Localized Nodal Indolent Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. National Cancer Institute. *Comprehensive Cancer Information*. http://www.cancer.gov/cancertopics/types/non-hodgkin. Accessed 12 April 2013.	Review/Other-Tx	N/A	Estimated new cases and deaths from NHL in the United States in 2012.	New cases: 70,130, Deaths: 18,940. NHLs can occur at any age and are often marked by lymph nodes that are larger than normal, fever, and weight loss. Prognosis and treatment depend on the stage and type of disease.	4
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013; 63(1):11-30.	Review/Other-Tx	N/A	To provide the expected numbers of new cancer cases and deaths in 2013 nationally and by state, as well as an overview of current cancer statistics using data through 2009, including incidence, mortality, and survival rates and trends. The article also estimate the total number of deaths averted as a result of the decline in cancer death rates since the early 1990s, and provide the actual reported numbers of deaths in 2009 by age for the 10 leading causes of death and the 5 leading cancer types.	In 2009, Americans had a 20% lower risk of death from cancer than in 1991, when cancer death rates peaked. Despite this substantial progress, all demographic groups have not benefitted equally, particularly for cancers such as colorectal and breast, for which mortality declines have been attributed to earlier detection and improvements in treatment. Further progress can be accelerated by applying existing cancer control knowledge across all segments of the population, with an emphasis on those groups in the lowest socioeconomic bracket as well as other disadvantaged populations.	4
3. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. *Blood* 1997; 89(11):3909-3918.	Review/Other-Tx	1,403 total patients from around the world: 1988-1990	A clinical evaluation of the International Lymphoma Study Group classification.	A diagnosis of NHL was confirmed in 1,378 (98.2%) of the cases. The most common lymphoma types were DLBCL (31%) and FL (22%), whereas the new entities comprised 21% of the cases. Diagnostic accuracy was at least 85% for most of the major lymphoma types, and reproducibility of the diagnosis was 85%. Immunophenotyping improved the diagnostic accuracy by 10% to 45% for a number of the major types. The clinical features of the new entities were distinctive.	4
4. Friedberg JW, Taylor MD, Cerhan JR, et al. Follicular lymphoma in the United States: first report of the national LymphoCare study. *J Clin Oncol* 2009; 27(8):1202-1208.	Review/Other-Tx	2,728 patients	Analysis of a large prospective cohort study to identify current demographics and patterns of care of FL in the United States.	The choice to initiate therapy rather than observe was associated with age, Follicular Lymphoma International Prognostic Index (FLIPI), stage, and grade (P<.01). Significant differences in treatment (P<.01) across regions of the United States were noted. Contrary to practice guidelines, treatment of stage I FL frequently omits RT.	4

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5. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. *Blood* 2006; 107(1):265-276.	Review/Other-Dx	114,548 lymphoid neoplasms	Comprehensive assessment of lymphoid neoplasms diagnosed during 1992-2001 in 12 Surveillance, Epidemiology, and End Results (SEER) registries according to the internationally recognized World Health Organization (WHO) lymphoma classification introduced in 2001to find incidence patterns.	In the elderly (75 years or older), rates of DLBCL and FL increased 1.4% and 1.8% per year, respectively, whereas rates of chronic lymphocytic leukemia/small lymphocytic lymphoma declined 2.1% per year. Although whites bear the highest incidence burden for most lymphoid neoplasm subtypes, most notably for hairy cell leukemia and FL, black predominance was observed for plasma cell and T-cell neoplasms. Asians have considerably lower rates than whites and blacks for chronic lymphocytic leukemia/small lymphocytic lymphoma and Hodgkin lymphoma.	4
6. Goldin LR, Bjorkholm M, Kristinsson SY, Turesson I, Landgren O. Highly increased familial risks for specific lymphoma subtypes. *Br J Haematol* 2009; 146(1):91-94.	Observational-Dx	2,668 FL patients, 2,517 DLBCL patients, 6,963 Hodgkin lymphoma patients	Evaluated risk of lymphoma subtypes among first-degree relatives of FL patients, DLBCL patients, and Hodgkin lymphoma patients compared to first-degree relatives of controls.	Relatives were at the highest risk for developing the same lymphoma subtype as the case. DLBCL was increased 10-fold among relatives of DLBCL patients, FL was increased fourfold among relatives of FL patients and Hodgkin lymphoma was increased fourfold among relatives of Hodgkin lymphoma patients.	4
7. Wahlin BE, Yri OE, Kimby E, et al. Clinical significance of the WHO grades of follicular lymphoma in a population-based cohort of 505 patients with long follow-up times. *Br J Haematol* 2012; 156(2):225-233.	Observational-Tx	505 patients	Retrospective review of the FL diagnoses according to the 2008 WHO classification in all diagnostic specimens from a population-based cohort of patients with a median follow-up time of 10.0 years (range, 4.6-16.0).	After excluding 43 patients with concomitant DLBCL, 345 remained with grade 1-2, 94 with grade 3A, and 23 with grade 3B FL. Grades 1-2 and 3A seemed equally indolent, with indistinguishable clinical courses, even in patients receiving anthracyclines. Compared with grades 1-3A and independently of clinical factors, grade 3B correlated with higher mortality (P=0.008), but outcome was improved after upfront anthracycline-containing therapy (P=0.015). In contrast to grade 1-3A patients, grade 3B patients experienced no relapses or deaths beyond 5-years of follow-up.	2

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8. Tsujimoto Y, Cossman J, Jaffe E, Croce CM. Involvement of the bcl-2 gene in human follicular lymphoma. *Science* 1985; 228(4706):1440-1443.	Review/Other-Dx	N/A	Study of the involvement of the bcl-2 gene in human FL.	Two of the probes detected DNA rearrangements in approximately 60% of the cases of FL screened. In FL, most of the breakpoints in band q21 of chromosome 18 were clustered within a short stretch of DNA, approximately 2.1 kilobases in length. Chromosome 18-specific DNA probes for the areas flanking the breakpoints also detected RNA transcripts 6 kilobases in length in various cell types. The gene coding for these transcript (the bcl-2 gene) seems to be interrupted in most cases of FLs carrying the t(14;18) chromosomal translocation.	4
9. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res* 1971; 31(11):1860-1861.	Review/Other-Dx	N/A	Report of the Committee on Hodgkin's Disease Staging Classification.	The Committee recognizes the wide diversity in the kinds and amounts of surgical removal of tissue to improve the accuracy of clinical staging at different institutions. To increase the amount of data reported and to allow for more precise comparisons, the use of a simultaneously recorded pathological staging in all patients is recommended. The pathological staging classification is to be subscripted by symbols indicating the tissue sampled and the results of histopathological examination by + when positive for Hodgkin's disease or – when negative.	4
10. Canioni D, Brice P, Lepage E, et al. Bone marrow histological patterns can predict survival of patients with grade 1 or 2 follicular lymphoma: a study from the Groupe d'Etude des Lymphomes Folliculaires. *Br J Haematol* 2004; 126(3):364-371.	Observational-Tx	390 patients	Patients with grade 1 or 2 FL were prospectively included in the multicentric Groupe d'Etude des Lymphomes Folliculaires trial and their BMB reviewed in order (i) to quantify the ratio of lymphomatous foci area to that of BMB size, (ii) to determine the BMB patterns for a practical grading of marrow infiltration, (iii) to assess the intra- and inter-observer reproducibility of this grading and (iv) to analyse this grading on EFS and OS, using univariate and multivariate analyses.	A total of 267 patients (68%) had BMB involvement, with inter- and intra-observer reproducibility for classifying the patterns of involvement of 91% and 96%, respectively. Uni- and multivariate analyses demonstrated the adverse influence of (i) a ratio of lymphomatous foci area to that of BMB ≥0.1, ie, 3 or 4 nodules/medullary space or ≥1 nodule + foci of diffuse involvement on EFS (P=0.03) and (ii) two different histological patterns in the same BMB on EFS (P=0.004) and OS (P=0.001). This latter finding was only significant in patients with a high tumour burden and remained significant in multivariate analysis.	2

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11. Wirth A, Foo M, Seymour JF, Macmanus MP, Hicks RJ. Impact of [18f] fluorodeoxyglucose positron emission tomography on staging and management of early-stage follicular non-hodgkin lymphoma. *Int J Radiat Oncol Biol Phys* 2008; 71(1):213-219.	Observational-Dx	42 patients	Accurate staging is critical to select patients with early-stage (I-II) FL suitable for IFRT and to define the RT portal. The impact of FDG-PET was evaluated on staging, treatment, and outcome for patients with early-stage FL on conventional staging.	FDG avidity was demonstrated in 97% of patients in whom disease was evident on conventional assessment after biopsy. PET findings suggested a change of stage or management in 19 patients: 13 (31%) who were upstaged to stage III-IV, altering ideal management from IFRT to systemic therapy, and 6 (14%) who had the involved field enlarged, including 4 upstaged from stage I to II. Of these 19 cases, PET findings were considered true positive in 8 patients, indeterminate in 10, and false positive in only 1 patient.	3
12. Le Dortz L, De Guibert S, Bayat S, et al. Diagnostic and prognostic impact of 18F-FDG PET/CT in follicular lymphoma. *Eur J Nucl Med Mol Imaging* 2010; 37(12):2307-2314.	Observational-Dx	45 patients	To assess the usefulness of PET/CT in staging, prognosis evaluation and restaging of patients with FL.	PET/CT detected more nodal (+51%) and extranodal (+89%) lesions than CT. PET/CT modified Ann Arbor staging in 8 patients (18%). 5 patients (11%) initially considered as being early stage (I/II) were eventually treated as advanced stage (III/IV). In this study, an initial PET/CT prognostic score was significantly more accurate than the FLIPI score in identifying patients with poor prognosis (ie, patients with incomplete therapeutic response or early relapse). The accuracy of PET/CT for therapeutic response assessment was higher than that of CT (0.97 vs 0.64), especially due to its ability to identify inactive residual masses. In addition, post-treatment PET/CT was able to predict patients' outcomes. The median PFS was 48 months in the PET/CT-negative group as compared with 17.2 months for the group with residual uptake (P<10(-4)).	3
13. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood* 2004; 104(5):1258-1265.	Observational-Tx	4,167 (patients with FL diagnosed between 1985 and 1992)	FL international prognostic index.	This FLIPI appeared more discriminant than the International Prognostic Index proposed for aggressive NHLs. Results were very similar in the confirmation group. The FLIPI may be used for improving treatment choices, comparing clinical trials, and designing studies to evaluate new treatments.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
14. Plancarte F, Lopez-Guillermo A, Arenillas L, et al. Follicular lymphoma in early stages: high risk of relapse and usefulness of the Follicular Lymphoma International Prognostic Index to predict the outcome of patients. *Eur J Haematol* 2006; 76(1):58-63.	Observational-Tx	48 patients	To analyze the clinical features and the outcome of a series of patients with FL in early stages with a long follow-up.	The histologic subtypes were: FL type I, 20 cases (42%); type II, 24 (50%); type III, three (6%); and unclassifiable, one (2%). Distribution according to FLIPI was: low risk (36 cases) and intermediate risk (5 cases). Treatment mainly consisted of combination chemotherapy (CHOP in 34 cases) plus IFRT in 26 cases. 40 patients (89%) achieved a CR, 3 (7%) a PR, and 2 (4%) were non-responders; the remaining 3 patients did not receive therapy. No initial variable predicted CR achievement. About 57% of the patients in CR eventually relapsed with a relapse risk of 46% at 10 years. Intermediate-risk FLIPI predicted failure-free survival. Histologic transformation was observed in 6 patients with a 10-years risk of transformation of 13%. 12 patients died during follow-up, in two cases as a result of unrelated causes. OS at 10 years was 79%. The FLIPI was the sole variable predicting OS.	2
15. Buske C, Hoster E, Dreyling M, Hasford J, Unterhalt M, Hiddemann W. The Follicular Lymphoma International Prognostic Index (FLIPI) separates high-risk from intermediate- or low-risk patients with advanced-stage follicular lymphoma treated front-line with rituximab and the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with respect to treatment outcome. *Blood* 2006; 108(5):1504-1508.	Observational-Tx	362 patients	Aimed at evaluating the predictive value of the FLIPI for treatment outcome in patients with advanced-stage FL treated front-line with R-CHOP in a prospective trial of the German Low Grade Lymphoma Study Group.	According to the FLIPI, 14% of the patients were classified as low-risk, 41% as intermediate-risk, and 45% as high-risk patients. With a 2-year time to treatment failure of 67%, high-risk patients had a significantly shorter time to treatment failure as compared with low- or intermediate-risk patients (2-year time to treatment failure of 92% and 90%, respectively; P<.001).	1

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16. Montoto S, Davies AJ, Matthews J, et al. Risk and clinical implications of transformation of follicular lymphoma to diffuse large B-cell lymphoma. *J Clin Oncol* 2007; 25(17):2426-2433.	Observational-Tx	325 patients	To study the clinical significance of transformation to DLBCL in patients with FL.	The risk of histologic transformation by 10 years was 28%, histologic transformation not yet having been observed after 16.2 years. The risk was higher in patients with advanced stage (P=.02), high-risk (FLIPI; P=.01), and International Prognostic Index (IPI; P=.04) scores at diagnosis. Expectant management (as opposed to treatment being initiated at diagnosis) also predicted for a higher risk of histologic transformation (P=.008). Older age (P=.005), low hemoglobin level (P=.03), high lactate dehydrogenase (P<.0001), and high-risk FLIPI (P=.01) or IPI (P=.003) score at the time of first recurrence were associated with the diagnosis of histologic transformation in a biopsy performed at that time. The median survival from transformation was 1.2 years. Patients with histologic transformation had a shorter OS (P<.0001) and a shorter survival from progression (P<.0001) than did those in whom it was not diagnosed.	2
17. Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. *J Clin Oncol* 2009; 27(27):4555-4562.	Observational-Tx	942 patients	To verify whether a prospective collection of data would enable the development of a more accurate prognostic index for FL by using parameters which could not be retrospectively studied before, and by choosing PFS as principal end point.	After a median follow-up of 38 months, 261 events for PFS evaluation were recorded. beta2-microglobulin higher than the upper limit of normal, longest diameter of the largest involved node longer than 6 cm, bone marrow involvement, hemoglobin level lower than 12 g/dL, and age older than 60 years were factors independently predictive for PFS. Using these variables, a prognostic model was devised to identify three groups at different levels of risk. The 3-year PFS rate was 91%, 69%, and 51% for patients at low, intermediate, and high risk, respectively (log-rank = 64.6; P<.00001). The 3-year survival rate was 99%, 96%, and 84% for patients at low, intermediate, and high risk, respectively (P<.0001).	2

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18. Bastion Y, Sebban C, Berger F, et al. Incidence, predictive factors, and outcome of lymphoma transformation in follicular lymphoma patients. *J Clin Oncol* 1997; 15(4):1587-1594.	Review/Other-Tx	220 patients	To assess the incidence of lymphoma transformation in the natural history of FL patients and the factors that is predictive of this event.	Transformation was proven by histology in 34 patients or by cytology in 13 patients and was considered as highly probable on clinical arguments in 5 patients for an overall incidence of 24%. The probability of transformation was 22% at 5 years and 31% at 10 years and tended to plateau after 6 years. Predictive factors for transformation were nonachievement of CR after initial therapy (P<10(-4), low serum albumin level (<35 g/L) (P=.001), and beta 2-microglobulin level >3 mg/L (P=.02) at diagnosis. In a multiparametric analysis, only beta 2-microglobulin level retained prognostic significance for freedom-from-transformation survival (P=.04). Transformation accounted for 44% of deaths and was associated with a poor outcome, with a median survival time of 7 months.	4
19. Conconi A, Ponzio C, Lobetti-Bodoni C, et al. Incidence, risk factors and outcome of histological transformation in follicular lymphoma. *Br J Haematol* 2012; 157(2):188-196.	Review/Other-Tx	281 patients	To assess the frequency and outcome of histological transformation to DLBCL and to document the risk factors that may predict for it in FL patients.	Histological transformation into DLBCL was documented in 37/281 (13%; 95% CI: 9-18) FL patients treated at our institute from 1979 to 2007. Histological transformation occurred at a median of 2.75 years from initial FL diagnosis and histological transformation rate was 15% at 10 years and 26% at 14 years, with a plateau from that point onward. Patients with bulky or extranodal disease, or those diagnosed before 1990 had a significantly higher risk of histological transformation. When initial treatment strategies were taken into account, a reduced histological transformation risk was seen in the patients initially managed with a 'watch and wait' policy, while the risk appeared significantly increased in the small subset of 18 patients initially managed with rituximab plus chemotherapy (P=0.0005). Histological transformation was associated with a significantly shorter cause-specific survival (P=0.0002). Predictors of survival after histological transformation were the FLIPI at diagnosis, as well as age and performance status at the time of histological transformation.	4

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20. Friedberg JW, Byrtek M, Link BK, et al. Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. J Clin Oncol 2012; 30(27):3368-3375.	Observational-Tx	206 patients	To analyze outcomes of patients with stage I FL enrolled onto the National LymphoCare database.	Of 471 patients with stage I FL, 206 patients underwent rigorous staging as defined by both a bone marrow aspirate and biopsy and an imaging study (a CT scan of the whole body, a PET/CT scan, or both). Rigorously staged patients had superior PFS compared with nonrigorously staged patients (HR, 0.63). Treatments given to rigorously staged patients were rituximab/chemotherapy (28%), external RT (27%), observation (17%), systemic therapy + external RT (13%), rituximab monotherapy (12%), and other (3%). With a median follow-up of 57 months for PFS, there were 44 progression events (in 21% of patients) for rigorously staged patients. For these patients, PFS was significantly improved with either rituximab/chemotherapy or systemic therapy + external RT compared with patients receiving external RT alone after adjustment for histology, lactate dehydrogenase, and the presence of B symptoms. There were no differences in OS.	2
21. Advani R, Rosenberg SA, Horning SJ. Stage I and II follicular non-Hodgkin's lymphoma: long-term follow-up of no initial therapy. *J Clin Oncol* 2004; 22(8):1454-1459.	Observational-Tx	43 patients	To analyze the outcome of no initial therapy in stage I and II follicular small-cleaved and follicular mixed NHL on OS, time to treatment, incidence and course of transformation, and cause of death.	Reasons for no initial therapy included: physician choice (n=20), large abdominal radiation field required (n=10), advanced age (n=7), concern for xerostomia (n=4), or patient refusal (n=2). At a median follow-up of 86 months, 27 patients (63%) had not been treated. The median time to treatment in the remaining 16 patients was 22 months. 4/16 patients transformed to a higher-grade lymphoma. 9 patients died, 6 due to progressive lymphoma. Estimated survivals at 5, 10, and 20 years were 97%, 85%, and 22%, respectively.	2
22. Soubeyran P, Eghbali H, Trojani M, Bonichon F, Richaud P, Hoerni B. Is there any place for a wait-and-see policy in stage I0 follicular lymphoma? A study of 43 consecutive patients in a single center. *Ann Oncol* 1996; 7(7):713-718.	Observational-Tx	43 patients	To test wait-and-see in a selected subset of the localized FL, i.e., patients in CR after the initial lymph node biopsy (stage I0).	13/26 untreated patients are still relapse-free, while 6 relapsed locally only (median: 4.2 years after diagnosis), and reattained CR with RT. 7 patients relapsed at distant sites (median: 1 year after diagnosis). No localized relapses were observed in the treated group, but there were 7 distant relapses.	1

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23. Mac Manus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. *J Clin Oncol* 1996; 14(4):1282-1290.	Observational-Tx	177: stage I (n=73) and II (n=104) follicular small cleaved-cell and follicular mixed small cleaved-cell and large-cell NHL	To evaluate retrospectively the results of RT for patients with stage I and II follicular small cleaved-cell and follicular mixed small cleaved-cell and large-cell NHL.	The median follow-up duration was 7.7 years. The longest follow-up duration was 31 years. Actuarial survival rates at 5, 10, 15, and 20 years were 82%, 64%, 44%, and 35%, respectively. The median survival time was 13.8 years. At 5, 10, 15, and 20 years, 55%, 44%, 40%, and 37% of patients, respectively, were relapse-free. Only 5/47 patients who reached 10 years without relapse subsequently developed recurrence. Survival and freedom from relapse were significantly worse for older patients. Relapse rates were lower following treatment on both sides of the diaphragm or staging laparotomy.	1
24. Gospodarowicz MK, Bush RS, Brown TC, Chua T. Prognostic factors in nodular lymphomas: a multivariate analysis based on the Princess Margaret Hospital experience. *Int J Radiat Oncol Biol Phys* 1984; 10(4):489-497.	Observational-Tx	1,394 patients	A multivariate analysis of prognostic factors in nodular lymphomas based on the Princess Margaret Hospital experience.	Overall actuarial survival of 525 patients with nodular lymphomas was 40% at 12 years; survival of patients with localized (stage I & III) nodular lymphomas treated with radical RT was 58%. Significant prognostic factors defined by multivariate analysis included patient's age, stage, histology, tumor bulk, and presence of B symptoms. Patients with stage I & II disease, small or medium bulk, <70 years of age achieved 92% 12 year actuarial survival and a 73% relapse-free rate in 12 years of follow-up.	2
25. Vaughan Hudson B, Vaughan Hudson G, MacLennan KA, Anderson L, Linch DC. Clinical stage 1 non-Hodgkin's lymphoma: long-term follow-up of patients treated by the British National Lymphoma Investigation with radiotherapy alone as initial therapy. *Br J Cancer* 1994; 69(6):1088-1093.	Observational-Tx	451: (Histopathologically 208 patients had low-grade disease and 243 patients high-grade disease)	A retrospective analysis was performed of adult patients with clinical stage 1/1E NHL treated initially with RT alone.	The CR rate was higher in patients with low-grade disease (98%) than in those with high-grade disease (84%) (P<0.0001). The relapse rate was similar in both histological categories, and relapse usually occurred within 5 years. The resulting overall actuarial percentage of patients achieving CR and remaining disease free (at 10 years) was 47% in patients with low-grade disease and 45% for those with high-grade disease.	2

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26. Pugh TJ, Ballonoff A, Newman F, Rabinovitch R. Improved survival in patients with early stage low-grade follicular lymphoma treated with radiation: a Surveillance, Epidemiology, and End Results database analysis. *Cancer* 2010; 116(16):3843-3851.	Observational-Tx	6,568 patients	A SEER database analysis of improved survival in patients with early stage low-grade FL treated with radiation.	A total of 6,568 patients were identified. Disease-specific survival at 5, 10, 15, and 20 years in the RT group was 90%, 79%, 68%, and 63% vs 81%, 66%, 57%, and 51% in the no RT group (HR, 0.61; 95% CI, 0.55-0.68; P<.0001). OS at 5, 10, 15, and 20 years in the RT group was 81%, 62%, 45%, and 35% vs 71%, 48%, 34%, and 23% in patients not receiving RT (HR, 0.68; 95% CI, 0.63-0.73; P<.0001). On multivariate analysis, upfront RT remained independently associated with improved disease-specific survival (P<.0001, Cox HR, 0.65; 95% CI, 0.57-0.72) and OS (P<.0001; Cox HR, 0.73; 95% CI, 0.67-0.79). Lymphoma was the most common cause of death (52%). Only 34% of patients received upfront RT. =	2
27. Kelsey SM, Newland AC, Hudson GV, Jelliffe AM. A British National Lymphoma Investigation randomised trial of single agent chlorambucil plus radiotherapy versus radiotherapy alone in low grade, localised non-Hodgkins lymphoma. *Med Oncol* 1994; 11(1):19-25.	Experimental-Tx	148 patients	A British National Lymphoma Investigation randomised trial of single agent chlorambucil plus RT vs RT alone in low grade, localized NHL.	After a maximum of 18 years follow up there was no significant difference in OS or disease free survival between the two treatment groups. Age greater than 50 years and low serum albumin at diagnosis correlated with a poor prognosis in the series overall.	1
28. Seymour JF, Pro B, Fuller LM, et al. Long-term follow-up of a prospective study of combined modality therapy for stage I-II indolent non-Hodgkin's lymphoma. *J Clin Oncol* 2003; 21(11):2115-2122.	Observational-Tx	102 patients	To investigate the potential for combined-modality therapy to increase the disease-free survival for patients with stage I-II indolent lymphoma.	There were no treatment-related deaths and 99% of patients attained CR. With a median follow-up of 10 years, the 10-year time to treatment failure and OS were 76% and 82%, respectively. For patients with FL, these figures were 72% and 80%, respectively. The only factor associated with treatment failure, for FL patients, was stage-modified International Prognostic Factors Index score (P=.02). None of 17 patients with diffuse small lymphocytic or mucosa-associated lymphoid tissue histology have relapsed. Elevated serum beta 2-microglobulin was associated with shorter survival (P<.0001). The 10-year survival after relapse was 46%. There have been two cases of myelodysplasia and 12 other new malignancies, including four arising within radiation fields.	2

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29. 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	361 sites of indolent NHL, 640 sites of aggressive NHL	This multicentre, prospective, randomised-controlled trial compared efficacy and toxicity of differing RT doses in NHL.	There was no difference in ORR between standard and lower-dose arms. In the indolent group, ORR was 93% and 92%, respectively, (P=0.72); in the aggressive group, ORR 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
30. Campbell BA, Voss N, Woods R, et al. Long-term outcomes for patients with limited stage follicular lymphoma: involved regional radiotherapy versus involved node radiotherapy. *Cancer* 2010; 116(16):3797-3806.	Observational-Tx	237 patients	Investigation of the long-term outcomes of patients with limited stage FL who received RT alone and studied the impact of reducing the RT field size from involved regional RT to involved node RT with margins up to ≤5 cm.	Patients identified (median follow-up, 7.3 years) included 48% men, 54% aged >60 years, stage IA disease in 76% of patients, elevated lactate dehydrogenase in 7% of patients, grade 3A tumors in 12% of patients, and lymph node size ≥5 cm in 19% of patients. The two RT groups were involved regional RT (142 patients; 60%) and involved node RT ≤5cm (95 patients; 40%). At 10 years, the PFS rate was 49%, and the OS rate was 66%. Only 2 patients developed recurrent disease beyond 10 years. The most common pattern of first failure was a distant recurrence only, which developed in 38% of patients who received involved regional RT and in 32% of patients who received involved node RT ≤5. After involved node RT ≤5, 1% of patients had a regional-only recurrence. Significant risk factors for PFS were lymph nodes ≥5 cm (P=.008) and male gender (P=.042). Risk factors for OS were age >60 years (P<.001), elevated lactate dehydrogenase (P=.007), lymph nodes ≥5 cm (P=.016), and grade 3A tumors (P=.036). RT field size did not have an impact on PFS or OS.	2

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31. NCCN Clinical Practice Guidelines in Oncology. Hodgkin Lymphoma. Version 1.2013. Available at: http://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf. Accessed 12 April 2013.	Review/Other-Tx	N/A	To provide NCCN practice guidelines on Hodgkin Lymphoma.	No abstract available.	4
32. Hohloch K, Delaloye AB, Windemuth-Kieselbach C, et al. Radioimmunotherapy confers long-term survival to lymphoma patients with acceptable toxicity: registry analysis by the International Radioimmunotherapy Network. *J Nucl Med* 2011; 52(9):1354-1360.	Review/Other-Tx	1,075: enrolled from December 2006 until November 2009, and 467 patients with an observation time of at least 12 months were included	Registry analysis by the International Radioimmunotherapy Network of long-term observational data about radioimmunotherapy-treated patients with malignant lymphoma outside randomized clinical studies.	Diagnoses were as follows: 58% FL and 42% other B-cell lymphomas. The mean OS was 28 months for FL and 26 months for other lymphoma subtypes. Hematotoxicity was mild for hemoglobin (WHO grade II), with a median nadir of 10 g/dL, but severe (WHO grade III) for platelets and leukocytes, with a median nadir of 7,000/muL and 2.2/muL, respectively.	4
33. Haas RL, Poortmans P, de Jong D, et al. High response rates and lasting remissions after low-dose involved field radiotherapy in indolent lymphomas. *J Clin Oncol* 2003; 21(13):2474-2480.	Observational-Tx	109 assessable patients with 304 symptomatic sites, (53 males and 56 females; median age, 62 years; range, 35 to 93), including 98 patients with FL (43 grade 1 and 55 grade 2)	To study the response rates and duration of response after LD-IFRT (4 Gy) in patients with recurrent indolent lymphoma.	The ORR was 92%; CR was reached in 67 patients (61%), PR in 34 patients (31%), stable disease in 6 patients (6%), and progressive disease in 2 patients (2%). The median time to progression was 14 months. The median time to local progression was 25 months. The 67 patients with CR showed a median time to progression of 25 months and a median time to local progression of 42 months.	2

Localized Nodal Indolent Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
34. Chan EK, Fung S, Gospodarowicz M, et al. Palliation by low-dose local radiation therapy for indolent non-Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys* 2011; 81(5):e781-786.	Observational-Tx	54 patients with NHL were treated to 85 anatomical sites: The median age at time of treatment was 71.1 years old, and 57% of them were male	To assess the efficacy of a 2x2 Gy (total dose, 4 Gy) palliative RT regimen for treating patients with indolent NHL in terms of response rate, response duration, and symptom relief.	Of the 85 disease sites treated, 56% of sites had indolent histology, 28% of sites were diagnosed with chronic lymphocytic leukemia, 13% of sites had aggressive histology, and 2% of sites were shown to have other histology. ORR was 81% (49% CR, 32% PR). The 2-year rate for freedom from local progression was 50% (95% CI, 37%-61%). The ORR for FL, Mucosa associated lymphoid tissue, and marginal zone lymphoma histology was 88%, compared with a 59% rate for chronic lymphocytic leukemia histology (P=0.005). While the ORR was similar for tumors of different sizes, the CR rate for patients with tumors <5 cm tended to be higher than those with tumors >10 cm (CR rate of 57% vs 27%, respectively; P=0.06). For the 48 sites with clearly documented symptoms at pretreatment, 92% of sites improved after low-dose RT.	2
35. Ganem G, Lambin P, Socie G, et al. Potential role for low dose limited-field radiation therapy (2 x 2 grays) in advanced low-grade non-Hodgkin's lymphomas. *Hematol Oncol* 1994; 12(1):1-8.	Review/Other-Tx	27 patients	To evaluate the efficacy of low-dose limited field RT in low-grade NHL patients, in order to outline its possible role.	After the first low-dose limited field RT course, an objective response in irradiated sites was observed in 24 of the 27 patients (89%). Ten and 14 patients respectively demonstrated a CR (37%) and PR (52%). Freedom from progression in irradiated volumes for evaluable patients ranged from 4 to 35 months. Among the 8 patients who received at least two low-dose limited field RT courses, a total of 20 different areas were irradiated, and 15 areas (75%) showed a CR. Toxicity due to low-dose limited field RT was minimal.	4

Localized Nodal Indolent Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
36. Girinsky T, Guillot-Vals D, Koscielny S, et al. A high and sustained response rate in refractory or relapsing low-grade lymphoma masses after low-dose radiation: analysis of predictive parameters of response to treatment. *Int J Radiat Oncol Biol Phys* 2001; 51(1):148-155.	Observational-Tx	48 patients	To determine the efficacy of small doses of radiation in patients with recurrent or refractory low-grade lymphoma masses.	An objective response was obtained in 81% of the sites, with 57% attaining a CR. The 2-year actuarial freedom from local progression rate was 56% (95% CI, 46%-66%). Tumor masses ≤5 cm in diameter had a significantly higher 2-year freedom from local progression rate than larger masses (51% vs 27%). It is noteworthy that the 2-year freedom from local progression rate for patients treated with <2 chemotherapy regimens before RT was significantly higher than the 2-year freedom from local progression rate for more heavily treated patients (96% vs 48%). The 2-year freedom from local progression rates for extranodal tumor sites and nodal sites were not significantly different. The tumor size ≤5 cm vs >5 cm), the number of chemotherapy regimens (0-1 vs more), and age at time of radiation treatment (≤65 years or >65 years) were significant predictive parameters of response to treatment.	2
37. Haas RL, Poortmans P, de Jong D, et al. Effective palliation by low dose local radiotherapy for recurrent and/or chemotherapy refractory non-follicular lymphoma patients. *Eur J Cancer* 2005; 41(12):1724-1730.	Observational-Tx	71 patients (177 symptomatic sites) 39 males and 32 females with a median age of 69 years (range 43-93)	A study of the response rates and duration of response after LD-IFRT (4 Gy) in relapsed or chemotherapy refractory indolent and aggressive lymphoma patients.	ORR was 87%; CR was reached in 34 patients (48%) and a PR in 28 patients (39%). Stable disease was maintained in 9 patients (13%). The median time to progression was 12 months and the median time to local progression was 22 months. The 34 CR patients showed a median time to progression of 16 months and a median time to local progression of 23 months. None of the factors studied (age, sex, lymphoma subtype, RT regimen, number of prior regimens or time since diagnosis, number of positive sites or largest lymphoma diameter) were found to relate to response. At time of death 70% of patients were without in-field progression after LD-IFRT.	1

Localized Nodal Indolent Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
38. Luthy SK, Ng AK, Silver B, et al. Response to low-dose involved-field radiotherapy in patients with non-Hodgkin's lymphoma. *Ann Oncol* 2008; 19(12):2043-2047.	Observational-Tx	33 patients, 43 sites	To analyze response to palliative LD-IFRT (two 2 Gy fractions), explore factors predicting for response, and determine the time course to subsequent treatment.	ORR was 95%. 36 sites (84%) had a CR, 5 sites (12%) had a PR, and 2 sites (5%) had progressive disease. The CR rate of head and neck sites was significantly higher than that of pelvic and/or inguinofemoral sites (95% vs 64%, P=0.04). The CR rate was significantly higher for sites ≤40 mm than for sites >40 mm (90% vs 56%, P=0.04). 10 sites (23%) had in-field progression diagnosed at a median of 9 months. 16 patients (48%) received systemic treatment at a median of 8 months. 14 patients (42%) did not require additional treatment.	2
39. Murthy V, Thomas K, Foo K, et al. Efficacy of palliative low-dose involved-field radiation therapy in advanced lymphoma: a phase II study. *Clin Lymphoma Myeloma* 2008; 8(4):241-245.	Experimental-Tx	36 patients, 47 sites	To confirm the efficacy of LD-IFRT as palliative treatment in patients symptomatic from advanced lymphoma.	The ORR at 1-3 months after the RT was 75%. A CR was observed in 13 patients (36%) lasting up to a maximum of 31.3 months and ongoing at analysis. A PR was achieved in 14 patients (39%) lasting up to 10 months. The response rate for non-DLBCL sites was 86%, while it was 50% for sites with DLBCL histology. Median time to local progression for the entire group was 15 months. There was no statistical difference between the quality-of-life before and after LD-IFRT.	1
40. Rossier C, Schick U, Miralbell R, Mirimanoff RO, Weber DC, Ozsahin M. Low-dose radiotherapy in indolent lymphoma. *Int J Radiat Oncol Biol Phys* 2011; 81(3):e1-6.	Observational-Tx	43 (24 women, 19 men)	To assess the response rate, duration of response, and OS after LD-IFRT in patients with recurrent low-grade lymphoma or chronic lymphocytic leukemia.	The ORR was 90%. 12 patients (28%) had a CR, 15 (35%) had a PR, 11 (26%) had stable disease, and 5 (11%) had progressive disease. The median OS for patients with a positive response (CR/PR/stable disease) was 41 months; for patients with progressive disease it was 6 months (P=0.001). The median time to in-field progression was 21 months (range, 0-24), and the median time to out-field progression was 8 months (range, 0-40). The 3-year in-field control was 92% in patients with CR (median was not reached). The median time to in-field progression was 9 months (range, 0.5-24) in patients with PR and 6 months (range, 0.6-6) in those with stable disease (P<0.05).	2

Localized Nodal Indolent Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
41. Sawyer EJ, Timothy AR. Low dose palliative radiotherapy in low grade non-Hodgkin's lymphoma. *Radiother Oncol* 1997; 42(1):49-51.	Review/Other-Tx	11 (mean age 69 years)	A report on experience with the use of low dose RT, 4 Gray in 2 fractions, over 3 days for the palliation of symptomatic disease in patients with disseminated, chemoresistant low grade NHL.	Of the 16 sites irradiated a CR was observed in 38% and PR in 56%. No response was observed in one patient with a gastric low grade B cell lymphoma. The mean duration of response is 7 months (range: 1-21 months). Eleven of the sites irradiated were <5 cm in size, and 8 were <10 cm. 3 patients had multiple sites treated and a response was seen in all sites (6 PRs and 1 CR). A further patient relapsed after 5 months following cervical node irradiation; however, a second course of low dose RT resulted in a second CR.	4
42. 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: 159 treated with RT alone and 126 with combined-modality therapy	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 <30 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 combined-modality therapy, all with tumors >6 cm, and 4 with less than a CR to chemotherapy.	2

Localized Nodal Indolent Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
43. Lawrence TS, Urba WJ, Steinberg SM, et al. Retrospective analysis of stage I and II indolent lymphomas at the National Cancer Institute. *Int J Radiat Oncol Biol Phys* 1988; 14(3):417-424.	Observational-Tx	54: (48 received some form of RT)	A retrospective review of patients with stages I and II indolent lymphoma treated at the National Cancer Institute between January 1958 and December 1984.	OS and disease-free survival at 10 years were 69% and 48%, respectively. There were no relapses among stage I patients after 6.5 years, with 11/27 patients followed beyond that time, suggesting that some patients may be cured. Of the 38 patients who received RT alone as primary treatment, 17 ultimately relapsed. 71% of these relapses were nodal.	2
44. Pendlebury S, el Awadi M, Ashley S, Brada M, Horwich A. Radiotherapy results in early stage low grade nodal non-Hodgkin's lymphoma. *Radiother Oncol* 1995; 36(3):167-171.	Observational-Tx	58: 40 stage I patients and 18 stage II patients (8 localized and 10 extensive)	RT results in early stage low grade nodal NHL.	The 5- and 10-year PFS for the total group were 59% and 43%, and corresponding OS figures were 93% and 79%. Age <60 years was a predictor of improved survival but not for PFS and we found no significance in histology, stage or extent of RT field for the other variables. All relapses occurred with disease outside the original volume, with 3 patient's also relapsing in-field. Treatment of this disease produced an OS at 10 years of 79%. The plateau on the PFS plot suggested that some patients are cured. Young age was the only prognostic factor found for survival. Relapse is most frequently outside the treated volume.	2
45. Taylor RE, Allan SG, McIntyre MA, et al. Low grade stage I and II non-Hodgkin's lymphoma: results of treatment and relapse pattern following therapy. *Clin Radiol* 1988; 39(3):287-290.	Observational-Tx	64: (37 stage I and 27 stage II) treated by surgical excision alone (two patients) or with RT (53 patients), chemo-therapy (5 patients) or both (4 patients)	Results of treatment and relapse pattern following therapy of low grade stage I and II NHL.	Actuarial survival was 80.7% at 5 years and 77.9% at 10 years. Actuarial recurrence-free survival at 10 years was 49.4% for stage I and 38.0% for stage II patients. Local control was achieved in 52 out of 56 (93%) patients treated with a radiation dose of 30 Gy or greater. There was no advantage for extended compared with involved, field irradiation. A multivariate analysis identified age, sex, stage and disease site as independent prognostic variables for survival.	2

Localized Nodal Indolent Lymphoma
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
46. Wilder RB, Jones D, Tucker SL, et al. Long-term results with radiotherapy for Stage I-II follicular lymphomas. *Int J Radiat Oncol Biol Phys* 2001; 51(5):1219-1227	Observational-Tx	80 patients with stage I (n=33) or II (n=47), WHO Grade 1 (n=50) or 2 (n=30) FL	To analyze the long-term results with RT for early-stage, low-grade FLs.	The follow-up of the surviving patients ranged from 3.5 to 28.7 years (median 19.0). No recurrences were found >17.0 years after RT, with 13 patients free of disease at their last follow-up visit 17.6-25.0 years after treatment. In 58% of cases, death was not from FL. The 15-year local control rate was 100% for 44 lymphomas <3.0 cm treated with only 27.8-30.8 Gy (median 30.0 in 20 fractions). PFS was affected by the maximal tumor size at the start of RT (15-year rate 49% vs 29% for lymphomas <3.0 cm vs ≥3.0 cm, respectively, P=0.04) and Ann Arbor stage (15-year rate 66% vs 26% for stages I and II, respectively, P=0.006). Ann Arbor stage also affected the cause-specific survival (15-year rate 87% vs 54% for stages I and II, respectively, P=0.01). No significant difference was found in OS between those treated with extended-field RT and those treated with involved-field RT or regional RT (15-year rate 49% and 40%, respectively, P=0.51).	2

Evidence Table Key

Study Quality Key

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

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

BMB = Bone marrow biopsy

CHOP = Cyclophosphamide, doxorubicin, vincristine, and prednisone

CI = Confidence interval

CR = Complete response

CT = Computed tomography

DLBCL = Diffuse large B-cell lymphoma

EFS = Event-free survival

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

FL = Follicular lymphoma

HR = Hazard ratio

IFRT = Involved-field radiotherapy

LD-IFRT = Low-dose involved-field radiotherapy

NHL = Non-Hodgkin's lymphoma

ORR = Overall response rate

OS = Overall survival

PFS = Progression-free survival

PR = Partial response

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

RT = Radiation therapy