

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Canellos GP, Rosenberg SA, Friedberg JW, Lister TA, Devita VT. Treatment of Hodgkin lymphoma: a 50-year perspective. <i>J Clin Oncol</i> . 2014;32(3):163-168.	Review/Other-Tx	N/A	A review on treatment of HL.	No results stated in abstract.	4
2. Townsend W, Linch D. Hodgkin's lymphoma in adults. <i>Lancet</i> . 2012;380(9844):836-847.	Review/Other-Tx	N/A	To review management of HL in early-stage disease, advanced-stage disease, and at relapse, with a focus on late effects of treatment.	Most patients with HL are cured and current developments are likely to lead to further, if small, improvements in OS because of both improved tumor eradication and reduction of late effects. Because of the success of the treatment of HL, proof of further advances will require very large trials with long-term follow-up, and international collaboration will be essential.	4
3. Jerusalem G, Beguin Y, Fassotte MF, et al. Early detection of relapse by whole-body positron emission tomography in the follow-up of patients with Hodgkin's disease. <i>Ann Oncol</i> . 2003; 14(1):123-130.	Review/Other-Dx	36 consecutive patients	Prospective study to examine the value of whole-body PET for the detection of preclinical relapse.	FDG-PET has the potential to detect preclinical relapse in patients with HL. Further studies needed to determine the impact of PET on treatment management and outcome.	4
4. Radford JA, Eardley A, Woodman C, Crowther D. Follow up policy after treatment for Hodgkin's disease: too many clinic visits and routine tests? A review of hospital records. <i>Bmj</i> . 1997; 314(7077):343-346.	Review/Other-Dx	210 patients	Review hospital records to examine the effectiveness of routine follow-up evaluation in detecting relapse.	210 patients generated 2,512 outpatient reviews, and 37 relapses were detected. Relapse of HL is usually detected as a result of the investigation of symptoms rather than by routine screening tests.	4
5. Torrey MJ, Poen JC, Hoppe RT. Detection of relapse in early-stage Hodgkin's disease: role of routine follow-up studies. <i>J Clin Oncol</i> . 1997; 15(3):1123-1130.	Review/Other-Dx	709 patients	Retrospective study to examine the costs and benefits of routine follow-up evaluation in patients treated with RT.	Relapse was suspected primarily by history in 55% of patients, physical examination in 14%, chest x-ray in 23%, and abdominal x-ray in 7%. Most relapses were identified by history and physical examination. Chest x-ray was useful during first 3 years.	4

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
6. Dryver ET, Jernstrom H, Tompkins K, Buckstein R, Imrie KR. Follow-up of patients with Hodgkin's disease following curative treatment: the routine CT scan is of little value. <i>Br J Cancer</i> . 2003; 89(3):482-486.	Review/Other-Dx	107 patients	Retrospective review to evaluate the costs and utility of the components of follow-up after HL therapy.	Two thirds of relapses were identified clinically while routine radiological tests identified a quarter of all relapses. Routine CT scan identified 9% of the relapses yet accounted for 29% of the follow-up costs. Based on data, the cost per true relapse was \$6000 US, 49% incurred by radiological tests. The majority of the cost of follow-up was incurred by routine follow-up (84%) as opposed to the investigation of suspected relapses (16%). The authors concluded that most true relapses are clinically symptomatic and that the routine CT is an expensive and inefficient mode of routine follow-up.	4
7. Zinzani PL, Stefoni V, Tani M, et al. Role of [18F]fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. <i>J Clin Oncol</i> . 2009; 27(11):1781-1787.	Observational-Dx	421 patients	To prospectively evaluate the role of FDG-PET in the follow-up of lymphoma. All patients who achieved the first complete remission were scheduled for serial FDG-PET at 6, 12, 18, and 24 months; further scans were then carried out on an annual basis.	PET enabled documentation of lymphoma relapse in 41 cases at 6 months, in 30 cases at 12 months, in 26 cases at 18 months, in 10 cases at 24 months, and in 11 cases at more than 36 months. All 36 patients with inconclusive positive PET underwent biopsy; only 12 (33%) of 36 patients had a concomitant suggestion of positivity on CT. A lymphoma relapse was diagnosed in 24 (66%) of 36 patients.	3
8. Friedmann AM, Wolfson JA, Hudson MM, et al. Relapse after treatment of pediatric Hodgkin lymphoma: outcome and role of surveillance after end of therapy. <i>Pediatr Blood Cancer</i> . 2013;60(9):1458-1463.	Observational-Tx	64 patients	To review the outcomes of pediatric patients with HL treated between 1990 and 2006 to determine the primary event that led to the detection of relapse. The authors determined the probability of relapse detection by routine follow-up procedures, including history, physical examination, laboratory tests, and imaging, and determined the impact of each of these screening methods on the likelihood of survival after relapse.	Relapse occurred in 64/402 evaluable patients (15.9%) at a median of 1.7 years from the time of diagnosis. The majority of relapses (60%) were diagnosed at a routine visit, and patient complaint was the most common initial finding that led to a diagnosis of relapse (47% of relapses). An abnormal finding on physical examination was the primary event in another 17% of relapses, and imaging abnormalities led to the diagnosis in the remaining 36%. Laboratory abnormalities were never the primary finding. The method of detection of relapse and timing (whether detected at a routine visit or an extra visit) did not impact survival.	2

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
9. Xavier MF, Schuster SJ, Andreadis C, Downs L, Diccion B, Nasta SD. Detection of Relapse in Diffuse Large B-Cell Lymphoma (DLBCL) and Hodgkin's Lymphoma (HL): Observations and Implications for Post-Remission Radiologic Surveillance. <i>ASH Annual Meeting Abstracts</i> . 2006; 108(11):2428.	Observational-Dx	40 patients	To retrospectively evaluate patients with relapses of HL and Diffuse Large B-Cell Lymphoma after complete remission from 3 referral lymphoma practices. Relapsed patients underwent post-remission surveillance CT scans with or without PET scans roughly every 3–4 months for the first 1–2 years and every 6–12 months thereafter for at least 5 years.	22 (55%) were detected with surveillance imaging and 18 (45%) were detected by clinical findings. In both diseases, a much higher proportion of relapses were detected by surveillance imaging.	3
10. Basciano BA, Moskowitz C, Zelenetz AD. Impact of Routine Surveillance Imaging on the Outcome of Patients with Relapsed Hodgkin Lymphoma. <i>ASH Annual Meeting Abstracts</i> . 2009; 114(22):1558.	Observational-Dx	94 patients	Retrospective study to determine the role of asymptomatic post-remission surveillance imaging in the diagnosis of first relapse and its impact on outcomes in patients with HL.	The median follow-up for surviving patients was 7.4 years. The prognostic risk group (low, intermediate/high) correlated to outcome, validating its applicability in this patient cohort: failure-free survival at 5 years was 64.8% and 49.4% respectively, P=0.045. Prognostic risk groups were evenly distributed between the asymptomatic surveillance and clinically indicated groups: Low: 64% vs 66%; intermediate/high: 36% vs 37% P=0.48. The failure-free survival at 5 years for patients in the asymptomatic surveillance and clinically indicated groups was 58.4% and 59.3% respectively, P=0.9; similar there was no difference in 5 year OS, asymptomatic surveillance 62.4% and clinically indicated 73.3% P=0.6. Within a given risk group (low or intermediate/high) patients in the asymptomatic surveillance group did not have a superior outcome compared to the clinically indicated group.	4
11. Guadagnolo BA, Punglia RS, Kuntz KM, Mauch PM, Ng AK. Cost-effectiveness analysis of computerized tomography in the routine follow-up of patients after primary treatment for Hodgkin's disease. <i>J Clin Oncol</i> . 2006; 24(25):4116-4122.	Review/Other-Dx	N/A	To estimate the clinical benefits and cost effectiveness of CT in the follow-up of patients with CR after treatment for HL. A decision-analytic model was developed to evaluate follow-up strategies for two hypothetical cohorts of 25-year-old patients with stage I-II or stage III-IV HL.	Annual CT follow-up is associated with minimal survival benefit. Routine CT should not be used in the surveillance of asymptomatic patients in CR after treatment for HL.	4

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
12. Voss SD, Chen L, Constine LS, et al. Surveillance computed tomography imaging and detection of relapse in intermediate- and advanced-stage pediatric Hodgkin's lymphoma: a report from the Children's Oncology Group. <i>J Clin Oncol.</i> 2012; 30(21):2635-2640.	Observational-Dx	216 patients	To determine the contribution of surveillance CT, as compared with clinical findings, to detection of disease recurrence.	With a median follow-up time of 7.4 years, 25 (11.6%) of 216 patients had experienced a relapse, of whom 23 experienced local relapse. Median time to relapse was 7.6 months (range, 0.2 to 48.9 months). 19 relapses (76%) were detected based on symptoms, laboratory or physical examination findings, and two relapses (8%) were detected by imaging within the first year after therapy. Only 4 patients (16%) had their recurrence detected exclusively by surveillance imaging after the first year. 6 deaths occurred, all in patients who experienced relapse within the first year after therapy. No patient with a recurrence after 1-year off treatment has died, regardless of how the recurrence was detected.	3
13. Hueltenschmidt B, Sautter-Bihl ML, Lang O, et al. Whole body positron emission tomography in the treatment of Hodgkin disease. <i>Cancer.</i> 2001; 91(2):302-310.	Observational-Dx	81 patients	Retrospective study to assess the clinical value of FDG-PET scan for primary staging, treatment monitoring and assessment in a suspected case of recurrent HL. PET scans were compared with conventional imaging modality.	In a staging-relevant lesion to lesion analysis, accuracy in the determination of the stage of disease was 96% for PET vs 56% for conventional imaging modality. PET led to a lower stage classification in 28% and a higher stage classification in 12% of cases, compared with the stage assumed with conventional imaging modality. With regard to treatment monitoring, PET showed an accuracy of 91% compared with 62% for conventional imaging modality. The NPV of PET was 96%. With regard to suspected recurrence, PET findings were true-positive in 10/12 PET scans and true-negative in 5/6 PET scans, resulting in accuracy of 83%, which compares favorably with the accuracy rate of 56% for conventional imaging modality. Conventional imaging modality PET scan showed a higher accuracy compared with conventional imaging modality for treatment monitoring and assessing suspected recurrence of HL.	3

Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
14. Mikosch P, Gallowitsch HJ, Zinke-Cerwenka W, et al. Accuracy of whole-body 18F-FDP-PET for restaging malignant lymphoma. <i>Acta Med Austriaca</i> . 2003; 30(2):41-47.	Observational-Dx	121 PET images of 93 patients	Retrospective study to analyze the accuracy of FDG-PET scan in the restaging of lymphoma and to compare the performance of PET imaging with CT and or US. Standard of reference used was biopsy data, clinical status at the time of investigation, and follow-up of at least 12 months.	Sensitivity, specificity, and accuracy of FDG-PET was 91%, 81%, and 85%; of CT/US, 88%, 35%, 56%, respectively. PET showed a comparable sensitivity but a higher specificity and accuracy compared with CT/US, reflecting the ability of PET to pick up active disease as opposed to residual scar tissue.	3
15. Cerci JJ, Trindade E, Pracchia LF, et al. Cost effectiveness of positron emission tomography in patients with Hodgkin's lymphoma in unconfirmed complete remission or partial remission after first-line therapy. <i>J Clin Oncol</i> . 2010; 28(8):1415-1421.	Observational-Dx	130 patients	Prospective study to assess the cost effectiveness of FDG-PET in patients with HL with unconfirmed complete remission or partial remission after first-line treatment.	Sensitivity, specificity PPV and NPV of FDG-PET were 100%, 92.0%, 92.3%, and 100%, respectively (accuracy of 95.9%). FDG-PET is highly cost effective and would reduce costs for the public health care program in Brazil.	3
16. Cheson BD. The International Harmonization Project for response criteria in lymphoma clinical trials. <i>Hematol Oncol Clin North Am</i> . 2007; 21(5):841-854.	Review/Other-Tx	N/A	Revised guidelines developed by the International Harmonization Project.	Aim of guidelines is to improve comparability among studies, leading to accelerated new agent development resulting in the rapid availability of improved therapies for patients who have lymphoma.	4
17. Mocikova H, Obrtlíkova P, Vackova B, Trnny M. Positron emission tomography at the end of first-line therapy and during follow-up in patients with Hodgkin lymphoma: a retrospective study. <i>Ann Oncol</i> . 2010; 21(6):1222-1227.	Observational-Dx	113 patients	Retrospective study to analyze the clinical impact of routine PET examination during the follow-up for relapse detection in PET-negative HL patients at the end of therapy.	327 PET scans evaluated. At the end of therapy, 94 (83.2%) patients were PET negative and 19 (16.8%) PET positive. Regular follow-up PET scans in 67/94 PET-negative patients correctly identified tumor in 6/155 PET scans (3.9%). In 27/94 patients with clinically suspected relapse, 5/27 PET scans (18.5%) confirmed tumor. Analysis revealed there is no need for regular follow-up with PET scans in PET-negative patients at the end of therapy.	3
18. El-Galaly TC, Mylam KJ, Brown P, et al. Positron emission tomography/computed tomography surveillance in patients with Hodgkin lymphoma in first remission has a low positive predictive value and high costs. <i>Haematologica</i> . 2012; 97(6):931-936.	Observational-Dx	211 routine and 88 PET/CT were performed in 161 patients	Multicenter retrospective study to evaluate the utility of FDG-PET/CT in patients with HL and in situations with suspected lymphoma relapse.	In 10/22 patients with recurrence of HL, routine imaging surveillance was the primary tool for the diagnosis of the relapse. Extranodal disease, interim PET-positive lesions and PET activity at response evaluation were all associated with a PET/CT-diagnosed preclinical relapse. The true positive rates of routine and clinically indicated imaging were 5% and 13%, respectively (P=0.02). The overall PPV and NPV of PET/CT were 28% and 100%, respectively. The estimated cost per routine imaging diagnosed relapse was US\$ 50,778.	3

* See Last Page for Key

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
19. Lee AI, Zuckerman DS, Van den Abbeele AD, et al. Surveillance imaging of Hodgkin lymphoma patients in first remission: a clinical and economic analysis. <i>Cancer</i> . 2010; 116(16):3835-3842.	Observational-Dx	192 patients	Retrospective study to assess the utility of surveillance PET/CT and CT scans for HL patients in first remission.	16 events (12 recurrent HL cases and 4 secondary malignancies) were detected during a median follow-up of 31 months. The PPV of surveillance PET/CT was 22.9% compared with 28.6% for CT (P=.73). Factors that were found to significantly improve the PPV of scans in detecting recurrent HL included PET and CT concordance, involvement of a prior disease site, or the occurrence of a radiographic abnormality within 12 months. There were too few events to determine whether event detection by PET/CT vs CT or the presence of symptoms at the time of event detection affected overall outcomes. The cost to detect a single event was approximately \$100,000. Radiation exposure to detect a single event was 146.6 millisieverts per patient for each of 9 patients.	3
20. Maeda LS, Horning SJ, Iagaru AH, et al. Role of FDG-PET/CT Surveillance for Patients with Classical Hodgkin's Disease in First Complete Response: The Stanford University Experience. <i>ASH Annual Meeting Abstracts</i> . 2009; 114(22):1563.	Observational-Dx	113 patients	Retrospective study to evaluate reports of FDG-PET/CT scans performed in follow-up of patients in first CR and correlate results with freedom from progression and OS.	Overall 326 scans were performed; year 1 (n=123), year 2 (n=103), year 3 (n=68), year 4 (n=26) and year 5 (n=6). 30 patients had one or more reports consistent with a positive scan, 26 had indeterminate or negative, and 57 had only negative scans. At a median follow-up of 3.2 years, the overall freedom from progression was 87% and OS 100%. Only 14/30 patients (47%) with a positive scan relapsed; 9/82 (11%) of stage I/II patients and 5/31(16%) of stage III/IV patients. None of the patients with indeterminate or negative scans relapsed. The median time to relapse was 236 days (range 58 to 835). 12/14 (85.7%) relapses occurred within the first year and were not associated with clinical symptoms/signs in 9/12 (75%) patients. 2 patients relapsed >1 year post CR (13 months and 2.3 years) and symptoms prompted imaging with FDG-PET/CT in both. All patients were salvaged successfully with high dose chemotherapy and stem cell support.	3

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
21. Petrausch U, Samaras P, Veit-Haibach P, et al. Hodgkin's lymphoma in remission after first-line therapy: which patients need FDG-PET/CT for follow-up? <i>Ann Oncol.</i> 2010; 21(5):1053-1057.	Observational-Dx	134 patients	To evaluate the impact of FDG-PET/CT during follow-up of patients with HL.	42 (31.3%) patients had a recurrence. The PPV of FDG-PET/CT was 0.98. Single-factor analysis identified morphological residual mass [P=0.0005, HR 3.4, 95% CI, 1.7-6.6] and symptoms (P<0.0001, HR 4.9, 95% CI 2.4-9.9) as significant risk factors for relapse. By multivariate analysis, morphological residual mass was the only significant risk factor for early follow-up (<24 months) (P=0.0019, HR 7.6, 95% CI, 2.1-27.3). Advanced stage (P=0.0426, HR 3.6, 95% CI, 1.1-12.3) and the presence of symptoms (P=0.0009, HR = 14.6, 95% CI, 3.0-69.7) were found to be significant risk factors for later follow-up (>24 months).	3
22. Hodgson DC, Gilbert ES, Dores GM, et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. <i>J Clin Oncol.</i> 2007; 25(12):1489-1497.	Review/Other-Dx	18,862 (5-year HL survivors)	To estimate the RR, excess absolute risk and cumulative incidence for specific attained ages and ages at HL diagnosis using multivariate modeling. Poisson regression was used to evaluate the effects of age at diagnosis, attained age, latency, sex, treatment, and year of diagnosis on the RR and excess absolute risk of solid cancers.	Among 1,490 identified solid cancers, 850 were estimated to be in excess. For most cancer sites, both RR and excess absolute risk decreased with age at HL diagnosis and showed strong dependencies on attained age. For a patient diagnosed at age 30 years and survived to ≥40 years, modeled risks were significantly elevated for cancers of the breast (RR = 6.1), other supradiaphragmatic sites (RR = 6.0), and infradiaphragmatic sites (RR = 3.7); the largest RR (20-fold) was observed for malignant mesothelioma. 30-year cumulative risks of solid cancers for men and women diagnosed at 30 years were 18% and 26%, respectively, compared with 7% and 9%, respectively, in the general population. For young HL patients, risks of breast and colorectal cancers were elevated 10 to 25 years before the age when routine screening would be recommended in the general population.	4

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
23. Swerdlow AJ, Higgins CD, Smith P, et al. Second cancer risk after chemotherapy for Hodgkin's lymphoma: a collaborative British cohort study. <i>J Clin Oncol.</i> 2011; 29(31):4096-4104.	Observational-Tx	5,798 patients	To investigate cancer risks in a large British cohort of patients with HL treated with chemotherapy.	Second malignancies occurred in 459 cohort members. RR of second cancer was raised after chemotherapy alone (RR, 2.0; 95% CI, 1.7 to 2.4) but was much lower than after combined modalities (RR, 3.9; 95% CI, 3.5 to 4.4). After chemotherapy alone, there were significantly raised risks of lung cancer, non-HL, and leukemia, each contributing approximately equal absolute excess risk. After combined modalities, there were raised risks of these and several other cancers. Second cancer risk peaked 5 to 9 years after chemotherapy alone, but it remained raised for 25 years and longer after combined modalities. Risk was raised after each common chemotherapy regimen except, based on limited numbers and follow-up, adriamycin, bleomycin, vinblastine, and dacarbazine. The age and time-course relations of lung cancer differed between chemotherapy alone and combined modalities.	2
24. Inskip PD, Robison LL, Stovall M, et al. Radiation dose and breast cancer risk in the childhood cancer survivor study. <i>J Clin Oncol.</i> 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 for trend <.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

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
25. Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. <i>JAMA</i> . 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
26. van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. <i>J Natl Cancer Inst</i> . 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(trend)=.01); 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 <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

* See Last Page for Key

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
27. De Bruin ML, Sparidans J, van't Veer MB, et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. <i>J Clin Oncol.</i> 2009; 27(26):4239-4246.	Observational-Tx	120 women	Cohort study among 1,122 female 5-year survivors treated for HL before the age of 51. Purpose of study is to assess the long-term risk of breast cancer after treatment for HL.	After a median follow-up of 17.8 years, 120 women developed breast cancer (standardized incidence ratio, 5.6; 95% CI, 4.6 to 6.8), absolute excess risk 57 per 10,000 patients per year. The overall cumulative incidence 30 years after treatment was 19% (95% CI, 16% to 23%); for those treated before age 21 years, it was 26% (95% CI, 19% to 33%). The RR remained high after prolonged follow-up (>30 years after treatment: standardized incidence ratio, 9.5; 95% CI, 4.9 to 16.6). Mantle field irradiation (involving the axillary, mediastinal, and neck nodes) was associated with a 2.7-fold increased risk (95% CI, 1.1 to 6.9) compared with similarly dosed (36 to 44 Gy) mediastinal irradiation alone. Women with ≥ 20 years of intact ovarian function after RT at young ages (<31 years) experienced significantly higher risks for breast cancer than those with fewer than 10 years of intact ovarian function.	2

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
28. Franklin J, Pluetschow A, Paus M, et al. Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trials. <i>Ann Oncol.</i> 2006; 17(12):1749-1760.	Review/Other-Tx	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 four comparisons. (i) RT vs chemoradiotherapy (15 trials, 3,343 patients): Second malignancy risk were lower with chemoradiotherapy than with RT as initial treatment (OR = 0.78, 95% CI, 0.62-0.98 and P=0.03). (ii) Chemotherapy vs chemoradiotherapy (16 trials, 2,861 patients): second malignancy risks 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 second malignancy risk (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.	4

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
29. Yahalom J, Petrek JA, Biddinger PW, et al. Breast cancer in patients irradiated for Hodgkin's disease: a clinical and pathologic analysis of 45 events in 37 patients. <i>J Clin Oncol.</i> 1992; 10(11):1674-1681.	Observational-Tx	37 women	Analysis of clinical data, mammograms, and pathologic specimens to characterize the clinical and pathologic features of patients who develop breast cancer after RT for HL.	All patients received RT to the upper part of their body, and 10 also had chemotherapy for HL. The median interval from the treatment of HL to the diagnosis of BC was 15 years (range, 8 to 34). The median age at diagnosis of breast cancer was 43 years (range, 27 to 75), 41% of patients were 39 years old or younger. Most mammograms (81%) showed abnormal findings of mass and/or microcalcifications. Of the 8 patients (22%) with bilateral tumors, 4 were synchronous and 4 were metachronous. Involvement of the medial half of the breast occurred more frequently than in patients with primary breast cancer (39% and 21%, respectively; P<.002). But, the histologic types, grades, presence of lymphocytic reaction, and lymphatic invasion were similar to those observed in 935 primary breast cancer patients who were previously analyzed at our center. The 6-year actuarial relapse-free survival for node-negative breast cancer after HL was 85%. Node-positive patients had a significantly lower relapse-free survival of 33% (P=.002).	2
30. Elkin EB, Klem ML, Gonzales AM, et al. Characteristics and outcomes of breast cancer in women with and without a history of radiation for Hodgkin's lymphoma: a multi-institutional, matched cohort study. <i>J Clin Oncol.</i> 2011; 29(18):2466-2473.	Observational-Tx	253 patients with breast cancer with a history of RT for HL matched with 741 patients with sporadic breast cancer	To compare characteristics and outcomes of breast cancer in women with and without a history of RT for HL.	Median time from HL to breast cancer diagnosis was 18 years. Median age at breast cancer diagnosis was 42 years. Breast cancer after RT for HL was more likely to be detected by screening, was more likely to be diagnosed at an earlier stage, and was more likely to be bilateral at diagnosis. HL survivors had an increased risk of metachronous contralateral breast cancer (adjusted HR, 4.3; 95% CI, 1.7 to 11.0) and death as a result of any cause (adjusted HR, 1.9; 95% CI, 1.1 to 3.3). Breast cancer-specific mortality was also elevated, but this difference was not statistically significant (adjusted HR, 1.6; 95% CI, 0.7 to 3.4).	2

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
31. Diller L, Medeiros Nancarrow C, Shaffer K, et al. Breast cancer screening in women previously treated for Hodgkin's disease: a prospective cohort study. <i>J Clin Oncol.</i> 2002; 20(8):2085-2091.	Observational-Dx	90 female long-term survivors of HL	Prospective cohort study to assess patient awareness of breast cancer risk and screening behavior, and to assess the utility of mammographic screening in HL survivors.	40% of female survivors of HL were unaware of their increased risk of breast cancer, although patients followed by an oncologist were significantly more likely to be aware of their increased risk. All 12 breast cancers diagnosed during the study period were detected mammographically.	4
32. Wolden SL, Hancock SL, Carlson RW, Goffinet DR, Jeffrey SS, Hoppe RT. Management of breast cancer after Hodgkin's disease. <i>J Clin Oncol.</i> 2000; 18(4):765-772.	Observational-Dx	65 patients with 71 cases of breast cancer	To evaluate the incidence, detection, pathology, management and prognosis of breast cancer after HL.	The RR of breast cancer was significantly increased at 4.7. 63% were detected by self-examination and 30% were detected by mammography screening. After 1990, majority of breast cancer cases were stage I, in part attributed to increased mammography screening.	3
33. Lee L, Pintilie M, Hodgson DC, Goss PE, Crump M. Screening mammography for young women treated with supradiaphragmatic radiation for Hodgkin's lymphoma. <i>Ann Oncol.</i> 2008; 19(1):62-67.	Observational-Dx	100 patients	To report the results of a prospective breast cancer surveillance program based on annual mammography for female HL survivors, focusing on the method of detection and characteristics of secondary breast cancers in a screened cohort.	12/100 women (12%) were diagnosed with breast cancer after a median of 5 years of surveillance (range, 1-9). Majority of breast cancers were detected clinically and had unfavorable pathologic characteristics.	3
34. Kwong A, Hancock SL, Bloom JR, et al. Mammographic screening in women at increased risk of breast cancer after treatment of Hodgkin's disease. <i>Breast J.</i> 2008; 14(1):39-48.	Review/Other-Dx	167 women	To examine mammographic screening in women at increased risk of breast cancer after treatment of HL. A cohort of 291 women between 25 and 55 years of age who had received thoracic irradiation before 35 years of age for HL with or without chemotherapy was contacted by mail.	High density breast tissue was common on mammography, and the recall and biopsy rates were unusually high in younger women. Early mammographic screening facilitated diagnosis of in situ and early invasive cancer in 3.5% of subjects.	4
35. Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. <i>Ann Intern Med.</i> 2008; 148(9):671-679.	Review/Other-Dx	11 studies	Systematic review to summarize the sensitivity, specificity, likelihood ratios, and post-test probability associated with adding MRI to annual mammography screening of women at very high risk for breast cancer. Prospective studies were used.	The summary negative likelihood ratio and the probability of a BI-RADS-suspicious lesion were 0.70 (95% CI, 0.59% to 0.82%) and 1.4% (CI, 1.2% to 1.6%) for mammography alone and 0.14 (CI, 0.05% to 0.42%) and 0.3% (CI, 0.1% to 0.8%) for the combination of MRI plus mammography. Screening with both MRI and mammography might rule out cancerous lesions better than mammography alone in women who are known or likely to have an inherited predisposition to breast cancer.	4

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
36. Ng AK, Garber JE, Diller LR, et al. Prospective study of the efficacy of breast magnetic resonance imaging and mammographic screening in survivors of Hodgkin lymphoma. <i>J Clin Oncol</i> . 2013;31(18):2282-2288.	Observational-Dx	148 women	To compare the sensitivity and specificity of breast MRI with those of mammography in women who received chest irradiation for HL.	With the screening, 63 biopsies were performed in 45 women; 18 (29%) showed a malignancy. All but one of the screen-detected malignancies were preinvasive or subcentimeter node-negative breast cancers. After excluding first-screen MRI and mammogram, mammogram sensitivity was 68% as compared with 67% for MRI (P=1.0). Sensitivity increased to 94% using both screening modalities. The specificities of mammogram alone, MRI alone, and both were 93%, 94%, and 90%, respectively.	2
37. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. <i>CA Cancer J Clin</i> . 2007; 57(2):75-89.	Review/Other-Dx	N/A	American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography.	Screening MRI is recommended for women with an approximately 20%-25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for HL.	4
38. American College of Radiology. <i>ACR Practice Guideline for the Performance of Contrast-Enhanced Magnetic Resonance Imaging (MRI) of the Breast</i> . Available at: http://www.acr.org/~media/ACR/Documents/PGTS/guidelines/MRI_Breast.pdf . Accessed 19 November 2012.	Review/Other-Dx	N/A	American College of Radiology practice guideline for the performance of contrast-enhanced MRI of the breast.	N/A	4

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
39. 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.	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

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
40. Swerdlow AJ, Schoemaker MJ, Allerton R, et al. Lung cancer after Hodgkin's disease: a nested case-control study of the relation to treatment. <i>J Clin Oncol.</i> 2001; 19(6):1610-1618.	Observational-Tx	88 cases; 176 controls	To investigate the causes of the raised risk of lung cancer in patients who have had HL, and in particular the relationship to treatment.	Risk of lung cancer was borderline significantly greater in patients treated with MOPP chemotherapy than those who did not receive this treatment (RR = 1.66; 95% CI, 0.99 to 2.82), and increased with number of cycles of MOPP (P=.07). Exclusion of lung cancers for which histologic confirmation was not available strengthened these associations (RR = 2.41; 95% CI, 1.33 to 4.51; P=.004 for any MOPP and P=.007 for trend with number of cycles of MOPP). Risks were not raised, however, after chlorambucil, vinblastine, procarbazine, and prednisone treatment. There was evidence that the raised risk of lung cancer occurring in relation to RT was restricted to histologies other than adenocarcinoma.	2
41. Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. <i>J Natl Cancer Inst.</i> 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 for trend <.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

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
42. van Leeuwen FE, Klokmann WJ, Stovall M, et al. Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. <i>J Natl Cancer Inst.</i> 1995; 87(20):1530-1537.	Observational-Tx	30 cases and 82 controls	To investigate the effects of radiation dose, chemotherapy and smoking on the risk of lung cancer after HL. Case-control study in a cohort of 1,939 patients treated for HL.	A statistically significant increase in risk of lung cancer was observed with increasing radiation dose (P for trend = .01) with an RR of 9.6 (95% CI, 0.93-98) for patients who received 9 Gy or more compared with those who received <1 Gy. Patients who smoked more than 10 pack-years after the diagnosis of HL had a six-fold increase in the risk of lung cancer compared with patients who smoked less than 1 pack-year (P=.03). Positive interaction on a multiplicative scale was observed between the carcinogenic effects of smoking and radiation. The increase in risk of lung cancer with increasing radiation dose was much greater among the patients who smoked after diagnosis of HL than among those who refrained from smoking (P=.04). There was no increase in lung cancer risk in relation to the number of cycles of chemotherapy or the cumulative doses of the drugs mechlorethamine and procarbazine.	2
43. 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.	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 HL, 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 combined modality therapy, and with time after HL. 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 HL continues to be increased after 15 to 20 years, and there does not appear to be a plateau.	2

* See Last Page for Key

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
44. Kovalchik SA, Tammemagi M, Berg CD, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. <i>N Engl J Med.</i> 2013;369(3):245-254.	Experimental-Dx	26,604 participants in the CT group and 26,554 in the radiography group	To assess the variation in efficacy, the number of false positive results, and the number of lung-cancer deaths prevented among 26,604 participants in the NLST who underwent low-dose CT screening, as compared with the 26,554 participants who underwent chest radiography, according to the quintile of 5-year risk of lung-cancer death (ranging from 0.15% to 0.55% in the lowest-risk group [quintile 1] to more than 2.00% in the highest-risk group [quintile 5]).	The number of lung-cancer deaths per 10,000 person-years that were prevented in the CT-screening group, as compared with the radiography group, increased according to risk quintile (0.2 in quintile 1, 3.5 in quintile 2, 5.1 in quintile 3, 11.0 in quintile 4, and 12.0 in quintile 5; P=0.01 for trend). Across risk quintiles, there were significant decreasing trends in the number of participants with false positive results per screening-prevented lung-cancer death (1,648 in quintile 1, 1,181 in quintile 2, 147 in quintile 3, 64 in quintile 4, and 65 in quintile 5). The 60% of participants at highest risk for lung-cancer death (quintiles 3 through 5) accounted for 88% of the screening-prevented lung-cancer deaths and for 64% of participants with false positive results. The 20% of participants at lowest risk (quintile 1) accounted for only 1% of prevented lung-cancer deaths.	3
45. Das P, Ng AK, Earle CC, Mauch PM, Kuntz KM. Computed tomography screening for lung cancer in Hodgkin's lymphoma survivors: decision analysis and cost-effectiveness analysis. <i>Ann Oncol.</i> 2006; 17(5):785-793.	Review/Other-Dx	N/A	Decision-analytic model to estimate the potential clinical benefits and cost-effectiveness of CT screening for lung cancer in HL survivors.	Annual CT screening increased survival by 0.64 years for smokers and 0.16 years for non-smokers. The corresponding benefits in quality-adjusted survival were 0.58 quality-adjusted life-years for smokers and 0.14 quality-adjusted life-years for non-smokers. The incremental cost-effectiveness ratios for annual CT screening compared with no screening were \$34,100/quality-adjusted life-years for smokers and \$125,400/quality-adjusted life-years for non-smokers.	4
46. De Bruin ML, Burgers JA, Baas P, et al. Malignant mesothelioma after radiation treatment for Hodgkin lymphoma. <i>Blood.</i> 2009; 113(16):3679-3681.	Observational-Tx	2,567 patients	A cohort study was performed in all patients who had been treated for HL to examine mesothelioma risk in 5-year survivors of HL.	The risk was almost 30-fold increase in HL patients treated with irradiation compared with the general population. Although histology and survival of the mesothelioma cases were comparable with cases from the general population, asbestos exposure and the proportion of males were lower than expected.	2

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
47. Hodgson DC, Grunfeld E, Gunraj N, Del Giudice L. A population-based study of follow-up care for Hodgkin lymphoma survivors: opportunities to improve surveillance for relapse and late effects. <i>Cancer</i> . 2010; 116(14):3417-3425.	Review/Other-Dx	2,071 patients	To evaluate the follow-up care received in an unselected, population-based cohort of HL survivors and, in particular, to determine the extent to which routine imaging, standard healthcare interventions, and HL-specific screening recommendations were used.	Most patients had visits with both a primary care provider and an oncologist in years 2 through 5 after their HL diagnosis. In year 5 after HL diagnosis, 31.8% of patients had at least 1 CT scan, and 62.9% had a chest x-ray. There were 5,352 CT scans performed in years 2 through 5, and 125 patients subsequently received chemotherapy within 6 months of a CT. Among the survivors who met age criteria for routine screening, 62.5% had no evidence of colorectal cancer screening during years 2 through 15, 32.3% had no evidence of breast cancer screening, and 19.9% had no evidence of cervical cancer screening. Among young women potentially at high risk of breast cancer because of RT, 87.1% had not received the recommended breast cancer screening.	4
48. Eriksson F, Gagliardi G, Liedberg A, et al. Long-term cardiac mortality following radiation therapy for Hodgkin's disease: analysis with the relative seriality model. <i>Radiother Oncol</i> . 2000; 55(2):153-162.	Observational-Tx	157 patients	To assess the risk of death due to ischemic heart disease in patients treated with RT for HL and to quantify the dose response of ischemic heart disease.	Of the 157 patients, 13 (8.3%) died due to ischemic heart disease. The standardized mortality ratio was 5.0 (95% CI, 2.7-8.6). Analysis of dose-volume histograms showed an increasing risk with increasing dose to a larger volume fraction. The observed individual clinical complication data could not be modeled unambiguously. The group analysis resulted in the dose-response parameters: D(50)=71 Gy, gamma=0.96 and s=1.0. A significantly increased risk of death due to ischemic heart disease following RT for HL was found. The risk was found to increase with higher dose and larger volume fraction irradiated.	2

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
49. Hoppe RT. Hodgkin's disease: complications of therapy and excess mortality. <i>Ann Oncol.</i> 1997; 8 Suppl 1:115-118.	Observational-Tx	2,498 patients	To assess the long-term complications and excess mortality after HL therapy.	The risk of death from HL is 17% at 15 years of follow-up and increases only slightly thereafter. The risk of death from other causes is also 17% at 15 years, but increases sharply thereafter. The major causes of mortality (other than HL) are secondary cancers and cardiac disease. Second cancers with significant increase in risk include leukemia (acute nonlymphocytic), non-HL, lung/pleural cancer, breast cancer, melanoma, soft tissue and bone sarcomas, stomach cancer, salivary gland tumors, thyroid cancer, and pancreatic cancer. The absolute excess risk of death from causes other than HL increases during each 5-year follow-up interval for at least 25 years. However, the absolute excess risk of death during similar follow-up periods is less for patients treated in more recent years (1980-1995) than in the prior treatment era (1962-1980).	2
50. Carver JR, Shapiro CL, Ng A, et al. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. <i>J Clin Oncol.</i> 2007; 25(25):3991-4008.	Review/Other-Tx	N/A	Review the evidence on the incidence of long-term cardiac or pulmonary toxicity secondary to chemotherapy, RT, or trastuzumab in symptomatic and asymptomatic cancer survivors. Reviewed literature included retrospective and cross-sectional studies.	Estimated aggregate incidence of radiation-induced cardiac disease is 10%-30% by 5 to 10 years post-treatment. Radiation pneumonitis is reported in 5%-15% of lung cancer patients receiving definitive external-beam RT. An increased incidence of cardiac and/or pulmonary dysfunction is observed in cancer survivors.	4
51. Glanzmann C, Huguenin P, Lutolf UM, Maire R, Jenni R, Gumpfenberg V. Cardiac lesions after mediastinal irradiation for Hodgkin's disease. <i>Radiother Oncol.</i> 1994; 30(1):43-54.	Observational-Tx	339 patients	To analyze the risk of myocardial infarctions in patients with HL treated with RT with or without chemotherapy. 112 patients underwent cardiac testing with echocardiography, rest and exercise electrocardiogram and myocardial scintigraphy.	There is a high incidence of sclerosis of the mitral and or the aortic valves developing into clinically important lesions in few patients. Decision on the treatment strategy and the RT technique should also involve consideration of the cardiac risk. Study recommends inclusion of an echocardiography in intervals between 3 and 4 years for routine follow-up.	2

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
52. Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. <i>JAMA</i> . 1993; 270(16):1949-1955.	Observational-Tx	2,232 consecutive patients	Retrospective study comparing treated patients with a matched general population to assess the risk of death from heart disease after HL therapy.	Of the 2,232 patients, 88 (3.9%) died of heart disease, 55 from acute myocardial infarction and 33 from other cardiac diseases, including congestive heart failure, radiation pericarditis or pancarditis, cardiomyopathy, or valvular heart disease. The RR for cardiac death was 3.1 (CI, 2.4 to 3.7). Mediastinal radiation of 30 Gy or less (n=385 patients) did not increase risk; above 30 Gy (n=1,830), RR was 3.5 (CI, 2.7 to 4.3). Blocking to limit cardiac exposure reduced the RR for other cardiac diseases from 5.3 (CI, 3.1 to 7.5) to 1.4 (CI, 0.6 to 2.9), but not acute myocardial infarction (RR, 3.7 vs 3.4). The RRs increased with duration after treatment (trend in acute myocardial infarction, P=.02; in other cardiac diseases, P=.004). The RR for acute myocardial infarction was highest after irradiation before 20 years of age and decreased with increasing age at treatment (P<.0001 for trend).	2

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
53. 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. <i>JAMA</i> . 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 CAD 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 CAD. The only treatment-related factor associated with the development of CAD 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

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
54. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. <i>Blood</i> . 2007; 109(5):1878-1886.	Observational-Tx	1,474 survivors of HL	To assess the long-term risk of various cardiovascular diseases in a cohort of 5-year survivors of HL treated between 1965 and 1995. Multivariable Cox regression and competing risk analyses were used to quantify treatment effects on cardiovascular diseases risk.	After a median follow-up of 18.7 years, risks of myocardial infarction and congestive heart failure were strongly increased compared with the general population (standardized incidence ratios = 3.6 and 4.9, respectively), resulting in 35.7 excess cases of myocardial infarction and 25.6 excess cases of congestive heart failure per 10,000 patients/year. Standardized incidence ratios of all cardiovascular diseases combined remained increased for at least 25 years and were more strongly elevated in younger patients. Mediastinal RT significantly increased the risks of myocardial infarction, angina pectoris, congestive heart failure, and valvular disorders (2- to 7-fold). Anthracyclines significantly added to the elevated risks of congestive heart failure and valvular disorders from mediastinal RT (HRs were 2.81 and 2.10, respectively). The 25-year cumulative incidence of congestive heart failure after mediastinal RT and anthracyclines in competing risk analyses was 7.9%.	2
55. Chen AB, Punglia RS, Kuntz KM, Mauch PM, Ng AK. Cost effectiveness and screening interval of lipid screening in Hodgkin's lymphoma survivors. <i>J Clin Oncol</i> . 2009; 27(32):5383-5389.	Review/Other-Dx	N/A	To evaluate the cost-effectiveness of lipid screening in survivors of HL and compare different screening intervals. A decision-analytic model to evaluate lipid screening in a hypothetical cohort of 30-year-old survivors of HL who survived 5 years after mediastinal irradiation was developed.	Lipid screening in survivors of HL, with statin therapy for screen-positive patients, improves survival and is cost effective. A screening interval of 3 years seems reasonable in the long-term follow-up of survivors of HL.	4

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
56. Heidenreich PA, Hancock SL, Lee BK, Mariscal CS, Schnittger I. Asymptomatic cardiac disease following mediastinal irradiation. <i>J Am Coll Cardiol</i> , 2003; 42(4):743-749.	Observational-Dx	294 asymptomatic patients	To evaluate the utility of echocardiography screening in patients who received RT for HL.	Valvular disease was common and increased with time following irradiation. Patients who had received irradiation more than 20 years before evaluation had significantly more mild or greater aortic regurgitation (60% vs 4%, P<0.0001), moderate or greater tricuspid regurgitation (4% vs 0%, P=0.06), and aortic stenosis (16% vs 0%, P=0.0008) than those who had received irradiation within 10 years. The number needed to screen to detect one candidate for endocarditis prophylaxis was 13 (95% CI, 7 to 44) for patients treated within 10 years and 1.6 (95% CI, 1.3 to 1.9) for those treated at least 20 years ago. Compared with the Framingham Heart Study population, mildly reduced left ventricular fractional shortening (<30%) was more common (36% vs 3%), and age- and gender-adjusted left ventricular mass was lower (90 +/- 27 g/m vs 117 g/m) in irradiated patients.	2
57. Heidenreich PA, Hancock SL, Vagelos RH, Lee BK, Schnittger I. Diastolic dysfunction after mediastinal irradiation. <i>Am Heart J</i> . 2005; 150(5):977-982.	Review/Other-Tx	294 patients	To determine the prevalence of diastolic dysfunction and its association with prognosis in asymptomatic patients after mediastinal irradiation.	The mean age of the included patients was 42 years, and 49% were male. Adequate measurements of diastolic function were obtained in 282 (97%) patients. Diastolic dysfunction was considered mild in 26 (9%) and moderate in 14 (5%). Exercise-induced ischemia was more common in patients with diastolic dysfunction (23%) than those with normal diastolic function (11%, P=.008). After adjustment for patient demographics, clinical characteristics, and radiation history, patients with diastolic dysfunction had worse event-free survival than patients with normal function (HR 1.66, 95% CI, 1.06-2.4).	4
58. Heidenreich PA, Schnittger I, Strauss HW, et al. Screening for coronary artery disease after mediastinal irradiation for Hodgkin's disease. <i>J Clin Oncol</i> . 2007; 25(1):43-49.	Review/Other-Dx	294 outpatients	To evaluate whether stress imaging can identify severe, unsuspected coronary stenoses in patients who had prior mediastinal irradiation for HL.	42 patients (14%) developed perfusion defects (n=26), impaired wall motion (n=8), or both abnormalities (n=8) during stress testing. Stress-induced signs of ischemia and significant CAD are highly prevalent after mediastinal irradiation in young patients. Stress testing identifies asymptomatic individuals at high risk for acute myocardial infarction or sudden cardiac death.	4

* See Last Page for Key

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
59. Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. <i>J Clin Oncol</i> . 2004; 22(15):3139-3148.	Review/Other-Tx	48 patients	To assess cardiovascular status in long-term HL survivors treated with chest RT. Patients completed the Short-Form 36 quality-of-life instrument and were screened by echocardiography, exercise stress testing, and resting and 24-hour echocardiography.	All patients received mediastinal irradiation (median, 40.0 Gy; range, 27.0 to 51.7 Gy) at a median age of 16.5 years (range, 6.4 to 25.0 years). 4 patients received an anthracycline. Although every patient described their health as good or better, and none had symptomatic heart disease at screening, all but one had cardiac abnormalities on screening. Restrictive cardiomyopathy was suggested by reduced average left ventricular dimension ($P<.001$) and mass ($P<.001$), without increased left ventricular wall thickness. Significant valvular defects were present in 42%; 75% had conduction defects. One survivor developed complete heart block shortly after the study visit. Autonomic dysfunction was suggested by a monotonous heart rate in 57%, persistent tachycardia in 31%, and blunted hemodynamic responses to exercise in 27%. Peak oxygen uptake during exercise, a predictor of mortality in heart failure, was significantly reduced (<20 mL/kg/m ²) in 30% of survivors. Peak oxygen uptake was correlated with increasing fatigue, increasing shortness of breath (both, $r = -0.35$; $P=.02$), and decreasing physical component score on the Short-Form-36 ($r = 0.554$; $P=.00017$).	4
60. Machann W, Beer M, Breunig M, et al. Cardiac magnetic resonance imaging findings in 20-year survivors of mediastinal radiotherapy for Hodgkin's disease. <i>Int J Radiat Oncol Biol Phys</i> . 2011; 79(4):1117-1123.	Review/Other-Dx	53 survivors	To present cardiac MRI findings in 20-year survivors of mediastinal RT for HL.	Clinical characteristics and reconstructed doses were not significantly different between survivors undergoing and not undergoing MRI. Pathologic findings were reduced left ventricular function (ejection fraction $<55\%$) in 7 (23%) patients, hemodynamically relevant valvular dysfunction in 13 (42%), late myocardial enhancement in 9 (29%), and any perfusion deficit in 21 (68%). An association of regional pathologic changes and reconstructed dose to cardiac structures could not be established.	4

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
61. Andersen R, Wethal T, Gunther A, et al. Relation of coronary artery calcium score to premature coronary artery disease in survivors >15 years of Hodgkin's lymphoma. <i>Am J Cardiol.</i> 2010; 105(2):149-152.	Observational-Tx	47 HL survivors	To quantify total coronary artery calcium in long-term HL survivors who had survived ≥15 years after treatment and relate it to the presence of verified CAD.	Total volume score was higher in 7 patients (15%) with verified CAD (median 439, range 8 to 2,057) compared to those without (median 68, 0 to 767, P=0.022). 10 patients had coronary artery calcium scores >200. Of these 10, 5 had undergone revascularization of coronary arteries. None of the 8 patients with a coronary artery calcium score 0 had symptomatic CAD. In conclusion, postirradiation coronary artery calcium can be quantified by coronary artery calcium score and this may be a simple and suitable method to screen for CAD in long-term HL survivors. Patients with a coronary artery calcium score >200 often have clinically significant CAD, and further investigation including angiography may be justified. Lower coronary artery calcium scores, however, do not exclude CAD and further studies should be undertaken to define the best algorithm for follow-up of this patient group.	2
62. Andersson A, Naslund U, Tavelin B, Enblad G, Gustavsson A, Malmer B. Long-term risk of cardiovascular disease in Hodgkin lymphoma survivors--retrospective cohort analyses and a concept for prospective intervention. <i>Int J Cancer.</i> 2009; 124(8):1914-1917.	Review/Other-Tx	6,946 patients	To identify stratifying risk factors for surveillance and define concepts for a clinical feasible and noninvasive prospective protocol for intervention of cardiovascular side effects.	In the HL survivors, a family history of congestive heart failure and CAD increased the risk for these diseases. The Swedish Hodgkin Intervention and Prevention study started in 2007. In the pilot feasibility study for prospective intervention (47 patients), about 25% of the cases had side effects and laboratory abnormalities. These patients were referred to a cardiologist or general practitioner. In the prospective cohort, a positive family history for congestive heart failure or CAD could be a stratifying risk factor when setting up a surveillance model. The prospective on-going study presents an intervention model that screens and treats for comorbidity factors. This article also presents an overview of the study concept.	4

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
63. Bowers DC, McNeil DE, Liu Y, et al. Stroke as a late treatment effect of Hodgkin's Disease: a report from the Childhood Cancer Survivor Study. <i>J Clin Oncol.</i> 2005; 23(27):6508-6515.	Observational-Tx	HL survivors (n=1,926) and siblings (n=3,846)	To examine the incidence of and risk factors for stroke among childhood HL survivors. Incidence rates of stroke among HL survivors and siblings were calculated and compared. This is a report from the Childhood Cancer Survivor Study, a multi-multicenter cohort study.	Incidence of late-occurring stroke among HL survivors treated with mantle radiation was 109.8 per 100,000 person-years. The RR of late-occurring stroke among HL survivors treated with mantle radiation was 5.62. Survivors of childhood HL are at increased risk of stroke.	2
64. 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. <i>J Natl Cancer Inst.</i> 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

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
65. Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. <i>N Engl J Med.</i> 1991; 325(9):599-605.	Observational-Tx	1,787 patients	Review records of patients with HL who were treated with RT alone (810 patients), RT and chemotherapy (920 patients), or chemotherapy alone (57 patients) to determine the risk of thyroid disease.	A total of 573 patients had clinical or biochemical evidence of thyroid disease. Among the 1,677 patients whose thyroid was irradiated, the actuarial risk of thyroid disease 20 years after treatment was 52%, and it was 67% at 26 years. Hypothyroidism was found in 513 patients. A total of 486 patients received thyroxine therapy for elevated serum thyrotropin concentrations and either low free thyroxine (208 patients) or normal free thyroxine values (278 patients); 27 had transient elevations of the serum thyrotropin level that were not treated. Graves' hyperthyroidism developed in 30 patients (2 of whom had not undergone thyroid irradiation), and ophthalmopathy developed in 17 of these patients. Ophthalmopathy developed in 4 other patients with Graves' disease during a period of hypothyroidism (n=3) or euthyroidism (n=1). The risk of Graves' disease was 7.2 to 20.4 times that for normal subjects. Silent thyroiditis with thyrotoxicosis developed in 6 patients. 44 patients were found to have single or multiple thyroid nodules, 26 of whom underwent thyroidectomy. 6/44 had papillary or follicular cancers. Among the patients who did not undergo operation, 12 had small functioning nodules, 4 had cysts, and 2 had multinodular goiters. The actuarial risk of thyroid cancer was 1.7%. The risk of thyroid cancer was 15.6 times the expected risk.	2

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
66. Sklar C, Whitton J, Mertens A, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. <i>J Clin Endocrinol Metab.</i> 2000; 85(9):3227-3232.	Observational-Tx	1,791 patients	Retrospective cohort study to assess the thyroid status of childhood HL survivors. Thyroid status was assessed in HL survivors from among 13,674 participants in the Childhood Cancer Survivor Study.	79% of subjects were treated with radiation (median dose of radiation to the thyroid, 3,500 cGy; range, 0.37-5,500 cGy). Control data were available from 2,808 (1,346 males) sibling controls. 34% of the entire cohort has been diagnosed with at least one thyroid abnormality. Hypothyroidism was the most common disturbance, with a RR of 17.1 (P<0.0001) compared to sibling controls. Increasing dose of radiation, older age at diagnosis of HL, and female sex were all independently associated with an increased risk of hypothyroidism. Actuarial risk of hypothyroidism for subjects treated with 4,500 cGy or more is 50% at 20 years from diagnosis. Hyperthyroidism was reported by 5% of survivors, which was 8-fold greater (P<0.0001) than the incidence reported by the controls. Thyroid dose of 3,500 cGy or more was the only risk factor identified for hyperthyroidism. The risk of thyroid nodules was 27 times (P<0.0001) that in sibling controls. Female sex and radiation dose to the thyroid of 2,500 cGy or more were independent risk factors for thyroid nodules. The actuarial risk of a female survivor developing a thyroid nodule is 20% at 20 years from diagnosis. Thyroid cancer was diagnosed in 20 survivors, which is 18 times the expected rate for the general population.	2
67. Koh ES, Sun A, Tran TH, et al. Clinical dose-volume histogram analysis in predicting radiation pneumonitis in Hodgkin's lymphoma. <i>Int J Radiat Oncol Biol Phys.</i> 2006; 66(1):223-228.	Observational-Tx	64 consecutive HL patients	To quantify the incidence of radiation pneumonitis and identify any clinically relevant parameters that may influence the risk of radiation pneumonitis.	Actuarial survival for all patients was 91% at 3 years. There were 2 (2/64) cases of Radiation Therapy Oncology Group (RTOG) Grade 2 radiation pneumonitis (incidence 3.1%). Both index cases with corresponding V (20) values of 47.0% and 40.7% were located in the upper quartile (2/16 cases), defined by a V (20) value of $\geq 36\%$, an incidence of 12.5% (P=0.03).	2

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
68. Ng AK, Li S, Neuberg D, et al. A prospective study of pulmonary function in Hodgkin's lymphoma patients. <i>Ann Oncol.</i> 2008; 19(10):1754-1758.	Observational-Tx	52 patients	To prospectively study changes in lung function in HL patients and to explore predictors for these changes over time.	With chemotherapy alone, the median %DLCO declined significantly at 1 month but returned to baseline by 6 months. The median %DLCO did not further decrease with RT, but remained reduced at 1 year. In patients who received RT, having >33% of lung volume receive 20 Gy (V20) and a mean lung dose of >13 Gy significantly predicted for persistently reduced %DLCO at 6 months (P=0.035). Smoking significantly predicted for a persistently reduced %DLCO at 1 year (P=0.036). On multivariable analysis, significant predictors for decline in %DLCO at 1 year were higher baseline %DLCO (P=0.01), higher mean lung dose (P=0.02), and a smoking history (P=0.02).	1
69. Tarbell NJ, Thompson L, Mauch P. Thoracic irradiation in Hodgkin's disease: disease control and long-term complications. <i>Int J Radiat Oncol Biol Phys.</i> 1990; 18(2):275-281.	Observational-Tx	590 patients	Analysis of recurrence patterns, pulmonary, cardiac and thyroid complications in patients with stage IA-IIIB HL who received mantle irradiation.	Pulmonary recurrence was more frequently seen in patients with large mediastinal adenopathy; 11% of patients with large mediastinal adenopathy recurred in the lung in contrast to 3.1% with small or no mediastinal disease, P=0.003. Hilar involvement, when corrected for size of mediastinal involvement, was not predictive of lung relapse. Data suggest that the long-term complications of mantle irradiation are uncommon with the use of modern radiotherapeutic techniques. The use of prophylactic whole lung irradiation is no longer recommended since its use increased the risk of pneumonitis.	2

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
70. Knobel H, Havard Loge J, Lund MB, Forfang K, Nome O, Kaasa S. Late medical complications and fatigue in Hodgkin's disease survivors. <i>J Clin Oncol.</i> 2001; 19(13):3226-3233.	Observational-Tx	92 patients	To determine whether late cardiac, pulmonary, and thyroid complications after curative treatment for HL may explain the high level of fatigue among HL survivors.	HL survivors with pulmonary dysfunction were more fatigued than HL survivors with normal pulmonary function (10.9 v 8.9; P<.05). Gas transfer impairment was the most prevalent pulmonary dysfunction, and three times as many patients with gas transfer impairment reported chronic fatigue (duration, 6 months or longer), compared with patients without pulmonary dysfunction (48% v 17%, P<.01). No associations were found between cardiac sequelae or hypothyroidism and fatigue. No associations were found between cardiac sequelae or hypothyroidism and fatigue.	2
71. Hirsch A, Vander Els N, Straus DJ, et al. Effect of ABVD chemotherapy with and without mantle or mediastinal irradiation on pulmonary function and symptoms in early-stage Hodgkin's disease. <i>J Clin Oncol.</i> 1996; 14(4):1297-1305.	Experimental-Tx	60 patients	Prospective study to examine the effect of ABVD chemotherapy alone and of ABVD with mantle or mediastinal RT on the pulmonary function of patients with early-stage HL.	ABVD chemotherapy induced acute pulmonary toxicity that required bleomycin dose modification in a substantial number of patients. The addition of RT resulted in a further decrease in forced vital capacity.	1
72. Horning SJ, Adhikari A, Rizk N, Hoppe RT, Olshen RA. Effect of treatment for Hodgkin's disease on pulmonary function: results of a prospective study. <i>J Clin Oncol.</i> 1994; 12(2):297-305.	Experimental-Tx	145 patients	Prospective study to assess the effects of mediastinal irradiation and bleomycin chemotherapy on pulmonary function. Patients were treated from 1980 to 1990 on randomized controlled trials.	A decrease in forced vital capacity and DLCO in the first 15 months after treatment followed by recovery after 36 months was observed for most patients. Patients who received mediastinal RT had a more pronounced reduction in pulmonary function and less complete recovery. Overall, 3 or more years after treatment, 32% of group I patients, 37% of group II patients, and 19% of group III patients had forced vital capacity values <80% of predicted, while only 7% of patients had a DLCO < 80% of predicted. Linear regression identified baseline measurement as the only significant predictor of change in percent predicted forced vital capacity or DLCO; patients with higher baseline values had greater decrements after therapy. Mantle RT was the only significant treatment variable, predictive of forced vital capacity and DLCO within 15 months and forced vital capacity at 36 or more months. No patient experienced pulmonary toxicity severe enough to require hospitalization.	1

* See Last Page for Key

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
73. 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.	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
74. Kulkarni SS, Sastry PS, Saikia TK, Parikh PM, Gopal R, Advani SH. Gonadal function following ABVD therapy for Hodgkin's disease. <i>Am J Clin Oncol.</i> 1997; 20(4):354-357.	Observational-Tx	38 patients	To assess the effect of combination chemotherapy with ABVD on gonadal function in patients treated for HL. 26 patients received ABVD therapy and 12 received a combination of ABVD with COPP or MOPP.	Azoospermia was seen in 1 patient from the ABVD group and 10 patients from the COPP/ABVD group (P<0.001). Serum follicle-stimulating hormone, levels were significantly higher in the COPP/ABVD group than in the ABVD group (23.5 vs 4.7 mlu/ml; P<0.001) The levels were in the normal range in 23 patients from the ABVD group, as compared to 4 patients in the COPP/ABVD group (88.5% vs 33.3%; P<0.001). Three patients treated with ABVD fathered children post-therapy. ABVD is associated with relatively better preservation of gonadal function.	2
75. Behringer K, Breuer K, Reineke T, et al. Secondary amenorrhea after Hodgkin's lymphoma is influenced by age at treatment, stage of disease, chemotherapy regimen, and the use of oral contraceptives during therapy: a report from the German Hodgkin's Lymphoma Study Group. <i>J Clin Oncol.</i> 2005; 23(30):7555-7564.	Review/Other-Tx	405 women answered study questions	To evaluate the menstrual status in survivors of successfully treated HL using a survey. The factors assessed concerning their influence on amenorrhea were age, treatment, stage, and the use of oral contraceptives during chemotherapy.	Most women treated for advanced-stage HL experience amenorrhea after therapy. Amenorrhea is significantly more frequent in women with advanced-stage HL receiving 8 cycles of dose-escalated BEACOPP and in women >30 years at first treatment. Data show a statistical association between the use of oral contraceptives and return of menstrual cycle, which is subject to further investigation.	4

**Follow-up of Hodgkin Lymphoma
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
76. Sieniawski M, Reineke T, Nogova L, et al. Fertility in male patients with advanced Hodgkin lymphoma treated with BEACOPP: a report of the German Hodgkin Study Group (GHSg). <i>Blood</i> . 2008; 111(1):71-76.	Observational-Tx	38 patients	To examine the impact of BEACOPP regimen on fertility status in male patients with advanced HL treated within prospectively randomized trials of the German Hodgkin Study Group.	There was no difference in azoospermia rate between patients treated with BEACOPP baseline and those given BEACOPP escalated (93% vs 87%, respectively; P>.999). After treatment, most patients (93%) had abnormal values of follicle-stimulating hormone, whereas the number of patients with abnormal levels of testosterone and luteinizing hormone was less pronounced 57% and 21%, respectively. Male patients with HL are at high risk of infertility after treatment with BEACOPP.	2
77. Mauch P, Ng A, Aleman B, et al. Report from the Rockefeller Foundation Sponsored International Workshop on reducing mortality and improving quality of life in long-term survivors of Hodgkin's disease: July 9-16, 2003, Bellagio, Italy. <i>Eur J Haematol Suppl</i> . 2005; (66):68-76.	Review/Other-Tx	N/A	Summary report on the findings of the Rockefeller Foundation Sponsored International Workshop. Purpose of workshop is to devise strategies to reduce mortality and improve quality of life of long-term survivors of HL.	Main areas of late effects of HL discussed were: second malignancy, cardiac disease, infection, pulmonary dysfunction, endocrine abnormalities, and quality of life.	4
78. Ng AK, Mauch PM. Late effects of Hodgkin's disease and its treatment. <i>Cancer J</i> . 2009; 15(2):164-168.	Review/Other-Tx	N/A	Review late effects of HL and its treatment.	Most data on late effects after HL are based on patients treated with outdated chemotherapy and RT. Continued documentation of late effects associated with newer treatment will be important for the follow-up of patients treated in the modern era as HL therapy evolve over time.	4

Evidence Table Key

Study Quality Category Definitions

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

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

ABVD = Doxorubicin, bleomycin, vinblastine, and dacarbazine

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

CAD = Coronary artery disease

CI = Confidence interval

COPP = Cyclophosphamide, vincristine, procarbazine, and prednisone

CR = Complete response

CT = Computed tomography

DLCO = Diffusing capacity of carbon monoxide

EFRT = Extended-field radiation therapy

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

HL = Hodgkin lymphoma

HR = Hazard ratio

IFRT = Involved-field radiation therapy

MOPP = Mechlorethamine, vincristine, procarbazine, and prednisone

MRI = Magnetic resonance imaging

NPV = Negative predictive value

OR = Odds ratio

OS = Overall survival

PPV = Positive predictive value

RR = Relative risk

RT = Radiation therapy

US = Ultrasound