vinblastine followed by STLI.	There was 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 chemo RT arm, compared with 34 on the RT arm (P<.001).	1
37. 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. <i>J Clin Oncol</i> 2006; 24(19):3128-3135.	1	722 patients stratified into favorable and unfavorable categories	The aim of this study was to evaluate a reduction in the treatment associated toxicity for HD patients using a combination of low-intensity CT and IFRT without jeopardizing disease control.	A treatment strategy for early-stage HD based on prognostic factors leads to high OS rates in both favorable and unfavorable patients. In favorable patients, the combination of EBVP and IFRT can replace STNI as standard treatment. This is not the case for unfavorable prognosis patients, where EBVP is significantly less efficient than MOPP/ABV.	2
38. Ferme C, Eghbali H, Meerwaldt JH, et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. <i>The New England journal of medicine</i> 2007; 357(19):1916-1927.	1	1,538	Comparative study to determine standard treatment for HD in patients with favorable and unfavorable prognostic features.	CT plus IFRT should be the standard treatment for HD with favorable prognostic features. In patients with unfavorable features, 4-courses of CT plus IFRT should be the standard treatment.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
39. 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. <i>J Clin Oncol</i> 2002; 20(3):630-637.	2	142	To report the efficacy and complications of a brief, dose-intense CT regimen (Stanford V) 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 freedom from progression (FFP) was 89% and the OS was 96%.	2
40. 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. <i>J Clin Oncol</i> 2003; 21(19):3601-3608.	1	1,204	RCT in which patients were randomized to receive two cycles of COPP (cyclophosphamide, vincristine, procarbazine and prednisone) and ABVD, followed by either EF-RT or IFRT.	There was no significant difference in the rates of freedom from treatment failure (5-year rates 85.8% vs 84.2%, P=0.56) or OS (5-year rates 90.8% vs 92.4%, P=0.24) between the two arms.	1
41. Ferme C, Eghbali H, Hagenbeek A, et al. MOPP/ABV hybrid and irradiation in unfavorable supradiaphragmatic clinical stages I-II Hodgkin's disease: Comparison of three treatment modalities. Preliminary results of the EORTC-GELA H8-U 244 American Society of Hematology randomized trial in 995 patients. <i>Blood</i> 2000; 96(11):A576.	1	995	RCT in which stage I and II unfavorable-prognosis patients were randomized to one of three arms: 6 cycles of MOPP/ABV followed by IFRT, 4 cycles of MOPP/ABV followed by IFRT, and 4 cycles of MOPP/ABV followed by EF-RT.	Preliminary results showed no significant difference in the rates of OS or failure-free survival between the three arms.	2
42. 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. <i>J Clin Oncol</i> 2004; 22(14):2835-2841.	1	140	RCT in which patients with stage I unfavorable and stage IIA favorable or unfavorable HD were randomized to receive 4 cycles of ABVD and either subtotal nodal and splenic irradiation, or IFRT.	There was no significant difference in the FFP rate (93% vs 94%) or OS rate (96% vs 94%) between the two arms.	2
43. Nachman JB, Spoto 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. <i>J Clin Oncol</i> 2002; 20(18):3765-3771.	1	501	RCT in which 501 patients younger than 21 years, who achieved a complete response to combination CT, were randomized to receive either low dose IFRT (21 Gy) or no RT.	The 3-year event-free survival (EFS) rate was 92% in the radiotherapy arm and 87% in the no-radiotherapy arm (P=0.057). OS was similar in the two arms (98% vs 99%).	1

**Hodgkin's Lymphoma—Favorable Prognosis Stage I and II  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
44. 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? <i>J Clin Oncol</i> 2004; 22(1):62-68.	1	179	RCT in which 179 patients who achieved a complete response to six cycles of ABVD, were randomized to receive either IFRT or no radiotherapy.	Patients in the RT arm had a significantly higher rate of OS than those in the no-radiotherapy arm (8-year rates 100% vs 89%, P=0.002). Patients in the RT arm also had a significantly higher rate of EFS (8-year rates 88% vs 76%, P=0.01).	2
45. 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. <i>Blood</i> 2004; 104(12):3483-3489.	1	152	RCT in which patients with stage IA-IIIa nonbulky HD, were treated with either six cycles of ABVD, or six cycles of ABVD followed by RT.	There was no significant difference between the CT and combined-modality arms for the 5-year rates of freedom from progression (81% vs 86%, P=0.61) or OS (90% vs 97%, P=0.08).	2
46. Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. <i>J Clin Oncol</i> 2005; 23(21):4634-4642.	1	399	Report the results of an RCT comparing ABVD with ABVD +IRT in favorable prognosis HD patients (with median follow-up of 4.2 years).	In comparison with ABVD alone, 5-year FFP is superior in patients allocated to RT (P=.006; 93% v 87%); no differences in EFS (P=.06; 88% vs 86%) or OS (P=.4; 94% vs 96%) were detected. In patients with limited-stage HD, no difference in OS was detected between patients randomly assigned to receive treatment that includes RT or ABVD alone. Although 5-year DFS was superior in patients receiving RT, this advantage is offset by deaths due to causes other than progressive HD or acute treatment-related toxicity.	1
47. 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). <i>J Clin Oncol</i> 2005; 23(16S):6505.	1	722	RCT in which patients with favorable prognosis, stage I-II HD were treated with 6 cycles of EBVP and those attaining a complete response were randomized to one of three arms: no radiotherapy, 20 Gy IFRT or 36 Gy IFRT.	The EFS rate was significantly lower in the no-RT arm (4-year rate 70%), compared to the 20 Gy (84%) and 36 Gy (87%) arms (P<0.001).	1

**Hodgkin's Lymphoma—Favorable Prognosis Stage I and II  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
48. 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. <i>J Clin Oncol</i> 2007; 25(24):3746-3752.	3a	190 - advanced disease (stages IIB through IVB) 70 -stage IIA with adverse prognostic factors	Patients with HD were enrolled in prospective trials to evaluate the prognostic role of an early interim FDG-PET scan and the International Prognostic Score (IPS) in advanced HD, treated with conventional ABVD therapy.	The 2-year survival 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), WBC more than 15,000 (P<.0001), lymphopenia (P<.001), IPS as a continuous variable (P<.0001), extranodal involvement (P<.0001), and bulky disease (P=.012). In multivariate analyses, only PET-2 turned out to be significant (P<.0001).	2
49. 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. <i>Blood</i> 2006; 107(1):52-59.	10	77	To prospectively assess the value of FDG-PET after 2 cycles of CT for prediction of PFS and OS in HD.	<ul style="list-style-type: none"> <li>Survival analyses showed strong associations between early FDG-PET after 2 cycles and PFS (P&lt;.001) and OS (P&lt;.01).</li> <li>In regression analyses, early interim FDG-PET was stronger than established prognostic factors.</li> </ul>	2
50. 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. <i>Ann Oncol</i> 2005; 16(7):1160-1168.	10	85	To assess the value of PET with FDG-PET after 2 or 3 cycles of CT in HD.	<ul style="list-style-type: none"> <li>63 patients – negative FDG-PET scans.</li> <li>9 patients – minimal residual uptake (MRU).</li> <li>13 patients – positive scans.</li> <li>Survival analyses showed highly significant associations between early interim FDG-PET and PFS (P&lt;0.0001) and OS (P&lt;0.03).</li> <li>FDG-PET is an accurate and independent predictor of PFS and OS in HD.</li> </ul>	2
51. Zinzani PL, Tani M, Fanti S, et al. Early positron emission tomography (PET) restaging: a predictive final response in Hodgkin's disease patients. <i>Ann Oncol</i> 2006; 17(8):1296-1300.	10	40	To determine value of early PET restaging in patients with advanced stage HD after treatment with ABVD CT for 6 cycles.	<ul style="list-style-type: none"> <li>After 2 cycles, PET was negative in 28/40 (70%), positive in 8/40 (20%), and MRU was present in the remaining 4 (10%) patients.</li> <li>After treatment, among 8 patients who were PET-2+, 7 showed refractory disease and one had relapse after 3 months.</li> <li>All 4 patients with MRU at the PET-2 became PET negative during the further 4 cycles and, after treatment, 3 were in complete response (CR) and one relapsed after 5 months.</li> <li>All PET negative patients at the PET-2 remained PET negative and all of them were in CR after treatment.</li> </ul>	3

**Hodgkin's Lymphoma—Favorable Prognosis Stage I and II**  
**EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
52. 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. <i>Leukemia &amp; lymphoma</i> 2007; 48(9):1721-1727.	1	260	To evaluate the role of consolidation radiation in HD patients, using EFS as end point.	Addition of irradiation helps improve EFS in HD patients with post-CT FDG-PET-negative residual masses.	2
53. Nogova L, Reineke T, Eich HT, et al. Extended field radiotherapy, combined modality treatment or involved field radiotherapy for patients with stage IA lymphocyte-predominant Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Study Group (GHSG). <i>Ann Oncol</i> 2005; 16(10):1683-1687.	3	131	To review patients with LP HD and compare different treatment approaches, such as EF-RT, IFRT and CMT.	98% of patients in the EF-RT group, 100% in the IFRT group and 95% in the combined-modality group achieved complete remission. There were four late relapses after EF-RT, 2 late relapses after IFRT and one early relapse after CMT. The 2-year OS rate was 100% in all three groups.	3

## Evidence Table Key

### Study Type Key

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

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

### Strength of Evidence Key

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