Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Jaffe ES, Harris NL, Stein H, Isaacson PG. Classification of lymphoid neoplasms: the microscope as a tool for disease discovery. *Blood*. 2008;112(12):4384-4399.	Review/Other-Tx	N/A	Classification of lymphoid neoplasms using microscopes.	The multiparameter approach to classification adopted by the World Health Organization (WHO) classification has been validated in international studies as being highly reproducible, and enhancing the interpretation of clinical and translational studies. In addition, accurate and precise classification of disease entities facilitates the discovery of the molecular basis of lymphoid neoplasms in the basic science laboratory.	4
2. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol.* 2007;25(5):571-578.	Review/Other-Dx	N/A	To develop guidelines for performing and interpreting PET imaging for treatment assessment in patients with lymphoma both in clinical practice and in clinical trials.	PET after completion of therapy should be performed at least 3 weeks and preferably at 6 to 8 weeks, after chemotherapy or chemoimmunotherapy, and 8 to 12 weeks after radiation or chemoradiotherapy. Visual assessment alone is adequate for interpreting PET findings as positive or negative when assessing response after completion of therapy. Mediastinal blood pool activity is recommended as the reference background activity to define PET positivity for a residual mass ≥2 cm in greatest transverse diameter, regardless of its location. A smaller residual mass or a normal sized lymph node (ie, ≤1 x 1 cm in diameter) should be considered positive if its activity is above that of the surrounding background. Specific criteria for defining PET positivity in the liver, spleen, lung, and bone marrow are also proposed. Use of attenuation-corrected PET is strongly encouraged. Use of PET for treatment monitoring during a course of therapy should only be done in a clinical trial or as part of a prospective registry.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
3. Yoo C, Lee DH, Kim JE, et al. Limited role of interim PET/CT in patients with diffuse large B-cell lymphoma treated with R-CHOP. *Ann Hematol.* 2011;90(7):797-802.	Observational-Dx	155 DLBCL patients	To investigate the ability of interim PET to monitor response to standard dose R-CHOP chemotherapy in chemotherapy-naive patients with DLBCL.	Interim PET/CT-negative patients (n=100) showed superior CR rates to interim PET/CT-positive patients (n=55; 93% vs 62%, $P<0.001$). However, there was no difference in PFS ($P=0.07$) and OS ($P=0.24$) between interim PET/CT-negative and positive group. We categorized patients into 3 groups, with 100 (64%) in the early mCR group, 35 (23%) in the delayed mCR group, and 20 (13%) in the never mCR group. Early mCR and delayed mCR group did not differ significantly in PFS ($P=0.84$) or OS ($P=0.20$). However, the survival outcome in the never mCR group was significantly inferior to the combined early and delayed mCR group.	4
4. Pregno P, Chiappella A, Bello M, et al. Interim 18-FDG-PET/CT failed to predict the outcome in diffuse large B-cell lymphoma patients treated at the diagnosis with rituximab-CHOP. *Blood.* 2012;119(9):2066-2073.	Observational-Dx	88 first-line DLBCL patients	To determine predictive value of interim-PET on PFS in DLBCL.	Interim-PET, 72% negative, 28% positive; final-PET, 88% negative, 12% positive; clinical CR 90%. Concordance between clinical response and final-PET negativity was 97% because of 2 false positive. With a median follow-up of 26.2 months, 2-year OS and PFS were 91% and 77%, respectively. 2-year PFS for interim-PET and final-PET negative vs positive were as follows: interim-PET 85% vs 72% ($P=.0475$); final-PET 83% vs 64% ($P<.001$).	3

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5. Dal Maso L, Polesel J, Serraino D, et al. Pattern of cancer risk in persons with AIDS in Italy in the HAART era. *Br J Cancer*. 2009;100(5):840-847.	Review/Other-Tx	Standardized incidence ratios were computed in 21,951 AIDS cases aged 16-69 years reported between 1986 and 2005. Of 101,669 person-years available, 45,026 were after 1996	Review of the study carried out between the Italian AIDS Registry and 24 Italian cancer registries to compare cancer excess among PWHA before and after the introduction of HAART in 1996.	Standardized incidence ratios for Kaposi sarcoma and NHL greatly decreased in 1997-2004 compared with 1986-1996, but high standardized incidence ratios for Kaposi sarcoma persisted in the increasingly large fraction of PWHA who had an interval of <1 year between first HIV-positive test and AIDS diagnosis. A significant excess of liver cancer (standardized incidence ratios=6.4) emerged in 1997-2004, whereas the standardized incidence ratios for cancer of the cervix (41.5), anus (44.0), lung (4.1), brain (3.2), skin (non-melanoma, 1.8); Hodgkin lymphoma (20.7), myeloma (3.9), and non-AIDS-defining cancers (2.2) were similarly elevated in the 2 periods. The excess of some potentially preventable cancers in PWHA suggests that HAART use must be accompanied by cancer-prevention strategies, notably antismoking and cervical cancer screening programs.	4
6. Franceschi S, Lise M, Clifford GM, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. *Br J Cancer*. 2010;103(3):416-422.	Review/Other-Tx	In total, 9,429 PWHA provided 20,615, 17,690, and 15,410 person-years in the pre-, early-, and late-HAART periods, respectively	To evaluate the changes in patterns of cancer incidence in the Swiss HIV Cohort Study in 9 different periods (pre-HAART, 1985–1996; early HAART, 1997–2001; and late HAART: 2002–2006), while taking into account large shifts in the age distribution of PWHA.	Incidence of Kaposi sarcoma and NHL decreased by several fold between the pre- and early-HAART periods, and additionally declined from the early- to the late-HAART period. Incidence of cancers of the anus, liver, non-melanomatous skin, and Hodgkin's lymphoma increased in the early- compared with the pre-HAART period, but not during the late-HAART period. The incidence of all non-AIDS-defining cancers combined was similar in all periods, and approximately double that in the general population.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
7. Geh JI, Spittle MF. Oncological problems in AIDS--a review of the clinical features and management. *Ann Acad Med Singapore.* 1996;25(3):380-391.	Review/Other-Tx	N/A	A review of the clinical features and management of oncological problems in AIDS.	There is evidence that in Kaposi's sarcoma, systemic NHL, primary central nervous system lymphoma and invasive cervical cancer an additional viral infection may be responsible for their pathogenesis. Kaposi's sarcoma-associated herpes virus is implicated in the development of Kaposi's sarcoma, Epstein-Barr virus in systemic NHL as well as primary central nervous system lymphoma and human papilloma virus in invasive cervical cancer. Developing effective treatment strategies with minimal toxicity for these patients remains the greatest challenge as they often have serious coexisting illnesses and tolerate chemotherapy poorly because of insufficient bone marrow function reserve.	4
8. van Leeuwen MT, Vajdic CM, Middleton MG, et al. Continuing declines in some but not all HIV-associated cancers in Australia after widespread use of antiretroviral therapy. *AIDS.* 2009;23(16):2183-2190.	Review/Other-Tx	20,232 HIV patients	To describe changes in cancer incidence in people with HIV in Australia since the introduction of HAART.	Incidence of Kaposi sarcoma and NHL declined significantly (Ptrend<0.001). Incidence of Hodgkin lymphoma was significantly higher during the early-HAART period (incidence rate ratio 2.34, 95% CI: 1.19-4.63) but declined thereafter (Pdiff=0.014). Incidence of anal cancer was unchanged (Ptrend=0.451) and remained raised more than 30-fold. Incidence declined significantly for melanoma (Ptrend=0.041) and prostate cancer (Ptrend= 0.026), and, during the late-HAART period, was lower than in the general population for both cancers. Incidence of colorectal cancer was consistently lower than in the general population.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
9. Safar V, Dupuis J, Jardin F, al. E. Early 18fluorodeoxyglucose PET Scan as a Prognostic Tool in Diffuse Large B-Cell Lymphoma Patients Treated with An Anthracycline-Based Chemotherapy Plus Rituximab. 2009; https://ash.confex.com/ash/2009/webprogram/Paper21587.html. Accessed June 22, 2012.	Observational-Dx	112 previously untreated patients	To evaluate the predictive value of early PET in a large prospective cohort of patients treated with immunochemotherapy for DLBCL.	Median age at diagnosis was 59 years (range 20-79 years) and 67% of patients were males, 44% were over 60 years, 81% presented with an advanced Ann Arbor stage (III-IV), 29% had a poor performance status (ECOG 2-4), 36% had more than 1 extra-nodal site involved and LDH were elevated in 68%. 9/70 (13%) PET2n and 15/42 (36%) PET2p patients died. The estimated 5-year OS was 88% for PET2n and 62% for PET2p patients (log rank test, $P<0.0034$). Prognostic value of early PET was significant in terms of OS for patients treated with R-CHOP-21 ($P=0.0225$) but not for those treated with dose-dense regimens ($P=0.133$).	3
10. Flowers CR, Sinha R, Vose JM. Improving outcomes for patients with diffuse large B-cell lymphoma. *CA Cancer J Clin.* 2010;60(6):393-408.	Review/Other-Dx	N/A	To review DLBCL and outcomes in patients.	No results stated in abstract.	4
11. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood.* 1994;84(5):1361-1392.	Review/Other-Tx	Discussed by 19 hemato-pathologists	To report the result of an international literature review of lymphomas in order to clarify some of the confusion surrounding the histologic categorization of lymphoma.	9 major categories of lymphoid malignancies: B-cell, T-cell, and Hodgkin's disease, with 9 general categories; definite, provisional, and unclassifiable were decided, though the utility of these histologically and immunologically defined categories in predicting clinical outcome was not determined.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
12. Carr R, Barrington SF, Madan B, et al. Detection of lymphoma in bone marrow by whole-body positron emission tomography. *Blood.* 1998;91(9):3340-3346.	Review/Other-Dx	50 patients	To determine whether the increased marrow uptake of FDG observed in some lymphoma patients during routine staging PET scans represented marrow involvement by disease.	PET scans of 50 patients with Hodgkin's (12) and non-Hodgkin's (38) lymphoma were analyzed by 3 independent observers and the marrow graded as normal or abnormal using a visual grading system. Unilateral iliac crest marrow aspirates and biopsies were performed on all patients. The PET scan and marrow histology agreed in 39 patients (78%), being concordant positive in 13 and concordant negative in 26 patients. In 8 patients the PET scan showed increased FDG uptake but staging biopsy was negative; in 4 of these 8 patients the PET scan showed a normal marrow background with focal FDG “hot spots” distant from the site biopsied. In 3 patients the marrow biopsy specimen was positive but the PET scan normal; 2 of these 3 patients had NHL whose malignant cells did not take up FDG at lymph node or marrow disease sites. Therefore, there were only 5 patients (10%) in whom there was a difference between the PET scan and biopsy result which could not be fully explained.	4
13. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Lister TA. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32(27):3059-3068.	Review/Other-Dx	N/A	To modernize recommendations for evaluation, staging, and response assessment of patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).	PET/CT should be used for response assessment in FDG-avid histologies, using the 5-point scale; CT is preferred for low or variable FDG avidity. A complete metabolic response even with a persistent mass is considered a CR. A partial response requires a decrease by more than 50% in the sum of the product of the perpendicular diameters of up to 6 representative nodes or extranodal lesions. Progressive disease by CT criteria only requires an increase in the perpendicular diameters of a single node by 50%. Surveillance scans after remission is discouraged, especially for DLBCL and Hodgkin lymphoma, although a repeat study may be considered after an equivocal finding after treatment. Judicious use of follow-up scans may be considered in indolent lymphomas with residual intra-abdominal or retroperitoneal disease.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
14. Khan AB, Barrington SF, Mikhaeel NG, et al. PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. *Blood.* 2013;122(1):61-67.	Observational-Dx	130 patients	To investigate whether PET/CT identifies clinically important bone marrow involvement by DLBCL with sufficient accuracy to replace routine staging bone marrow biopsy.	Of 130 patients, 35 (27%) were judged to have marrow involvement; 33 were identified by PET/CT compared with 14 by marrow histology. PET identified all clinically important marrow lymphoma, while biopsy did not upstage any patient. Sensitivity and specificity were 94% and 100% for PET/CT and 40% and 100% for marrow biopsy. As a secondary aim, we compared the prognosis of marrow involvement, as detected by PET/CT or biopsy. Cases with marrow deposits identified by PET/CT but not biopsy had PFS and OS similar to stage IV disease without involved marrow. Positive biopsy conferred significantly inferior PFS (P=0.003); these cases frequently had other markers of poor-risk disease.	2
15. Moog F, Bangerter M, Kotzerke J, Guhlmann A, Frickhofen N, Reske SN. 18-F-fluorodeoxyglucose-positron emission tomography as a new approach to detect lymphomatous bone marrow. *J Clin Oncol.* 1998;16(2):603-609.	Observational-Dx	78 patients	To investigate the efficacy of FDG-PET as a new method to evaluate bone marrow involvement in patients with malignant lymphoma.	In addition to 7 concordant positive and 57 concordant negative findings, biopsy revealed another 4 cases with bone marrow involvement not detectable by FDG-PET analysis (+5.1%). On the contrary, PET showed bone marrow areas of intensive FDG uptake that suggested bone marrow lymphoma in 10 patients with negative biopsies (+12.8%). In 8 patients, FDG-PET findings were confirmed by either histologic verification (n = 4), magnetic resonance imaging (n = 2), polymerase chain reaction for rearranged immunoglobulin H sequences (n = 1), or clinical presentation (n = 1). 2 cases remained unresolved.	2
16. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007;25(5):579-586.	Review/Other-Dx	N/A	Guidelines to help improved therapies for patients with lymphoma.	No results stated in abstract.	4

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17. Buchmann I, Reinhardt M, Elsner K, et al. 2-(fluorine-18)fluoro-2-deoxy-D-glucose positron emission tomography in the detection and staging of malignant lymphoma. A bicenter trial. *Cancer*. 2001;91(5):889-899.	Observational-Dx	52 patients	A prospective evaluation of the clinical value of FDG-PET in the detection and staging of malignant lymphoma compared with CT and bone marrow biopsy.	Altogether, 1,297 anatomic regions (lymph nodes, organs, and bone marrow) were evaluated. FDG-PET and CT scans were compared by receiver operating characteristic curve analysis. The area under the receiver operating characteristic curve were as follows: lymph nodes, 0.996 (PET) and 0.916 (CT); extranodal, 0.999 (PET) and 0.916 (CT); supradiaphragmatic, 0.996 (PET) and 0.905 (CT); and infradiaphragmatic, 0.999 (PET) and 0.952 (CT). In these analyses, FDG-PET was significantly superior to CT ($P<0.05$), except in infradiaphragmatic regions, in which the 2 methods produced equivalent results. In detecting bone marrow infiltration, FDG-PET was superior to CT and was equivalent to bone marrow biopsy. In 4/52 patients (8%), FDG-PET led to an upstaging and a change of therapy.	1
18. Pelosi E, Pregno P, Penna D, et al. Role of whole-body [18F] fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) and conventional techniques in the staging of patients with Hodgkin and aggressive non Hodgkin lymphoma. *Radiol Med*. 2008;113(4):578-590.	Observational-Dx	65 patients	To evaluate the role of FDG-PET/CT in the staging of Hodgkin's and aggressive NHL, comparing it with conventional diagnostic methods, ie, contrast-enhanced CT and bone marrow biopsy.	PET correctly staged 93.8% of enrolled patients (61/65), whereas conventional techniques correctly staged 89.2% (58/65; P=NS, Chi(2) test). There was complete concordance in 54/65 patients (83.1%); among the remaining 11 cases, PET upstaged 8 patients (7 true positive and 1 false positive), and downstaged 3 (all false negative). In 5/65 patients, chemotherapy treatment was modified on the basis of PET findings.	3

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19. Wirth A, Seymour JF, Hicks RJ, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography, gallium-67 scintigraphy, and conventional staging for Hodgkin's disease and non-Hodgkin's lymphoma. *Am J Med.* 2002;112(4):262-268.	Observational-Dx	50 patients	To compare FDG-PET and gallium scanning with each other and with conventional staging, for patients with Hodgkin's disease NHL.	PET and gallium scanning each upstaged 14% of patients (n = 7). Management was altered by PET in 9 cases (18%) and by gallium scanning in 7 (14%, *P*=0.6). Disease was evident in 117 sites in 42 patients. The case positivity rate for conventional assessment was 90%; for PET, 95%; for gallium scanning, 88%; for conventional assessment plus PET, 100%; and for conventional assessment plus gallium scanning, 98%. Site positivity rates for conventional assessment were 68%; for PET, 82%; for gallium scanning, 69% (conventional vs PET, *P*=0.01; conventional vs gallium scanning, *P*=0.9; PET vs gallium scanning, *P*=0.01); for conventional assessment plus PET, 96%; and for conventional assessment plus gallium scanning, 94%. PET and gallium scanning were entirely concordant in 31 patients; in the other 19 patients, PET identified 25 sites missed by gallium scanning, whereas gallium scanning identified 10 sites missed by PET.	3
20. NCCN Clinical Practice Guidelines in Oncology. Non-Hodgkin's Lymphomas. Version 2.2014. 2014; Available at: http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf. Accessed May 27, 2014.	Review/Other-Tx	N/A	To provide guidelines on NHLs.	No results stated in abstract.	4

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21. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med*. 1993;329(14):987-994.	Review/Other-Tx	2,031 adults from 16 institutions and cooperative groups in the United States, Europe, and Canada who were treated between 1982 and 1987	To develop a model for predicting outcome in patients with aggressive NHL on the basis of the patients' clinical characteristics before treatment.	The model based on age, tumor stage, serum LDH concentration, performance status, and number of extranodal disease sites, identified 4 risk groups with predicted 5-year survival rates of 73%, 51%, 43%, and 26%. In 1,274 patients, 60 or younger, an age-adjusted model based on tumor stage, LDH level, and performance status identified 4 risk groups with predicted 5-year survival rates of 83%, 69%, 46%, and 32%. In both models, the increased risk of death was due to both a lower rate of CRs and a higher rate of relapse from CR. These 2 indexes, called the international index and the age-adjusted international index, were significantly more accurate than the Ann Arbor classification in predicting long-term survival.	4
22. Ziepert M, Hasenclever D, Kuhnt E, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28(14):2373-2380.	Review/Other-Tx	1,062 patients	To investigate whether the IPI has maintained its power for risk stratification when rituximab is combined with CHOP by analyzing the prognostic relevance of IPI in 9 prospective clinical trials.	IPI score was significant for all 9 end points. Rituximab significantly improved treatment outcome within each IPI group resulting in a quenching of the Kaplan-Meier estimators. However, IPI was a significant prognostic factor in all 9 end points and the ordering of the IPI groups remained valid. The relative risk estimates of single IPI factors and their order in patients treated with R-CHOP were similar to those found with CHOP.	4

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23. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol.* 2006;24(19):3121-3127.	Experimental-Tx	267 R-CHOP and 279 CHOP patients	To address early and late treatment failures in older patients with DLBCL.	3-year FFS rate was 53% for R-CHOP patients and 46% for CHOP patients (*P*=.04) at a median follow-up time of 3.5 years. 2-year FFS rate from second random assignment was 76% for maintenance rituximab compared with 61% for observation (*P*=.009). No significant differences in survival were seen according to induction or maintenance therapy. FFS was prolonged with maintenance rituximab after CHOP (*P*=.0004) but not after R-CHOP (*P*=.81) with 2-year FFS rates from second random assignment of 77%, 79%, 74%, and 45% for R-CHOP, R-CHOP + maintenance rituximab, CHOP + maintenance rituximab, and CHOP, respectively. In a secondary analysis excluding maintenance rituximab patients, R-CHOP alone reduced the risks of treatment failure (*P*=.003) and death (*P*=.05) compared with CHOP alone.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
24. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol.* 2008;9(2):105-116.	Experimental-Tx	1,222 elderly patients	A randomized trial to assess whether 6 or 8 cycles of R-CHOP-14 can improve outcome of these patients compared with 6 or 8 cycles of CHOP-14.	3-year EFS was 47.2% after 6 cycles of CHOP-14 (95% CI, 41.2-53.3), 53.0% (47.0–59.1) after 8 cycles of CHOP-14, 66.5% (60.9–72.0) after 6 cycles of R-CHOP-14, and 63.1% (57.4–68.8) after 8 cycles of R-CHOP-14. Compared with 6 cycles of CHOP-14, the improvement in 3-year EFS was 5.8% (-2.8–14.4) for 8 cycles of CHOP-14, 19.3% (11.1–27.5) for 6 cycles of R-CHOP-14, and 15.9% (7.6–24.2) for 8 cycles of R-CHOP-14. 3-year OS was 67.7% (62.0–73.5) for 6 cycles of CHOP-14, 66.0% (60.1–71.9) for 8 cycles of CHOP-14, 78.1% (73.2–83.0) for 6 cycles of R-CHOP-14, and 72.5% (67.1-77.9) for 8 cycles of R-CHOP-14. Compared with treatment with 6 cycles of CHOP-14, OS improved by -1.7% (-10.0–6.6) after 8 cycles of CHOP-14, 10.4% (2.8–18.0) after 6 cycles of R-CHOP-14, and 4.8% (-3.1–12.7) after 8 cycles of R-CHOP-14. In a multivariate analysis that used 6 cycles of CHOP-14 without rituximab as the reference, and adjusting for known prognostic factors, all 3 intensified regimens improved 3-year EFS (8 cycles of CHOP-14: relative risk 0.76 [0.60–0.95], P=0.0172; 6 cycles of R-CHOP-14: relative risk 0.51 [0.40–0.65], P<0.0001; 8 cycles of R-CHOP-14: relative risk 0.54 [0.43–0.69], P<0.0001). PFS improved after 6 cycles of R-CHOP-14 (relative risk 0.50 [0.38–0.67], P<0.0001), and 8 cycles of R-CHOP-14 (relative risk 0.59 [0.45–0.77], P=0.0001). OS improved only after 6 cycles of R-CHOP-14 (relative risk 0.63 [0.46–0.85], P=0.0031). In patients with a partial response after 4 cycles of chemotherapy, 8 cycles were not better than 6 cycles.	1

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25. Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol.* 2006;7(5):379-391.	Experimental-Tx	824 patients	To compare CHOP-like chemotherapy and R-CHOP-like chemotherapy alone in young patients with good-prognosis DLBCL.	After a median follow-up of 34 months (range 0.03-61), patients assigned chemotherapy and rituximab had increased 3-year EFS compared with those assigned chemotherapy alone (79% [95% CI: 75-83] vs 59% [54-64]; difference between groups 20% [13-27], log-rank $P<0.0001$), and had increased 3-year OS (93% [90-95] vs 84% [80-88]; difference between groups 9% [3-13], log-rank $P=0.0001$). EFS was affected by treatment group, presence of bulky disease, and age-adjusted IPI: after chemotherapy and rituximab, a favorable subgroup (ie, IPI=0, no bulk) could be defined from a less-favorable subgroup (ie, IPI=1 or bulk, or both). Groups did not differ in the frequency of adverse events.	1
26. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood.* 2007;109(5):1857-1861.	Observational-Tx	365 patients	To perform a retrospective analysis of patients with DLBCL treated with R-CHOP to assess the current value of the IPI and to determine if a different grouping of the prognostic factor scores would permit more clinically relevant assignment of patients to prognostic groups.	Redistribution of the IPI factors into a R-IPI provides a more clinically useful prediction of outcome. The R-IPI identifies 3 distinct prognostic groups with a very good (4-year PFS 94%, OS 94%), good (4-year PFS 80%, OS 79%), and poor (4-year PFS 53%, OS 55%) outcome, respectively ($P<.001$). The IPI (or R-IPI) no longer identifies a risk group with <50% chance of survival.	2

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27. Advani RH, Chen H, Habermann TM, et al. Comparison of conventional prognostic indices in patients older than 60 years with diffuse large B-cell lymphoma treated with R-CHOP in the US Intergroup Study (ECOG 4494, CALGB 9793): consideration of age greater than 70 years in an elderly prognostic index (E-IPI). *Br J Haematol.* 2010;151(2):143-151.	Observational-Tx	267 patients	To evaluate the performance of the standard IPI and following modifications: age adjusted-IPI, revised R-IPI, and an elderly-IPI with age cut-off 70 years in patients >60 years treated with R-CHOP.	In 267 patients, by IPI/age adjusted -IPI 60% were high-intermediate, 53% high and 12% low risk. With R-IPI, 60% were poor risk and none very good risk. Using elderly-IPI, 45% were high-intermediate/high risk and 27% low risk. No differences in outcome were seen in the low/low-intermediate groups with IPI/age adjusted-IPI. For elderly-IPI, FFS and OS were significantly different for low/low-intermediate groups. No differences were detected in the 4 indices with model fit/discrimination measures; however, elderly-IPI ranked highest. For elderly R-CHOP treated patients, distribution of IPI/age adjusted-IPI skewed toward high/high-intermediate risk with no differences in FFS/OS between low/low-intermediate risk. In contrast, with elderly-IPI, more are classified as low risk with significant differences in FFS/OS for low-intermediate compared to low risk. The R-IPI does not identify a very good risk group, thus minimizing its utility in this population.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
28. Advani R, Li H, Hong F, et al. ELDERLY INTERNATIONAL PROGNOSTIC INDEX IN DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS AGE >60 YEARS TREATED WITH RCHOP: INTERNATIONAL VALIDATION STUDY USING DATA FROM RICOVER-60 (GERMAN HIGH-GRADE NON-HODGKIN LYMPHOMA STUDY GROUP) AND LNH 98-5 (GROUPE D'ETUDE DE LYMPHOME D'ADULTES). *Hematological Oncology.* 2013;31(S1):abstract 222.	Observational-Tx	812 patients	To independently validate the elderly international prognostic index (EIPI).	812 patients were included. The median follow-up was 7.4 years. Patient characteristics were stage III/IV, 58%; >1 EN site, 26%; elevated LDH, 53%; and ECOG PS ≥17%. The median age was 68.5 years with 39% >70 years. On univariate analysis, all characteristics were significant for 5-year OS. Both the IPI and EIPI provided prognostic discrimination for OS of the 4 groups. The area under the receiver operator curve ranked the EIPI higher than the IPI over all event times. Similar rankings were obtained using Akaike's information criteria and concordance probability estimate. EIPI vs IPI classified more patients as low risk (40% vs 25%) and fewer as high (18% vs 25%). For patients reclassified (e.g. IPI-LI to EIPI-L), the 5-year EIPI OS (80%) matched the 5-year observed OS (80%) compared with the 5-year IPI OS (70%). Reclassification calibration indicated a significantly better fit for OS over time starting at 2 years for the EIPI vs IPI.	2
29. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature.* 2000;403(6769):503-511.	Review/Other-Tx	N/A	To conduct a systematic characterization of gene expression in B-cell malignancies in patients with DLBCL using DNA microarrays.	It was shown that there is diversity in gene expression among the tumors of DLBCL patients, apparently reflecting the variation in tumor proliferation rate, host response and differentiation state of the tumor. We identified 2 molecularly distinct forms of DLBCL which had gene expression patterns indicative of different stages of B-cell differentiation. One type expressed genes characteristic of 'GCB-like DLBCL'; the second type expressed genes normally induced during in vitro activation of peripheral blood B cells ('ABC DLBCL'). Patients with GCB DLBCL had a significantly better OS than those with ABC DLBCL.	4

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
30. Rosenwald A, Wright G, Leroy K, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. *J Exp Med.* 2003;198(6):851-862.	Review/Other-Tx	36 biopsy specimens from 35 patients for whom the diagnosis of PMBL was considered	The use of gene expression profiling to develop a more precise molecular diagnosis of PMBL.	PMBL patients had a relatively favorable clinical outcome, with a 5-year survival rate of 64% compared with 46% for other DLBCL patients. Gene expression profiling strongly supported a relationship between PMBL and Hodgkin lymphoma: over one third of the genes that were more highly expressed in PMBL than in other DLBCLs were also characteristically expressed in Hodgkin lymphoma cells. PDL2, which encodes a regulator of T cell activation, was the gene that best discriminated PMBL from other DLBCLs and was also highly expressed in Hodgkin lymphoma cells. The genomic loci for PDL2 and several neighboring genes were amplified in over half of the PMBLs and in Hodgkin lymphoma cell lines.	4

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
31. Savage KJ, Monti S, Kutok JL, et al. The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin lymphoma. *Blood.* 2003;102(12):3871-3879.	Review/Other-Tx	Previously untreated MLBCL patients (34) and DLBCL patients (176)	The comparison of gene expression profiles of newly diagnosed MLBCL and DLBCL and development of a classifier of these diseases.	MLBCLs had low levels of expression of multiple components of the B-cell receptor signaling cascade, a profile resembling that of Reed-Sternberg cells of classical Hodgkin lymphoma. Like classical Hodgkin lymphoma, MLBCLs also had high levels of expression of the interleukin-13 receptor and downstream effectors of interleukin-13 signaling (Janus kinase-2 and signal transducer and activator of transcription-1), tumor necrosis factor family members, and tumor necrosis factor receptor-associated factor-1. Increased expression of signal transducer and activator of transcription-1 and tumor necrosis factor receptor-associated factor-1 in MLBCL was confirmed by immunohistochemistry. Given the tumor necrosis factor receptor-associated factor-1 expression and known link to nuclear factor-kappa B, MLBCLs were also evaluated for nuclear translocation of c-REL protein. In almost all cases, c-REL was localized to the nucleus, consistent with activation of the nuclear factor-kappa B pathway. These studies identify a molecular link between MLBCL and classical Hodgkin lymphoma and a shared survival pathway.	4
32. Wright G, Tan B, Rosenwald A, Hurt EH, Wiestner A, Staudt LM. A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. *Proc Natl Acad Sci U S A.* 2003;100(17):9991-9996.	Observational-Tx	274 DLBCL cases	To classify cancer specimens by their gene expression profiles, a statistical method was created based on Bayes' rule that estimates the probability of membership in 1 of 2 cancer subgroups. This method was then used to classify DLBCL biopsy samples into 2 gene expression subgroups based on data obtained from spotted cDNA microarrays.	The GCB DLBCL subgroup expressed genes characteristic of normal GCB whereas the ABC DLBCL subgroup expressed a subset of the genes that are characteristic of plasma cells, particularly those encoding endoplasmic reticulum and golgi proteins involved in secretion. We next used this predictor to discover these subgroups within a second set of DLBCL biopsies that had been profiled by using oligonucleotide microarrays. The GCB and ABC DLBCL subgroups identified in this data set had significantly different 5-year survival rates after multiagent chemotherapy (62% vs 26%; P≤0.0051), in accord with analyses of other DLBCL cohorts.	2

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
33. Meyer PN, Fu K, Greiner TC, et al. Immunohistochemical methods for predicting cell of origin and survival in patients with diffuse large B-cell lymphoma treated with rituximab. *J Clin Oncol.* 2011;29(2):200-207.	Observational-Tx	262 cases of de novo DLBCL	To compare immunohistochemical algorithms in a well characterized group of patients with DLBCL treated with standard chemotherapy including rituximab and to evaluate new methods to predict the cell of origin and survival in DLBCL.	The Choi algorithm and Hans algorithm had high concordance with the microarray results. Modifications of the Choi and Hans algorithms for ease of use still retained high concordance with the microarray results. Although the Nyman and Muris algorithms had high concordance with the microarray results, each had a low value for either sensitivity or specificity. The use of LMO2 alone showed the lowest concordance with the microarray results. A new algorithm (Tally) using a combination of antibodies, but without regard to the order of examination, showed the greatest concordance with microarray results. All of the algorithms divided patients into groups with significantly different OS and EFSs, but with different HRs. With the exception of the Nyman algorithm, this survival prediction was independent of the IPI. Although the Muris algorithm had prognostic significance, it misclassified a large number of cases with ABC type DLBCL.	1
34. Nyman H, Jerkeman M, Karjalainen-Lindsberg ML, Banham AH, Leppa S. Prognostic impact of activated B-cell focused classification in diffuse large B-cell lymphoma patients treated with R-CHOP. *Mod Pathol.* 2009;22(8):1094-1101.	Observational-Tx	88 samples of DLBCL patients treated uniformly with R-CHOP	To determine whether modified immunohistochemical classification of cell of origin focusing on ABC markers could be used to predict the outcome of immunochemotherapy-treated DLBCL patients.	When the modified classification using MUM1/IRF4 and FOXP1 positivity as ABC markers was applied to distinguish the patients between the ABC and other DLBCL subtypes, a significantly worse outcome was seen for the patients with the ABC phenotype (3-year FFS 63% vs 82%, P=0.048, OS 69% vs 85%, P=0.110). Similarly, according to the Muris algorithm, the group 2 patients representing Bcl-2-positive post-germinal center patients showed an inferior outcome in comparison to the group 1 patients (FFS 59% vs 81%, P=0.041, OS 67% vs 82%, P=0.159). In contrast, when the classification of the same cohort was performed according to the Hans algorithm, no significant difference in survival was observed between the germinal center and non-germinal center patients.	2

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
35. Aukema SM, Siebert R, Schuuring E, et al. Double-hit B-cell lymphomas. *Blood.* 2011;117(8):2319-2331.	Review/Other-Tx	N/A	To explore the existing literature for the most recurrent types of double-hit B-cell lymphomas and the involved genes with their functions, as well as their pathology and clinical aspects including therapy and prognosis.	Most double-hits have a $BCL2^+/MYC^+$ combination, and most $BCL6^+/MYC^+$ double-hit lymphomas represent $BCL2^+/BCL6^+/MYC^+$ TH lymphomas. $CCND1^+/MYC^+$ double-hit lymphomas may be more frequent than anticipated and should receive more attention. Patients with double-hit lymphoma generally have rapidly progressive disease and a dismal outcome, even with high-intensity chemotherapy. The course of disease might reflect not only the synergistic actions of the ≥2 oncogenes involved but also the high genomic complexity in most of these tumors.	4
36. Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program. *Blood.* 2013;121(20):4021-4031; quiz 4250.	Observational-Tx	893 de novo DLBCL cases	To use IHC to assess the prognostic value of MYC and BCL2 expression, and particularly MYC/BCL2 coexpression, in a large cohort of de novo DLBCL patients treated with R-CHOP therapy.	MYC/BCL2 coexpression in DLBCL is associated with an aggressive clinical course, is more common in the ABC subtype, and contributes to the overall inferior prognosis of patients with ABC-DLBCL. The data suggest that MYC/BCL2 coexpression, rather than cell-of-origin classification, is a better predictor of prognosis in patients with DLBCL treated with R-CHOP.	2
37. Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol.* 2012;30(28):3452-3459.	Observational-Tx	167 patients	To investigate whether expression of MYC protein, with or without BCL2 protein expression, could risk-stratify patients at diagnosis.	In the training cohort (n = 167), MYC and BCL2 proteins were detected in 29% and 44% of patients, respectively. Concurrent expression (MYC positive/BCL2 positive) was present in 21% of patients. MYC protein correlated with presence of high MYC mRNA and MYC translocation (both $P<.001$), but the latter was less frequent (both 11%). MYC protein expression was only associated with inferior overall and PFS when BCL2 protein was coexpressed ($P<.001$). Importantly, the poor prognostic effect of MYC positive/BCL2 positive was validated in an independent cohort of 140 patients with DLBCL and remained significant ($P<.05$) after adjusting for presence of high-risk features in a multivariable model that included elevated IPI score, activated B-cell molecular subtype, and presence of concurrent MYC and BCL2 translocations.	1

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
38. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med.* 1993;328(14):1002-1006.	Experimental-Tx	899 patients	To compare the standard regimen (CHOP) with 9 intensive chemotherapy regimens for advanced NHL.	At 3 years, 44% of all patients were alive without disease; there were no significant differences between the groups (41% in the CHOP and MACOP-B groups and 46% in the m-BACOD and ProMACE-CytaBOM groups; *P*=0.35). OS at 3 years was 52% (50% in the ProMACE-CytaBOM and MACOP-B groups, 52% in the m-BACOD group, and 54% in the CHOP group; *P*=0.90). There was no subgroup of patients in which survival was improved by a third-generation regimen. Fatal toxic reactions occurred in 1% of the CHOP group, 3% of the ProMACE-CytaBOM group, 5% of the m-BACOD group, and 6% of the MACOP-B group (*P*=0.09).	1
39. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med.* 2002;346(4):235-242.	Experimental-Tx	197 patients	To compare CHOP chemotherapy plus R-CHOP alone in elderly patients with DLBCL.	The rate of CR was significantly higher in the group that received R-CHOP than in the group that received CHOP alone (76% vs 63%, *P*=0.005). With a median follow-up of 2 years, EFS and OS times were significantly higher in the R-CHOP group (*P*<0.001 and *P*=0.007, respectively). The addition of R-CHOP chemotherapy significantly reduced the risk of treatment failure and death (risk ratios, 0.58 [95% CI: 0.44 to 0.77] and 0.64 [0.45 to 0.89], respectively). Clinically relevant toxicity was not significantly greater with R-CHOP.	1

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
40. Pfreundschuh M, Kuhnt E, Trumper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncol.* 2011;12(11):1013-1022.	Experimental-Tx	410 patients assigned to chemo-therapy alone and 413 assigned to chemo-therapy plus rituximab	CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis DLBCL: 6-year results of an open-label randomized study of the MabThera International Trial (MInT) Group.	After a median follow-up of 72 months (range 0.03-119), 6-year EFS was 55.8% (95% CI; 50.4-60.9; 166 events) for patients assigned to chemotherapy alone and 74.3% (69.3-78.6; 98 events) for those assigned to chemotherapy plus rituximab (difference between groups 18.5%, 11.5-25.4, log-rank $P<0.0001$. After chemotherapy and rituximab, a favorable subgroup (IPI=0, no bulk) could be defined from a less favorable subgroup (IPI=1 or bulk, or both; EFS 84.3% [95% CI; 74.2-90.7] vs 71.0% [65.1-76.1], log-rank $P=0.005$). 18 (4.4%, 95% CI; 2.6-6.9) second malignancies occurred in the chemotherapy-alone group and 16 (3.9%, 2.2-6.2) in the chemotherapy and rituximab group (Fisher's exact $P=0.730$).	1
41. Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. *J Clin Oncol.* 2008;26(16):2717-2724.	Experimental-Tx	72 patients	To assess the clinical outcome and the influence of biomarkers associated with apoptosis inhibition (Bcl-2), tumor proliferation (MIB-1), and cellular differentiation on the outcome with dose-adjusted EPOCH plus rituximab infusional therapy in DLBCL with analysis of GCB and post-GCB subtypes by immunohistochemistry.	At 5 years, PFS and OS were 79% and 80%, respectively, with a median potential follow-up of 54 months. PFS was 91%, 90%, 67%, and 47%, and OS was 100%, 90%, 74%, and 37%, for 0 to 1, 2, 3, and 4 to 5 IPI factors, respectively, at 5 years. The Bcl-2 and MIB-1 biomarkers were not associated with PFS or OS. Based on dose-adjusted-EPOCH historical controls, rituximab only benefited Bcl-2 positive tumors. Bcl-6 expression was associated with higher PFS whereas GCB exhibited a marginally significant higher PFS compared with post-GCB DLBCL.	2
42. Andre M, Mounier N, Leleu X, et al. Second cancers and late toxicities after treatment of aggressive non-Hodgkin lymphoma with the ACVBP regimen: a GELA cohort study on 2837 patients. *Blood.* 2004;103(4):1222-1228.	Review/Other-Tx	2,837 patients	Study of second cancers and late toxicities after treatment of aggressive NHL with the ACVBP regimen.	With a median follow-up time of 74 months, the 5-year OS and EFS rates were 60% and 52%. 202 occurrences of nonneoplastic late toxicity were reported, resulting in a 5.35% cumulative probability of incidence at 7 years. 81 second tumors developed, for which the 7-year cumulative incidence rate was 2.75%; 64 were solid tumors, and 17 were hematologic malignancies. In multivariate analysis, age was the only risk factor for the second development of cancer.	4

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
43. Tilly H, Lepage E, Coiffier B, et al. Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma. *Blood.* 2003;102(13):4284-4289.	Experimental-Tx	635 patients	To compare the intensive conventional chemotherapy regimen ACVBP with standard CHOP in previously untreated patients with poor-risk aggressive lymphoma.	The rate of CR was 58% in the ACVBP group and 56% in the CHOP group (*P*=.5). Treatment-related death occurred in 13% of the ACVBP group and 7% of the CHOP group (*P*=.014). At 5 years, the EFS was 39% in the ACVBP group and 29% in the CHOP group (*P*=.005). The OS was significantly longer for patients treated with ACVBP, at 5 years it was 46% compared with 38% for patients treated with CHOP (*P*=.036). Central nervous system progressions or relapses were more frequent in the CHOP group (*P*=.004).	1
44. Recher C, Coiffier B, Haioun C, et al. Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial. *Lancet.* 2011;378(9806):1858-1867.	Experimental-Tx	196 patients in the R-ACVBP group, 183 in the R-CHOP group	To assess, in patients aged 18-59 years, the potential survival benefit provided by a dose-intensive immunochemotherapy regimen plus rituximab compared with standard treatment plus rituximab.	After a median follow-up of 44 months, our 3-year estimate of EFS was 81% (95% CI: 75-86) in the R-ACVBP group and 67% (59-73) in the R-CHOP group (HR 0.56, 95% CI: 0.38-0.83; *P*=0.0035). 3-year estimates of PFS (87% [95% CI: 81-91] vs 73% [66-79]; HR 0.48 [0.30-0.76]; *P*=0.0015) and OS (92% [87-95] vs 84% [77-89]; HR 0.44 [0.28-0.81]; *P*=0.0071) were also increased in the R-ACVBP group. 82 (42%) of 196 patients in the R-ACVBP group experienced a serious adverse event compared with 28 (15%) of 183 in the R-CHOP group. Grade 3-4 hematological toxic effects were more common in the R-ACVBP group, with a higher proportion of patients experiencing a febrile neutropenic episode (38% [75/196] vs 9% [16/183]).	1
45. Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. *Blood.* 2004;104(3):634-641.	Experimental-Tx	689 patients	To determine whether biweekly CHOP (CHOP-14) with or without etoposide is more effective than CHOP-21, patients were randomized to 6 cycles of CHOP-21, CHOP-14, CHOEP-21, or CHOEP-14.	CR rates were 60.1% (CHOP-21), 70.0% (CHOEP-21), 76.1% (CHOP-14), and 71.6% (CHOEP-14). 5-year EFS and OS rates were 32.5% and 40.6%, respectively, for CHOP-21 and 43.8% and 53.3%, respectively, for CHOP-14. In a multivariate analysis, the relative risk reduction was 0.66 (*P*=.003) for EFS and 0.58 (*P*<.001) for OS after CHOP-14 compared with CHOP-21. Toxicity of CHOP-14 and CHOP-21 was similar, but CHOEP-21 and in particular CHOEP-14 were more toxic.	1

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
46. Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. *Blood.* 2004;104(3):626-633.	Experimental-Tx	710 patients	To determine whether CHOP given every 2 weeks (CHOP-14) or the addition of etoposide (CHOEP-21, CHOEP-14) can improve results in aggressive lymphoma patient's ages 18 to 60 years with good prognosis (normal LDH level).	CHOEP achieved better CR (87.6% vs 79.4%; *P*=.003) and 5-year EFS rates (69.2% vs 57.6%; *P*=.004, primary end point) than CHOP, whereas interval reduction improved OS (*P*=.05; *P*=.044 in the multivariate analysis). Although the CHOEP regimens induced more myelosuppression, all regimens were well tolerated.	1
47. Held G, Murawski N, Ziepert M, et al. Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. *J Clin Oncol.* 2014;32(11):1112-1118.	Experimental-Tx	164 patients	A prospective trial to investigate the role of additive RT to bulky and extralymphatic disease.	After a median observation time of 39 months, 164/166 RICOVER-no RT patients were evaluable. In a multivariable analysis of the intention-to-treat population adjusting for IPI risk factors and age (>70 years), EFS of patients with bulky disease was inferior without additive RT (HR, 2.1; 95% CI, 1.3 to 3.5; *P*=.005), with trends for inferior PFS; HR, 1.8; 95% CI, 1.0 to 3.3; *P*=.058) and OS; HR, 1.6; 95% CI, 0.9 to 3.1; *P*=.127). In a per-protocol analysis with 11 patients in RICOVER-no RT excluded for receiving unplanned RT, multivariable analysis revealed HRs of 2.7 (95% CI, 1.3 to 5.9; *P*=.011) for EFS, 4.4 (95% CI, 1.8 to 10.6; *P*=.001) for PFS, and 4.3 (95% CI, 1.7 to 11.1; *P*=.002) for OS for patients not receiving RT to bulky disease.	1

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
48. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet.* 2013;381(9880):1817-1826.	Experimental-Tx	1,080 patients	To investigate whether this survival benefit from dose intensification with a combination of CHOP persists in the presence of R-CHOP in all age groups.	1,080 patients were assigned to R-CHOP-21 (n=540) and R-CHOP-14 (n=540). With a median follow-up of 46 months (IQR 35–57), 2-year OS was 82.7% (79.5–85.9) in the R-CHOP-14 group and 80.8% (77.5–84.2) in the R-CHOP-21 (standard) group (HR 0.90, 95% CI 0.70-1.15; *P*=0.3763). No significant improvement was noted in 2-year PFS (R-CHOP-14 75.4%, 71.8–79.1, and R-CHOP-21 74.8%, 71.0–78.4; 0.94, 0.76–1.17; *P*=0.5907). High IPI, poor-prognosis molecular characteristics, and cell of origin were not predictive for benefit from either schedule. Grade 3 or 4 neutropenia was higher in the R-CHOP-21 group (318 [60%] of 534 vs 167 [31%] of 534), with no prophylactic use of recombinant human granulocyte-colony stimulating factor mandated in this group, whereas grade 3 or 4 thrombocytopenia was higher with R-CHOP-14 (50 [9%] vs 28 [5%]); other frequent grade 3 or 4 adverse events were febrile neutropenia (58 [11%] vs 28 [5%]) and infection (125 [23%] vs 96 [18%]). Frequencies of nonhaematological adverse events were similar in the R-CHOP-21 and R-CHOP-14 groups.	1

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
49. Delarue R, Tilly H, Mounier N, et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. *Lancet Oncol.* 2013;14(6):525-533.	Experimental-Tx	602 patients	To ascertain if a dose-dense R-CHOP regimen administered every 2 weeks (R-CHOP-14) was superior to the standard 3-week schedule (R-CHOP-21).	2 patients allocated R-CHOP-21 were ineligible for the study and were excluded from analyses. After median follow-up of 56 months (IQR 27–60), 3-year EFS was 56% (95% CI 50–62) in the R-CHOP-14 group and 60% (55–66) in the R-CHOP-21 group (HR 1.04, 95% CI, 0.82–1.31; *P*=0.7614). Grade 3-4 neutropenia occurred in 224 (74%) of 304 patients allocated R-CHOP-14 and 189 (64%) of 296 assigned R-CHOP-21, despite increased use of granulocyte colony-stimulating factor in the R-CHOP-14 group compared with the R-CHOP-21 group. 143 (47%) patients in the R-CHOP-14 group received at least 1 red-blood-cell transfusion vs 93 (31%) in the R-CHOP-21 group (*P*=0.0001). 35 (12%) patients allocated R-CHOP-14 received at least 1 platelet transfusion vs 25 (8%) assigned R-CHOP-21 (*P*=0.2156). 155 (51%) patients who were assigned R-CHOP-14 had at least 1 serious adverse event compared with 140 (47%) who were allocated R-CHOP-21.	1
50. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *N Engl J Med.* 1998;339(1):21-26.	Observational-Tx	200 patients received CHOP plus RT, 201 received CHOP alone	To evaluate pilot studies which suggest that 8 cycles of CHOP alone or 3 cycles of CHOP followed by IFRT are effective in patients with clinically localized, intermediate- or high-grade NHL through a prospective, randomized, multi-institutional study.	Patients treated with 3 cycles of CHOP plus RT had significantly better PFS (*P*=0.03) and OS (*P*=0.02) than patients treated with CHOP alone. The 5-year estimates of PFS for patients receiving CHOP plus RT and for patients receiving CHOP alone were 77% and 64%, respectively. The 5-year estimates of OS for patients receiving CHOP plus RT and for patients receiving CHOP alone were 82% and 72%, respectively. The adverse effects included 1 death in each treatment group. Life-threatening toxic effects of any type were seen in 61/200 patients treated with CHOP plus RT and in 80/201 patients treated with CHOP alone (*P*=0.06). The left ventricular function was decreased in 7 patients who received CHOP alone, whereas no cardiac events were recorded in the group receiving CHOP plus RT (*P*=0.02).	1

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
51. Bucci MK. CHOP Alone Compared to CHOP Plus Radiotherapy for Early Stage Aggressive Non-Hodgkin's Lymphomas: Update of the Southwest Oncology Group (SWOG) Randomized Trial. 2004; http://www.oncolink.org/conferences/article.cfm?id=471&ss=66. Accessed June 22, 2012.	Experimental-Tx	401 patients were randomly assigned to 3 cycles of CHOP followed by IFRT (40-55 Gy) or 8 cycles of CHOP	A median follow-up (update) of 8.2 years to a 1998 SWOG study that reported on randomized trial comparing 8 cycles of CHOP with 3 cycles of CHOP + IFRT: initial median follow-up of 4.4 years.	5-year OS with 8.2 years of follow-up is 82% for the IFRT arm and 74% for the chemo alone arm. 5-year FFS with 8.2 years of follow-up is 76% for the IFRT arm and 67% for the chemo only arm. The OS curves cross at 9 years. The FFS curves cross at 7 years. There were 15 relapses and deaths due to lymphoma in the IFRT arm between 5 and 10 years. There were 8 relapses and deaths due to lymphoma in the chemotherapy alone arm during 5 and 10 years. The 5-year OS for stage-modified IPI (modified to Stage I vs Stage II) favorable prognostic group (no adverse risk factors: Stage I, age <60, normal serum LDH, performance status 0-1) was 94%. 5-year OS for patients with 1 adverse risk factor on the stage-modified IPI was 71%. 5-year OS for patients with 3 adverse risk factors was 50%.	1
52. Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. *J Clin Oncol.* 2004;22(15):3032-3038.	Observational-Tx	172 CR patients	To compare low-dose (30 Gy) RT with observation in limited-stage aggressive lymphoma patients achieving CR after chemotherapy, and to measure conversion from partial response to CR with high-dose (40 Gy) RT.	Among 172 CR patients, the 6-year disease-free survival was 73% for low-dose RT vs 56% for observation (2-sided *P*=.05). FFS (2-sided *P*=.06), and time to progression (2-sided *P*=.06) also favored RT. Intent-to-treat analyses yielded similar results. No survival differences were observed. 9 RT vs 15 observation patients relapsed in initial disease sites. At 6 years, FFS was 63% in partial response patients; conversion to CR did not significantly influence clinical outcome.	1
53. Reyes F, Lepage E, Ganem G, et al. ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. *N Engl J Med.* 2005;352(12):1197-1205.	Experimental-Tx	329 patients	To determine the optimal therapy for nonelderly persons with low-risk localized lymphoma, a randomized trial comparing chemoradiotherapy with chemotherapy alone was performed.	With a median follow-up of 7.7 years, EFS and OS rates were significantly higher in the group given chemotherapy alone than in the group given CHOP plus RT (*P*<0.001 and *P*=0.001, respectively). The 5-year estimates of EFS were 82% (95% CI: 78-87) for patients receiving chemotherapy alone and 74% (95% CI: 69-78) for those receiving chemoradiotherapy. The respective 5-year estimates of OS were 90% (95% CI: 87-93) and 81% (95% CI: 77-86).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
54. Bonnet C, Fillet G, Mounier N, et al. CHOP alone compared with CHOP plus radiotherapy for localized aggressive lymphoma in elderly patients: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol.* 2007;25(7):787-792.	Experimental-Tx	299 patients in CHOP plus IFRT group and 277 patients in chemotherapy group	A trial comparing chemoradiotherapy with chemotherapy alone in elderly patients with low-risk localized lymphoma.	With a median follow-up time of 7 years, EFS and OS did not differ between the 2 treatment groups (P=.6 and P=.5, respectively). The 5-year estimates of EFS were 61% for patients receiving chemotherapy alone and 64% for patients receiving CHOP plus RT; the 5-year estimates of OS were 72% and 68%, respectively. In a multivariate analysis, OS was affected by stage II disease (P<.001) and male sex (P=.03).	1
55. Pfreundschuh M, Ho AD, Cavallin-Stahl E, et al. Prognostic significance of maximum tumour (bulk) diameter in young patients with good-prognosis diffuse large-B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: an exploratory analysis of the MabThera International Trial Group (MInT) study. *Lancet Oncol.* 2008;9(5):435-444.	Observational-Tx	802 total patients	To assess the effect of maximum tumor diameter in young patients (ie, aged 18-60 years) with good-prognosis DLBCL, who have been treated with CHOP-like chemotherapy with or without rituximab.	Martingale residual analysis showed an adverse prognostic effect of maximum tumor diameter on EFS and OS, which increased linearly. For CHOP-like treatment, any cut-off point between 5.0 cm and 10.0 cm separated 2 populations with a significant EFS difference (P<0.0001 for all log-rank tests) and OS difference (P≤0.003 for all log-rank tests). For CHOP-like treatment and rituximab, only a cut-off point of 10.0 cm separated 2 populations with a significant EFS difference (log-rank P=0.047), but any cut-off point of 6.0 cm or more separated 2 populations with a significant OS difference (log-rank P values 0.0009-0.037).	1
56. German High-Grade Non-Hodgkin's Lymphoma Study Group. Rituximab and Combination Chemotherapy With or Without Radiation Therapy in Treating Patients With B-Cell Non-Hodgkin's Lymphoma. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). February 18, 2014. Available from: http://www.clinicaltrials.gov/ct2/show/record/NCT00278408?term=NCT00278408&rank=1. NLM Identifier: NCT00278408.	Review/Other-Tx	Ongoing	This randomized phase III trial is studying 2 different schedules of rituximab and combination chemotherapy with or without RT to compare how well they work in treating patients with aggressive DLBCL.	This trial is still recruiting study subjects and results are not available yet.	4

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
57. Held G. The Role of Radiotherapy in the Treatment of DLBCL. A Perspective of the German High-grade Non-Hodgkin's-Lymphoma Study Group [PowerPoint Slides 36-37]. American Society of Hematology; 2012.	Experimental-Tx	164 patients	To investigate the role of additive RT to bulky and extralymphatic disease.	After a median observation time of 39 months, 164/166 RICOVER-no RT patients were evaluable. In a multivariable analysis of the intention-to-treat population adjusting for IPI risk factors and age (>70 years), EFS of patients with bulky disease was inferior without additive RT (HR, 2.1; 95% CI, 1.3 to 3.5; *P*=.005), with trends for inferior (PFS; HR, 1.8; 95% CI, 1.0 to 3.3; *P*=.058) and (OS; HR, 1.6; 95% CI, 0.9 to 3.1; *P*=.127). In a per-protocol analysis with 11 patients in RICOVER-no RT excluded for receiving unplanned RT, multivariable analysis revealed HRs of 2.7 (95% CI, 1.3 to 5.9; *P*=.011) for EFS, 4.4 (95% CI, 1.8 to 10.6; *P*=.001) for PFS, and 4.3 (95% CI, 1.7 to 11.1; *P*=.002) for OS for patients not receiving RT to bulky disease.	1
58. Persky DO, Unger JM, Spier CM, et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014. *J Clin Oncol.* 2008;26(14):2258-2263.	Observational-Tx	60 patients	To evaluate the effect of rituximab in limited-stage DLBCL, we conducted a multicenter phase II trial combining rituximab with 3 cycles of CHOP; R-CHOP followed by IFRT.	60 patients with aggressive NHL were eligible. With the median follow-up of 5.3 years, treatment resulted in a PFS of 93% at 2 years and 88% at 4 years. OS was 95% at 2 years and 92% at 4 years. These results were compared with those from a historic group of patients treated without rituximab on S8736, demonstrating PFS of 78% and OS of 88% at 4 years.	1
59. Ferreri AJ, Bruno-Ventre M, Donadoni G, et al. Risk-tailored CNS prophylaxis in a mono-institutional series of 200 patients with diffuse large B-cell lymphoma treated in the rituximab era. *Br J Haematol.* 2014:[E-pub ahead of print].	Observational-Tx	200 patients	To report a retrospective analysis of risk-tailored CNS prophylaxis in 200 HIV-negative adults with DLBCL treated with R-CHOP or similar.	CNS relapse risk was low in 93 patients and high in 107; 40 high-risk patients received prophylaxis, which consisted of intrathecal chemotherapy alone in 7. At a median follow-up of 60 months, 1 low-risk and 9 high-risk patients (1% vs. 8%; *P*=0.01) experienced CNS relapse. In the high-risk group, CNS relapses occurred in 8/67 (12%) patients who did not receive prophylaxis and in 1/40 (2.5%) patients who did; the latter occurred in a patient managed with intrathecal chemotherapy alone. CNS relapse rate was 12% (9/74) for patients treated with "inadequate" prophylaxis (none or IT only) and 0% (0/33) for patients managed with intravenous prophylaxis (*P*=0.03).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
60. Murawski N, Held G, Ziepert M, et al. The role of radiotherapy and intrathecal CNS prophylaxis in extralymphatic craniofacial aggressive B-cell lymphomas. *Blood.* 2014;124(5):720-728.	Review/Other-Tx	11 trials	To define the role of RT and intrathecal prophylaxis ECFI of aggressive B-cell lymphoma.	11 consecutive German High-Grade Non-Hodgkin Lymphoma Study Group trials were analyzed. ECFI occurred in 290/4155 (7.0%) patients (orbita, 31; paranasal sinuses, 93; main nasal cavity, 38; tongue, 27; remaining oral cavity, 99; salivary glands, 54). In a multivariable analysis adjusted for IPI rituximab improved EFS and OS both in patients with and without ECFI. 3-year EFS (79% vs 79%; *P*=.842) and OS (86% vs 88%; *P*=.351) rates were similar in 145 patients receiving and 57 not receiving RT. Without rituximab, the 2-year cumulative rate of CNS disease was increased in 205 ECFI patients compared with 2,586 non-ECFI patients (4.2% vs 2.8%; *P*=.038), whereas this was not observed with rituximab (1.6% in 83 ECFI vs 3.4% in 1,252 non-ECFI patients; *P*=.682). In 88 ECFI patients who received intrathecal prophylaxis with methotrexate, the 2-year rate of CNS disease was 4.2% compared with 2.3% in 191 patients who did not (*P*=.981). In conclusion, rituximab eliminates the increased risk for CNS disease in patients with ECFI.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
61. Kamath SS, Marcus RB, Jr., Lynch JW, Mendenhall NP. The impact of radiotherapy dose and other treatment-related and clinical factors on in-field control in stage I and II non-Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys.* 1999;44(3):563-568.	Observational-Tx	285 consecutive patients	To assess local (in-field) disease control, identify potential prognostic factors, and elucidate the optimal RT dose in various clinical settings of stage I and II NHL.	The 5-, 10-, and 20-year actuarial absolute survival rates were 73%, 46%, and 33% for patients with low-grade lymphomas and 64%, 44%, and 18% for patients with intermediate or high-grade lymphomas, respectively. The 5-, 10-, and 20-year actuarial freedom from relapse rates were 62%, 59%, and 49% for patients with low-grade lymphomas and 66%, 57%, and 57% for patients with intermediate or high-grade lymphomas, respectively. Significant prognostic factors identified by the multivariate analysis were age, tumor size, and histology for absolute survival; tumor size and treatment for freedom from relapse; and only tumor size for in-field disease control. There were 95 total failures, with only 12 occurring infield. Most failures (65%) were in contiguous unirradiated sites. All 4 in-field failures in patients with low-grade lymphomas occurred after RT doses <30 Gy, although none occurred in 10 patients with small-volume low-grade lymphomas of the orbit treated with doses <0 Gy. The 8 in-field failures in patients with intermediate or high-grade lymphomas were distributed evenly throughout the RT dose range; 5 occurred in patients treated with combine-modality therapy, all with tumors >6 cm, and 4 with less than a CR to chemotherapy.	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
62. Lowry L, Smith P, Qian W, et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase III trial. *Radiother Oncol.* 2011;100(1):86-92.	Experimental-Tx	816 patients	A multicenter, prospective, randomized-controlled trial compared efficacy and toxicity of differing RT doses in NHL.	There was no difference in overall response rate between standard and lower-dose arms. In the indolent group, overall response rate was 93% and 92%, respectively, (P=0.72); in the aggressive group, overall response rate was 91% in both arms (P=0.87). With a median follow-up of 5.6 years, there was no significant difference detected in the rate of within-radiation field progression (HR = 1.09, 95% CI, 0.76–1.56, P=0.64 in the indolent group; HR = 0.98, 95% CI, 0.68–1.4, P=0.89 in the aggressive group). There was also no significant difference detected in the PFS or OS. There was a trend for reduced toxicities in the low-dose arms; only the reduction in reported erythema reached significance.	1
63. Campbell BA, Connors JM, Gascoyne RD, Morris WJ, Pickles T, Sehn LH. Limited-stage diffuse large B-cell lymphoma treated with abbreviated systemic therapy and consolidation radiotherapy: involved-field versus involved-node radiotherapy. *Cancer.* 2012;118(17):4156-4165.	Observational-Tx	288 total patients	Retrospective review of the long-term outcomes of limited-stage DLBCL treated with abbreviated systemic therapy and RT focusing on field size: IFRT vs INRT.	The 2 RT groups were IFRT (138 patients; 48%) and INRT ≤5 cm (150 patients; 52%); median follow-up was 117 and 89 months, respectively. Distant relapse was the most common site of failure in both groups. After INRT ≤5 cm, marginal recurrence was infrequent (2%). Time to progression (P=.823), PFS (P=.575), and OS (P=.417) were not significantly different between the RT cohorts.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
64. Hoskin PJ, Diez P, Williams M, Lucraft H, Bayne M. Recommendations for the use of radiotherapy in nodal lymphoma. *Clin Oncol (R Coll Radiol).* 2013;25(1):49-58.	Review/Other-Tx	N/A	Guidelines developed to define the use of RT for lymphoma in the current era of combined modality treatment taking into account increasing concern over the late side-effects associated with previous RT.	The planning of radical RT for lymphoma patients, both Hodgkin and NHL, should be based upon contrast-enhanced 3 mm contiguous CT imaging with 3-D definition of volumes using the convention of GTV, CTV and PTV. All patients should be treated with involved-site RT unless no pre-chemotherapy imaging is available, when IFRT is used. Patients who are treated outside combined modality protocols with RT alone due to poor performance status should also receive IFRT. The lowest dose compatible with efficacy should be used; for Hodgkin lymphoma this is 20–30 Gy; for indolent NHL this is 24 Gy, for natural killer cell lymphoma it is at least 50 Gy, and for all other NHL 30 Gy is adequate. Doses as low as 4 Gy in 2 fractions may be effective in follicular lymphoma.	4
65. Illidge T, Specht L, Yahalom J, et al. Modern Radiation Therapy for Nodal Non-Hodgkin Lymphoma-Target Definition and Dose Guidelines From the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys.* 2014;89(1):49-58.	Review/Other-Tx	N/A	Guidelines to provide a consensus position on the modern approach to RT delivery in the treatment of nodal NHL and to outline a new concept of involved-site RT, in which reduced treatment volumes are planned for the effective control of involved sites of disease.	No results stated in abstract.	4

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
66. Pfreundschuh M, Ziepert M, Reiser M, et al. The Role of Radiotherapy to Bulky Disease in the Rituximab Era: Results from Two Prospective Trials of the German High-Grade Non-Hodgkin-Lymphoma Study Group (DSHNHL) for Elderly Patients with DLBCL. *ASH Annual Meeting Abstracts.* 2008;112(11):584-.	Review/Other-Tx	166 elderly patients	To study the relevance of additional Rx to bulky disease we subsequently initiated a prospective study in which no Rx was planned after 6 x R-CHOP-14.	164/166 R-CHOP-noRx patients are evaluable with a median observation time of 17 months. Patients from both studies were well balanced for many known prognostic factors, but patients in R-CHOP-noRx were older (71 vs 69 years; *P*=0.018), more frequently in advanced stages (60% vs 50%; *P*=0.037), and with extranodal involvement (63% vs 53%; *P*=0.024), while bulky disease was more frequent in the R-CHOP-Rx study (38% vs 29%; *P*=0.038). Adherence to the immuno-chemotherapy protocol was excellent in both studies with median relative rituximab and cytotoxic drug doses of 99%. Overall response to therapy was similar in the 2 studies: CR/CRu: 76% vs 78%; progressions 5.5% vs 6.5%; relapses after CR/CRu 8% vs 10%; therapy-associated deaths 7% vs 6% in R-CHOP-noRx and R-CHOP-Rx, respectively. Similarly, there were no significant differences between the 2 studies with respect to EFS, PFS and OS. This also holds in multivariate models adjusting for the prognostic imbalances between the cohorts. However, the patients with bulky disease in the R-CHOP-Rx trial assigned to receive additional RT to bulky disease had a 25% better 18-month EFS (68% [95% CI: 59-76] vs 43% [29-58]; *P*=0.002), a 10% better PFS (77% [70-85] vs 67% [52-82]; *P*=0.123), and a 4% better OS (80% [72-87] vs 76% [63-90]; *P*=0.509) compared with R-CHOP-noRx. The lower EFS rate in the R-CHOP-noRx study was due to patients with bulky disease not achieving CR or CRu after 6xRCHOP, while patients with bulky disease in CR or CRu after 6xR-CHOP-14 fared equally well with and without additional RT (18-month-EFS: 84% vs 86%; *P*=0.512).	4

Diffuse Large B-Cell Lymphoma
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
67. Dorth JA, Prosnitz LR, Broadwater G, et al. Impact of consolidation radiation therapy in stage III-IV diffuse large B-cell lymphoma with negative post-chemotherapy radiologic imaging. *Int J Radiat Oncol Biol Phys.* 2012;84(3):762-767.	Observational-Tx	79 patients	To examine the role of consolidation RT by reviewing all patients with DLBCL treated predominantly with R-CHOP and with or without consolidation RT.	79 patients were identified. Chemotherapy (median, 6 cycles) consisted of anti-CD20 antibody R-CHOP; 65%; CHOP; 22%; or other (13%). Post-chemotherapy imaging consisted of PET/CT (73%); gallium with CT (14%); or CT only (13%). Consolidation RT (median, 25 Gy) was given to involved sites of disease in 38 (48%) patients. Receipt of consolidation RT was associated with improved in-field control (92% vs 69%, respectively, P=0.028) and EFS (85% vs. 65%, respectively, P=0.014) but no difference in OS (85% vs 78%, respectively, P=0.15) when compared to patients who did not receive consolidation RT. On multivariate analysis, no RT was predictive of increased risk of in-field failure (HR, 8.01, P=0.014) and worse EFS (HR, 4.3, P=0.014).	2
68. Shi Z, Das S, Okwan-Duodu D, et al. Patterns of failure in advanced stage diffuse large B-cell lymphoma patients after complete response to R-CHOP immunochemotherapy and the emerging role of consolidative radiation therapy. *Int J Radiat Oncol Biol Phys.* 2013;86(3):569-577.	Observational-Tx	211 patients	To evaluate the institutional experience when consolidative RT is delivered to initial presenting sites or bulky sites in these patients.	Detailed treatment records were available for 163 patients. After a median 6 cycles of R-CHOP, 110 patients (67.5%) achieved CR and were entered for analysis. 14 patients (12.7%) received consolidative RT. After median follow-up of 32.9 months, 43.8% of patients who received R-CHOP alone failed at the initial sites with or without distant recurrence, whereas isolated distant recurrence only occurred in 3.7% of these patients. Consolidative RT was associated with significantly improved local control (91.7% vs 48.8%), distant recurrence (92.9% vs 71.9%), PFS (85.1% vs 44.2%), and OS (92.3% vs 68.5%; all Ps<.0001) at 5 years compared with patients with R-CHOP alone. On multivariate analysis, consolidative RT and nonbulky disease were predictive of increased local control and PFS, whereas bone marrow involvement was associated with increased risk of distant recurrence and worse OS. Consolidative RT was also associated with marginal improved OS.	2

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
69. Dabaja B, Vanderplas A, Crosby-Thompson A, et al. Radiation for Diffuse Large B Cell Lymphoma in the Rituximab Era: Analysis of the National Comprehensive Cancer Network Lymphoma Outcomes Project. *Cancer*. 2014:[E-pub ahead of print].	Observational-Tx	841 patients	To examine the role of consolidation RT for patients with DLBCL treated at institutions of the National Comprehensive Cancer Network during the rituximab era.	Of 841 patients, most (710 [84%]) had received 6-8 cycles of R-CHOP, and 294 (35%) had received consolidation RT. Failure occurred in 181 patients, 126 (70%) who did not receive RT and 55 (30%) who did. At 5 years, both OS and FFS rates were better for patients who received RT than for those who did not (OS 91% vs 83%, *P*=0.01; FFS 83% vs 76%, *P*=0.05). Matched-pair analysis (217 pairs, matched by age, stage, IPI score, B symptoms, disease bulk, and response to chemotherapy) showed that receipt of RT improved OS and FFS for patients with stage III/IV disease (HRs 0.53 [*P*=0.07] and 0.77 [*P*=0.34]), but too few events took place among those with stage I/II disease for meaningful comparison (HR for OS=0.94 [*P*=0.89]; for FFS=1.81 [*P*=0.15]). Multivariate analysis suggested that IPI score and response to chemotherapy had the greatest influence on outcome.	1
70. Phan J, Mazloom A, Medeiros LJ, et al. Benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. *J Clin Oncol*. 2010;28(27):4170-4176.	Observational-Tx	469 patients	A retrospective study of DLBCL patients treated mostly with R-CHOP regimen, with or without consolidative RT to clarify the issue of whether RT is helpful in patients with DLBCL treated with the current standard of care and what subset of patients would benefit from its use.	Of 469 patients, 190 (40.5%) had stage I or II disease and 279 (59.5%) had stage III or IV disease, 327 (70%) had at least 6 cycles of R-CHOP, and 142 (30.2%) had IFRT (dose, 30 to 39.6 Gy) after CR to chemotherapy. Median follow-up was 36 months (range, 8 to 85 months). Multivariate analysis showed that RT (*P*<.0001), IPI score (*P*=.001), response to therapy (*P*=.001), use of 6 to 8 cycles of R-CHOP (*P*<.001), and combined presence (*P*=.006) or absence (*P*=.025) of high Ki67, high PET SUV, and bulky disease influenced OS and PFS. Matched-pair analyses of patients who received 6 to 8 cycles of R-CHOP with stage I or II disease (44 pairs) and all stages (74 pairs) indicated that RT improved OS (HR, 0.52 and 0.29, respectively) and PFS (HR, 0.45 and 0.24, respectively) compared with no RT.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
71. Greb A, Bohlius J, Schiefer D, Schwarzer G, Schulz H, Engert A. High-dose chemotherapy with autologous stem cell transplantation in the first line treatment of aggressive non-Hodgkin lymphoma (NHL) in adults. *Cochrane Database Syst Rev.* 2008(1):CD004024.	Review/Other-Tx	15 randomized control trials including 3,079 patients	To determine whether high-dose chemotherapy with autologous stem cell transplantation as part of first-line treatment improves survival in patients with aggressive NHL.	Overall treatment-related mortality was 6.0% in the high-dose chemotherapy group and not significantly different compared to conventional chemotherapy (OR 1.33 [95% CI: 0.91 to 1.93], *P*=0.14). 13 studies including 2,018 patients showed significantly higher CR rates in the group receiving high-dose chemotherapy (OR 1.32, [95% CI: 1.09 to 1.59], *P*=0.004). However, high-dose chemotherapy did not have an effect on OS, when compared to conventional chemotherapy. The pooled HR was 1.04 ([95% CI: 0.91 to 1.18], *P*=0.58).	4
72. Martelli M, Gherlinzoni F, De Renzo A, et al. Early autologous stem-cell transplantation versus conventional chemotherapy as front-line therapy in high-risk, aggressive non-Hodgkin's lymphoma: an Italian multicenter randomized trial. *J Clin Oncol.* 2003;21(7):1255-1262.	Experimental-Tx	150 patients	To evaluate the role of early intensification with high-dose therapy and autologous stem-cell transplantation as front-line chemotherapy for patients with high-risk, histologically aggressive NHL.	The rate of CR was 68% in arm A and 76% in arm B (*P*=NS). 3 toxic deaths (4%) occurred in arm B and 1 (1%) occurred in arm A (*P*=NS). In arm B, 30 patients (40%) did not undergo high-dose therapy and autologous stem-cell transplantation. According to the intention-to-treat analysis at a median follow-up of 24 months, 5-year OS probability in arms A and B was 65% and 64% (*P*=.95), 5-year PFS was 49% and 61% (*P*=.21), and 5-year relapse-free survival was 65% and 77% (*P*=.22), respectively.	1
73. Vitolo U, Liberati AM, Cabras MG, et al. High dose sequential chemotherapy with autologous transplantation versus dose-dense chemotherapy MegaCEOP as first line treatment in poor-prognosis diffuse large cell lymphoma: an "Intergruppo Italiano Linfomi" randomized trial. *Haematologica.* 2005;90(6):793-801.	Experimental-Tx	130 DLBCL patients	A multicenter, randomized trial to compare FFS and OS in patients with poor prognosis DLBCL treated with high-dose sequential chemotherapy followed by autologous stem-cell transplantation or an outpatient dose-dense chemotherapy regimen.	The CR rate was 59% in arm A and 70% in arm B (*P*=0.18). After a median follow-up of 78 months, the 6-year FFS was 45% in arm A and 48% in arm B (HR = 1.15, 95% CIs = 0.72-1.84, *P*=0.56). The 5-year OS was 49% in arm A and 63% in arm B (HR = 1.67, 95% CI = 0.98-2.85, *P*=0.06). 2 cases of secondary acute myeloid leukemia were observed after treatment in group A.	1

Diffuse Large B-Cell Lymphoma
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
74. Vitolo U, Chiappella A, Angelucci E, et al. Dose-dense and high-dose chemotherapy plus rituximab with autologous stem cell transplantation for primary treatment of diffuse large B-cell lymphoma with a poor prognosis: a phase II multicenter study. *Haematologica.* 2009;94(9):1250-1258.	Experimental-Tx	94 patients	To investigate the addition of rituximab to dose-dense and high-dose chemotherapy with autologous stem cell transplantation in patients with untreated poor-prognosis DLBCL.	The CR and toxic death rates were 82% and 5%, respectively. FFS and OS rates at 4 years were 73% and 80%, respectively. The outcomes of these patients were retrospectively compared to those of 41 patients with similar characteristics enrolled into a previous phase II trial of high-dose chemotherapy without rituximab. This historical group was treated with 8 weekly infusions of MACOP-B, 2 courses of MAD and BEAM with autologous stem cell transplantation. The 4-year FFS rates for the rituximab and historical groups were 73% vs 44%, respectively (P=0.001); the 4-year OS rates were 80% and 54%, respectively (P=0.002). A Cox's multivariable model was applied to adjust the effect of treatment for unbalanced or important prognostic factors: failure and death risks were significantly reduced in the rituximab group compared to the historical group, with an adjusted HR of 0.44 (P=0.01) for FFS and 0.46 (P=0.02) for OS	1
75. Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. *N Engl J Med.* 2013;369(18):1681-1690.	Experimental-Tx	370 patients	To determine the efficacy of autologous stem-cell transplantation during the first remission in patients with diffuse, aggressive NHL.	Of 370 induction-eligible patients, 253 were randomly assigned to the transplantation group (125) or the control group (128). 46 patients in the transplantation group and 68 in the control group had disease progression or died, with 2-year PFS rates of 69% and 55%, respectively (HR in the control group vs the transplantation group, 1.72; 95% CI, 1.18 to 2.51; P=0.005). 37 patients in the transplantation group and 47 in the control group died, with 2-year OS rates of 74% and 71%, respectively (HR, 1.26; 95% CI, 0.82 to 1.94; P=0.30). Exploratory analyses showed a differential treatment effect according to risk level for both PFS (P=0.04 for interaction) and OS (P=0.01 for interaction). Among high-risk patients, the 2-year OS rate was 82% in the transplantation group and 64% in the control group.	1

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
76. Haioun C, Itti E, Rahmouni A, et al. [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. *Blood.* 2005;106(4):1376-1381.	Observational-Dx	90 patients	To determine the early prognostic value of FDG-PET at midinduction in patients presenting with previously untreated aggressive lymphoma.	At midinduction, "early PET" was considered negative in 54 patients and positive in 36. After completion of induction, 83% of PET-negative patients achieved CR compared with only 58% of PET-positive patients. Outcome differed significantly between PET-negative and PET-positive groups; the 2-year estimates of EFS reached 82% and 43%, respectively (P<.001), and the 2-year estimates of OS reached 90% and 61%, respectively (P=.006). Predictive value of "early PET" was observed in both the lower-risk and higher-risk groups, indicating prognostic independence from the IPI.	2
77. Safar V, Dupuis J, Itti E, et al. Interim [18F]fluorodeoxyglucose positron emission tomography scan in diffuse large B-cell lymphoma treated with anthracycline-based chemotherapy plus rituximab. *J Clin Oncol.* 2012;30(2):184-190.	Observational-Dx	112 patients	To retrospectively evaluate whether interim PET is a valid prognostic tool for patients with DLBCL treated with rituximab and chemotherapy.	Visual analysis showed that 70 patients (62.5%) presented with a negative PET scan after 2 cycles of treatment. The 3-year PFS and OS rates were 84% and 88%, respectively, in patients with PET-negative results vs 47% and 62%, respectively, in patients with PET-positive results (P<.0001 and P<.003, respectively). A second analysis was performed on 85 patients by using interim PET in a quantitative approach on the basis of a DeltaSUV(max) evaluation of more than 66%. The 3-year PFS was 77% for patients with PET-negative results and 37.5% for patients with PET-positive results (P=.002).	4
78. Horning SJ, Juweid ME, Schoder H, et al. Interim positron emission tomography scans in diffuse large B-cell lymphoma: an independent expert nuclear medicine evaluation of the Eastern Cooperative Oncology Group E3404 study. *Blood.* 2010;115(4):775-777; quiz 918.	Observational-Dx	38 cases; 3 reviewers	To determine the reproducibility of interim PET interpretation, an expert panel of 3 external nuclear medicine physicians visually scored baseline and interim PET scans.	The binary ECOG study criteria were based on modifications of the Harmonization Criteria; the London criteria were also applied. Of 38 interim scans, agreement was complete in 68% and 71% by ECOG and London criteria, respectively. The range of PET(+) interim scans was 16% to 34% (P=not significant) by reviewer. Moderate consistency of reviews was observed: kappa statistic = 0.445 using ECOG criteria, and kappa statistic = 0.502 using London criteria. These data, showing only moderate reproducibility among nuclear medicine experts, indicate the need to standardize PET interpretation in research and practice.	4

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
79. Moskowitz CH, Schoder H, Teruya-Feldstein J, et al. Risk-adapted dose-dense immunochemotherapy determined by interim FDG-PET in Advanced-stage diffuse large B-Cell lymphoma. *J Clin Oncol.* 2010;28(11):1896-1903.	Observational-Tx	98 total patients	To clarify the significance of interim FDG-PET scans in DLBCL, a prospective study of interim FDG-positive disease within a risk-adapted sequential immunochemotherapy program was performed.	At a median follow-up of 44 months, OS and PFS were 90% and 79%, respectively. 97 patients underwent interim FDG-PET scans; 59 had a negative scan, 51 of whom are progression free. 38 patients with FDG-PET-positive disease underwent repeat biopsy; 33 were negative, and 26 remain progression free after ifosfamide, carboplatin, and etoposide consolidation therapy. PFS of interim FDG-PET-positive/biopsy-negative patients was identical to that in patients with a negative interim FDG-PET scan (P=.27).	1
80. Dabaja B, Liang F, Shihadeh F, et al. Mid-therapy Positron Emission Tomography Scans Significantly Predict Outcome in Patients With Diffuse Large B-cell Lymphoma (DLBCL) Treated With Chemotherapy Alone But Not When Consolidation Radiation is Added. *Int J Radiat Oncol Biol Phys.* 2012;84(3):S73.	Observational-Tx	294 patients	To address the role of mid-therapy-PET according to the use of consolidation RT.	For all 294 patients the 5-year PFS and OS rates were significantly affected by the status of mid-therapy-PET scan: the PFS and OS were 75% and 81%, respectively for negative mid-therapy-PET (P=0.0009) compared to 59% and 58%, respectively for positive mid-therapy-PET (P=0.001). For patients who received chemotherapy alone, mid-therapy-PET significantly affected the PFS and OS: 5-year PFS and OS were 71% and 78% for mid-therapy-PET– vs 52% and 50% for mid-therapy-PET+ (P=0.02 and 0.004, respectively). However, it lost its significance in patients who received consolidation RT (PFS and OS, 85% and 90%, respectively for mid-therapy-PET–; P=0.87 vs 82% and 81%, respectively for mid-therapy-PET+; P=0.38).	2

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
81. Dabaja BS, Phan J, Mawlawi O, et al. Clinical implications of positron emission tomography-negative residual computed tomography masses after chemotherapy for diffuse large B-cell lymphoma. *Leuk Lymphoma.* 2013;54(12):2631-2638.	Observational-Tx	303 patients with histologically confirmed DLBCL	To evaluate potential differences in OS and PFS according to PET and CT disease status at completion of chemotherapy for patients with DLBCL.	On multivariate analysis, both OS and PFS were significantly influenced by: the presence of PET negative residual mass on CT at completion of therapy ($P<0.001$ for OS and $P<0.001$ for PFS); number of cycles and type of chemotherapy ($P<0.001$ for OS and $P<0.001$ for PFS); Combined presence ($P=0.01$ for OS and $P=0.003$ for PFS) of high Ki 67, high PET standard uptake volume, and bulky disease; and IPI score ($P=0.001$ for OS and $P<0.001$ for PFS). Same factors remained significant when replacing response to therapy with size of the residual mass on CT, or number of residual sites ($P<0.0001$ OS and $P<0.0001$ PFS).	2
82. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol.* 2014;32(27):3048-3058.	Review/Other-Dx	N/A	To represent the consensus reached regarding the use of PET/CT in lymphoma in clinical practice and late-phase trials.	A working paper was circulated for comment and presented at the Fourth International Workshop on PET in Lymphoma in Menton, France, and the 12th ICML in Lugano, Switzerland, to update the International Harmonisation Project guidance regarding PET. Recommendations were made to optimize the use of PET/CT in staging and response assessment of lymphoma, including qualitative and quantitative methods.	4

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
83. Traverse-Glehen A, Pittaluga S, Gaulard P, et al. Mediastinal gray zone lymphoma: the missing link between classic Hodgkin's lymphoma and mediastinal large B-cell lymphoma. *Am J Surg Pathol.* 2005;29(11):1411-1421.	Review/Other-Tx	21 mediastinal gray zone lymphomas cases	A study of "mediastinal gray zone lymphomas", with features transitional between classic Hodgkin lymphoma-nodular sclerosis and primary MLBCL to better understand the morphologic and immunophenotypic spectrum of such cases.	All patients had a large mediastinal mass. Immunohistochemical studies focused on markers known to discriminate between classic Hodgkin lymphoma and MLBCL, including B-cell transcription factors. VJ-PCR was performed in 8 cases to look at clonality of the immunoglobulin heavy chain gene. Of the gray zone cases, 11 had morphology reminiscent of classic Hodgkin lymphoma-nodular sclerosis, but with unusual features, including a large number of mononuclear variants, diminished inflammatory background, absence of classic Hodgkin phenotype, and strong CD20 expression (11/11). 10 cases had morphology of MLBCL, but with admixed Hodgkin/Reed-Sternberg and lacunar cells, absent (3/10) or weak (7/10) CD20 expression, and positivity for CD15 in 7 cases. B-cell transcription factor expression in the gray zone cases more closely resembled MLBCL than classic Hodgkin lymphoma with expression of Pax5, Oct2, and BOB.1 in all but 1 case studied (14/15). MAL staining was found in 7/10 mediastinal gray zone lymphomas, and in at least 1 component of 6/7 evaluable composite or sequential MLBCL/classic Hodgkin lymphoma cases. 2 cases of sequential lymphoma showed rearrangements of the immunoglobulin heavy chain gene of identical size: 1 in which MLBCL was the first diagnosis and 1 in which MLBCL was diagnosed at relapse, indicating clonal identity for the 2 components of classic Hodgkin lymphoma and MLBCL.	4

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
84. Zinzani PL, Martelli M, Bertini M, et al. Induction chemotherapy strategies for primary mediastinal large B-cell lymphoma with sclerosis: a retrospective multinational study on 426 previously untreated patients. *Haematologica.* 2002;87(12):1258-1264.	Observational-Tx	426 previously untreated patients	A retrospective study to compare the outcomes of patients with primary MLBCL with sclerosis after first-generation (dose-intensive regimens), third-generation (alternating regimens) and high-dose chemotherapy strategies, frequently with adjuvant RT.	With chemotherapy, CR rates were 49% (50/105), 51% (142/277) and 53% (23/44) with first generation, third generation and high-dose chemotherapy strategies, respectively; partial response rates were 32%, 36% and 35%, respectively. All patients who achieved CR and 124/142 (84%) with partial response had RT on the mediastinum. The final CR rates became 61% for CHOP/CHOP-like regimens, 79% for MACOP-B and other regimens, and 75% for high-dose sequential/ABMT.	2
85. Rodriguez J, Conde E, Gutierrez A, et al. Primary mediastinal large cell lymphoma (PMBL): frontline treatment with autologous stem cell transplantation (ASCT). The GEL-TAMO experience. *Hematol Oncol.* 2008;26(3):171-178.	Observational-Tx	71 patients	To present patients with PMBL receiving induction chemotherapy, followed by autologous stem cell transplantation as frontline therapy from the GEL-TAMO registry.	With a median follow-up of 52.5 months, the OS, PFS and disease-free survival at 4 years from diagnosis were, respectively, 84%, 81% and 81% for the first CR patients and 49%, 42% and 82% for the induction failure (partial response and refractory) patients. Disease progression was the main cause of death (79%). By multivariate survival analysis the tumor score, refractory disease at transplant and RT were independent variables associated with OS and PFS. Our experience, with a prolonged follow-up, shows that patients with PMBL presenting at diagnosis with high-risk features or PR response to induction therapy have an encouraging survival with frontline autologous stem cell transplantation. However, patients who received the transplant after failing the induction regimen have a very poor prognosis and should be tested with other innovative approaches.	2

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
86. Todeschini G, Secchi S, Morra E, et al. Primary mediastinal large B-cell lymphoma (PMLBCL): long-term results from a retrospective multicentre Italian experience in 138 patients treated with CHOP or MACOP-B/VACOP-B. *Br J Cancer*. 2004;90(2):372-376.	Observational-Tx	138 patients	To compare the long-term results of CHOP vs MACOP-B/VACOP-B, the 2 most commonly employed regimens in PMBL patients in USA and Europe, respectively and to evaluate the role of consolidation IFRT on the long-term outcome after CR achievement.	From 1982 to 1999, 138 consecutive patients affected by PMBL were treated in 13 Italian institutions with CHOP (43) or MACOP-B/VACOP-B (95). The 2 groups of patients were similar as regard to age, gender, presence of bulky mediastinal mass, pleural effusion, stage and international prognostic indexes category of risk. Overall, 75.5% of patients in CR received IFRT as consolidation. CR was 51.1% in the CHOP group and 80% in MACOP-B/VACOP-B ($P<0.001$). Relapse occurred in 22.7% of CHOP and in 9.2% of MACOP-B/VACOP-B-treated patients (n.s.). Event-free patients were 39.5% in CHOP and 75.7% in the MACOP-B/VACOP-B group ($P<0.001$). The addition of IFRT as consolidation improved the outcome, irrespectively of the type of chemotherapy ($P=0.04$). At a multivariate analysis, achievement of CR ($P<0.0001$) and type of CT (MACOP-B/VACOP-B) retained the significance for OS ($P=0.008$) and EFS ($P=0.03$).	2

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
87. Kirn D, Mauch P, Shaffer K, et al. Large-cell and immunoblastic lymphoma of the mediastinum: prognostic features and treatment outcome in 57 patients. *J Clin Oncol.* 1993;11(7):1336-1343.	Observational-Tx	57 patients	A retrospective study was performed to define clinical characteristics and therapeutic outcome for patients with large-cell and immunoblastic lymphoma of the mediastinum.	56/57 patients had disease that was confined to sites above the diaphragm. Bulky disease and extensive intrathoracic infiltration were common in these patients. All patients were treated with intensive chemotherapy regimens, and 44% of patients received chest RT. The overall 5-year survival by Kaplan-Meier estimation was 50% with a freedom-from-relapse rate of 45%. Predictors of disease relapse after chemotherapy included the presence of a pleural effusion (P=.015), a number of involved extranodal sites (P<.01), and a LDH ratio >3.0 (LDH value/upper limit of assay; P=.04) as well as an incomplete treatment response as evidenced by residual mass on chest radiograph (P=.02) or persistent gallium 67 avidity (P=.01) after chemotherapy. Predictors of decreased survival included the presence of pleural effusion (P=.001), the number of involved extranodal sites (P=.022), and a positive post-treatment gallium 67 scan (P=.027).	2
88. Lazzarino M, Orlandi E, Paulli M, et al. Treatment outcome and prognostic factors for primary mediastinal (thymic) B-cell lymphoma: a multicenter study of 106 patients. *J Clin Oncol.* 1997;15(4):1646-1653.	Observational-Tx	106 total patients, 99 received chemotherapy	To define clinicopathologic features, response to treatment, and prognostic factors of PMBL, a CD20+ tumor recognized as a distinct entity among NHLs.	35/99 patients were primarily chemotherapy-resistant, and 64 responded: 23 achieved CR and 41 achieved response with residual mediastinal abnormality. 77% of responders received mediastinal RT. Of 64 responders, 18 (28%) relapsed: none of 23 CR patients and 18/41 (44%) with residual mediastinal abnormality. Relapse-free survival rate of responders was 71% at 3 years. Actuarial 3-year survival rate was 52% for all patients and 82% for responders.	2
89. Soumerai JD, Hellmann MD, Feng Y, et al. Treatment of primary mediastinal B-cell lymphoma with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone is associated with a high rate of primary refractory disease. *Leuk Lymphoma.* 2014;55(3):538-543.	Observational-Tx	63 patients	A comprehensive retrospective analysis of all patients with PMBL treated at our center in the modern era with R-CHOP, with or without radiation.	80% had limited stage disease and 71% were bulky. By age-adjusted IPI, 15% were low-risk, 52% low-intermediate, 27% high-intermediate and 6% high-risk. Some 77% of responding patients received consolidative RT. Overall and complete response rates were 79% and 71%. Primary induction failure occurred in 13 (21%) patients. 5-year PFS and OS were 68% and 79%, respectively.	2

Diffuse Large B-Cell Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
90. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. *N Engl J Med*. 2013;368(15):1408-1416.	Observational-Tx	51 patients	To develop a strategy that improves the rate of cure and obviates the need for RT.	The patients had a median age of 30 years (range, 19 to 52) and a median tumor diameter of 11 cm; 59% were women. During a median of 5 years of follow-up, the EFS rate was 93%, and the OS rate was 97%. Among the 16 patients who were involved in the retrospective analysis at another center, over a median of 3 years of follow-up, the EFS rate was 100%, and no patients received RT. No late morbidity or cardiac toxic effects were found in any patients. After follow-up ranging from 10 months to 14 years, all but 2 of the 51 patients (4%) who received DA-EPOCH-R alone were in CR. The 2 remaining patients received RT and were disease-free at follow-up.	1

Evidence Table Key

Study Quality Category Definitions

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

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

ABC = Activated B cell-like

ACVBP = Doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone

AIDS = Acquired immunodeficiency syndrome

CHOEP = Cyclophosphamide, doxorubicin, vincristine, and prednisone plus etoposide

CHOP = Cyclophosphamide, doxorubicin, vincristine, and prednisone

CI = Confidence interval

CNS = Central nervous system

CR = Complete remission

CT = Computed tomography

DA-EPOCH = dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin

DLBCL = Diffuse large B-cell lymphoma

ECFI = Extralymphatic craniofacial involvement

EFS = Event-free survival

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

FFS = Failure-free survival

GCB = Germinal center B cell-like

HAART = Highly active antiretroviral therapy

HIV = Human immunodeficiency virus

HR – Hazard ratio

IFRT = Involved-field radiation therapy

INRT = Involved-node radiation therapy

IPI = International Prognostic Index

LDH = Lactate dehydrogenase

MACOP-B = Methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin

m-BACOD = Methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone

MLBCL = Mediastinal large B-cell lymphoma

NHL = Non-Hodgkin lymphoma

OS = Overall survival

PFS = Progression-free survival

PMBL = Primary mediastinal B-cell lymphoma

ProMACE-CytaBOM = Prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue

PWHA = Persons with HIV/AIDS

R-ACVBP = Rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone

R-CHOP = Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

R-IPI = Revised-International Prognostic Index

RT = Radiation therapy