53 ■ INDOLENT NON-HODGKIN'S LYMPHOMA

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QUICK HIT ■ Indolent NHLs are a diverse group of diseases with survival measured in years to decades. Most common histologies are grade 1 to 2 follicular lymphoma and extranodal MALT lymphoma. Limited-stage disease (stages I–II) is typically treated with definitive RT alone. Advanced disease (stages III–IV) is typically treated with initial observation, with initiation of CHT for symptomatic disease and RT for palliation. ILROG guidelines are useful for treatment selection and field design (Table 53.1).

Table 53.1: General Treatment Paradigm for Indolent NHLs

	Treatment Options	Common RT Regimens
Stages I to II	Definitive RT	Follicular/other histologies: 24 Gy/12 fx
		Gastric MALT: 30 Gy/15 fx
Stages III to IV	Observation, CHT, and/or palliative RT	24–30 Gy/12–15 fx
		4 Gy/2 fx (i.e., "boom boom")

EPIDEMIOLOGY: A total of 77,240 cases annually with 19,940 deaths of all NHL subtypes, ninth-leading cause of death.[1] Indolent NHL is usually a disease of older adults; median age 65, peak incidence >70. More common in North America, Europe, and Australia.[2] Follicular type represents ~22% of all NHLs (second-most common NHL after DLBCL), SLL/CLL represents ~6%, and MALT/marginal zone is ~5%.[3] Other subtypes are less common.

RISK FACTORS: Four broad risk factors: immunosuppression, autoimmune diseases, infections, and environmental exposures. See Chapter 52 for details.

ANATOMY: Indolent NHLs can present as nodal or extranodal. Nodal anatomy is detailed further in Chapter 52. Extranodal presentation is more common among indolent NHL. Common extranodal lymphoid sites include thymus, spleen and tonsils, and adenoids (Waldeyer's ring). Extralymphatic sites include bone marrow, skin, CNS, ovary, testicle, ocular adnexae, liver, stomach, bowel, breast, and lung.

PATHOLOGY/GENETICS: B-cell indolent NHLs are more common than T cell. WHO 2016 classification defines subtypes.[4] System is complex, but a few pearls are as follows. *Follicular NHL:* Graded by number of centroblasts per high-powered field. Grade 1: 0 to 5/HPF, grade 2: 6 to 15/HPF, grade 3: >15, sometimes subdivided into 3A and 3B with 3B demonstrating sheets of centroblasts and often treated as DLBCL. t(14:18) is classic translocation, results in overexpression of BCL-2, blocking apoptosis. *Marginal zone NHL:* Both nodal and extranodal (i.e., MALT). See Table 53.2 for details.

CLINICAL PRESENTATION: Often presents only with slow-growing lymphadenopathy, hepatosplenomegaly, cytopenias, or nonspecific constitutional symptoms, such as fatigue, malaise, or low-grade fever. Most common in neck, inguinal, axilla, and abdominal lymphadenopathy. Less commonly involves skin, which manifests as rash or pruritus. Bone marrow involvement is common. Follicular NHLs commonly present as stage III to IV, whereas marginal zone NHL more commonly presents as localized disease. B symptoms are usually associated with aggressive histologies or extensive disease.

WORKUP: H&P with attention to lymphatic, liver, spleen, and/or skin exam. Lymph node biopsy of peripheral lymph node is ideal. Endoscopic biopsy for gastric MALT. FNA is insufficient for final diagnosis but may distinguish benign lymphadenopathy from clonal B-cell proliferation via flow cytometry. Bone marrow biopsy (unilateral generally sufficient) for most but not for extranodal MZL.[7] Lumbar puncture for testicular, paravertebral, parameningeal, positive bone marrow, HIV.

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Table 53.2: Pathology, Immunophenotype, and Genetics of Common Indolent Non-Hodgkin's Lymphomas				
Disease	**Common Immunotype**		**Common Genetics**	**Notes**
Follicular NHL	CD19+, CD20+	CD10+, CD21+, CD22+, CD79a+ CD5–, CD43–	t(14:18)	BCL-2 expression result of t(14:18), marrow involvement common, risk of transformation 28% at 10 years[5]
Nodal marginal zone (MZL)		CD22+, CD3 –, 5–, 10–, 23–	Trisomy 3, t(11:18)	Less common than extranodal
Extranodal MZL (MALT)				Frequently localized, t(11:18) associated with triple-antibiotic therapy failure for gastric MALT[6]
SLL/CLL		CD5+, 23+, HLA-DR CD22–	t(14:19), karyotype aberrations (trisomy 12) common but not diagnostic	SLL has morphology similar to CLL but with too low circulating leukemia cell count

Labs: CBC, peripheral smear, ESR, CMP, LDH, HIV, hepatitis B, hepatitis C, β-2 microglobulin (see the following FLIPI2 prognostic model), urea breath test for *Helicobacter pylori* (gastric MALT). Pregnancy test.

Imaging: Contrast-enhanced CT chest, abdomen, pelvis for peripheral lymphadenopathy. PET/CT in all nodal lymphomas (not CLL/SLL or MALT). PET SUV >10 in patients with indolent NHL may suggest transformation to high-grade histology and can be used to target biopsy (i.e., Richter transformation from CLL/hairy cell leukemia to DLBCL).[8] Obtain MRI brain/spine for symptoms. Obtain echocardiogram or MUGA scan if anthracycline CHT planned.

PROGNOSTIC FACTORS: FLIPI and updated FLIPI2 useful for prognostic assessment for follicular patients. FLIPI was designed pre-rituximab but remained prognostic in rituximab era.[9] See Table 53.3. Other prognostic factors include IRF4 gene rearrangement (follicular grade 3B), high Ki67 index (>30%, suggests rapid proliferation).

Table 53.3: FLIPI and FLIPI2 Risk Factors						
Original FLIPI Risk Factors[9,10]			**FLIPI2 Risk Factors[11]**			
Hemoglobin < 12 ng/dL			Hemoglobin < 12 ng/dL			
Age > 60			Age > 60			
Stage III–IV			Serum β-2 microglobulin elevated			
Nodal sites > 4			Bone marrow involvement			
LDH elevated			Maximal diameter of lymph node > 6 cm			
		FLIPI Pre-Rituximab[10]		**FLIPI2[11]**		
Score	**Risk Group**	**5-Yr OS**	**10-Yr OS**	**Score**	**Risk Group**	**5-Yr PFS**
0–1	Low	91%	71%	0	Low	80%
2	Intermediate	78%	51%	1–2	Intermediate	51%
≥ 3	High	52%	36%	3–5	High	19%

STAGING: See Chapter 52 for Ann Arbor Staging.

TREATMENT PARADIGM

Observation: Considered for older or asymptomatic patients with stage III/IV indolent NHLs; see CHT paradigm in the following for discussion on observation versus treatment.

Medical: Triple therapy often first line for *H. pylori*–positive gastric MALT and includes proton pump inhibitor, clarithromycin, and either amoxicillin or metronidazole. Give triple therapy as first line with endoscopic biopsy at 3 months to confirm resolution. If *H. pylori* negative and lymphoma negative, observation. If *H. pylori* positive and lymphoma negative, give second-line antibiotics. If *H. pylori* negative and lymphoma positive, can either continue observation with repeat biopsy or treat with RT for symptoms. If both remain positive, treat with second-line antibiotics with immediate or delayed RT. Response to doxycycline has been noted (65%) for ocular and cutaneous MZL.[12]

Surgery: Minimal role for NHL, used mostly for biopsy, but in small bowel can be therapeutic.

Chemotherapy: Used for later stage (stage III/IV typically). Note that grade 3B follicular NHL is often treated as per DLBCL regimens (see Chapter 52). When considering treatment for indolent stage III to IV NHL, factors such as rate of progression, symptoms, end-organ function, cytopenias, and bulk are considered. If none, then NCCN suggests observation.[13] If indications are present, treatment can be initiated and may consist of regimens such as bendamustine + rituximab, R-CHOP, R-CVP (rituximab, cyclophosphamide, vincristine, prednisone), or rituximab alone. Rituximab is chimeric monoclonal antibody against CD20; classic toxicities include infusion reactions, hepatitis B reactivation, and progressive multifocal leukoencephalopathy. Obinutuzumab is an alternative anti-CD20 monoclonal antibody with similar effects as rituximab but binds slightly different epitope of CD20.

Radiation

Indications: In limited-stage indolent NHLs (stage I–II), RT is treatment of choice for cure and is usually delivered to whole organ, particularly for gastric, thyroid, orbit (but not conjunctiva), breast, and salivary gland extranodal indolent NHL. In advanced disease, RT is typically used for focal palliation. ISRT is often appropriate when entire organ need not be treated. ILROG guidelines exist for both nodal and extranodal NHL.[14,15]

Dose: See Table 53.4 for NCCN dosing guidelines. Doses usually delivered at 1.8 to 2 Gy/fx. Some have advocated doses up to 36 Gy for bulky disease. Effective palliation can be provided via "boom boom" regimen of 4 Gy/2 fx (see the following data).

Table 53.4: NCCN Dosing Guidelines for Indolent Non-Hodgkin's Lymphomas	
Follicular	24–30 Gy
Gastric MALT	30 Gy
Other extranodal Sites (orbit, skin, thyroid, etc.)	24–30 Gy
Nodal MZL	24– 30 Gy
Palliation of indolent lymphoma	4 Gy (i.e., "boom boom")

Toxicity: Generally, toxicity mild, given in low total doses. Fatigue is common; others are related to location of delivery.

Procedure: See *Handbook of Treatment Planning in Radiation Oncology*, Chapter 10.[16]

Unsealed sources: Y-90 ibritumomab tiuxetan (Zevalin®) and I-131 tositumomab (Bexxar®, now discontinued) are radiolabeled antibodies against CD20, indicated in use of previously untreated, relapsed, or refractory indolent NHL (primarily follicular) and often produce response in patients refractory to rituximab.

■ EVIDENCE-BASED Q&A

■ What data suggest that follicular NHL (grades 1–2) can be cured with RT alone?

Multiple RRs are available, but one example is as follows.

Campbell, British Columbia (*Cancer* 2010, PMID 20564082): RR of 237 patients with stage I to II grade 1 to 3A follicular NHL treated with RT alone. Involved regional RT included LN group with

≥1 adjacent uninvolved LN group (60%), or INRT (40%). MFU 7.3 years; 10-year PFS 49%, OS 66%. Distant recurrence alone was the most common pattern of failure, occurring in 38% of involved regional RT and 32% of INRT. **Conclusion: Cure is possible with RT, and reducing field size does not compromise outcome.**

For limited-stage follicular NHL, is there detriment to initial observation as compared to initial RT?

Indolent lymphoma is slowly progressive, and no treatment may be a reasonable first approach. However, for early stage disease, this is not supported by observational data. Therefore, definitive treatment with RT should remain standard of care.

Pugh, SEER (*Cancer* 2010, PMID 20564102): SEER analysis of 6,568 patients with stage I to II, grade 1 to 2 follicular NHL diagnosed from 1973 to 2004; 34% received initial RT. Those observed were younger, stage I, and without extranodal disease. RT was associated with improved 20-year DSS (63% vs. 51%, HR 0.61, $P < .0001$) and OS (35% vs. 23%, HR 0.68, $P < .0001$). **Conclusion: Initial RT is standard for early-stage follicular NHL and deferring treatment until time of salvage is associated with worse outcomes. RT is greatly underused.**

Vargo, NCDB (*Cancer* 2015, PMID 26042364): NCDB analysis of 35,961 patients with stage I to II, grade 1 to 2 follicular NHL. RT use decreased from 37% to 24% between 1999 and 2012; 10-year OS was 68% for RT patients compared to 54% for no RT patients ($p < .0001$). **Conclusion: RT is significantly underutilized and is associated with improved survival in early stage follicular lymphoma. RT should remain standard.**

What RT dose is optimal for indolent NHL?

For definitive RT of early stage indolent lymphoma, 24 to 30 Gy is usually sufficient, with some advocating for 36 Gy in rare case of bulky disease. For palliation, 4 Gy/2 fx or 24 Gy/12 fx are both reasonable. Note that "boom boom" regimen of 4 Gy/2 fx was inferior for definitive treatment of limited-stage patients in FoRT trial and should not be extrapolated to aggressive NHL.

Lowry, British National Lymphoma Investigation (*Radiother Oncol* 2011, PMID 21664710): PRT including any subtype and stage of NHL requiring RT for local control. 361 sites of indolent NHL randomized to either 40 to 45 Gy/20 to 23 fx (standard) vs. 24 Gy/12 fx (low dose). For indolent patients, 59% were grade 1 to 2 follicular NHL, 19% MZL/MALT, and 69% were stage I to II. MFU 5.6 years. ORR no different: 93% vs. 92% in standard vs. low-dose groups, respectively. PFS and OS were also not significantly different. **Conclusion: 24 Gy is sufficient for indolent lymphomas.**

Hoskin, FoRT Trial (*Lancet Oncol* 2014, PMID 24572077; Update Lancet Oncol 2021, PMID 33539729): Noninferiority trial of patients with either follicular NHL or MZL requiring RT for either definitive or palliative treatment. Randomized between 4 Gy/2 fx (i.e., "boom boom") vs. 24 Gy/12 fx. Primary endpoint LC. Trial closed early with 548 patients, 614 sites, MFU 74 mos. 60% stage I to II. Response rate 81% vs. 74% in 24 Gy vs. 4 Gy arms, respectively. 5-year local progression-free rate was 89.9% for 24 Gy and 70.4% for 4 Gy (HR 3.46, p<0.0001). No difference in OS. **Conclusion: 24 Gy is more effective when durable local control is the goal. However, "boom boom" is useful in palliation and often induces response.**

Is there benefit to adjuvant CHT after definitive RT for early-stage indolent NHL?

Adjuvant CHT does not appear to improve OS based on results of at least five randomized trials from pre-rituximab era (Denmark, Milan, British, EORTC, MSKCC)[17–21] as well as the more recent TROG study outlined below.

MacManus, TROG 99.03 (*JCO* 2018, PMID 29975623): Multicenter PRT enrolling 150 patients with stage I to II low-grade follicular NHL after CT and bone marrow biopsies. PET was not mandatory. Patients randomized to 30 Gy IFRT alone vs. IFRT plus 6 cycles CVP. After 2006, rituximab was added to CVP (41% of CVP arm); 75% stage I. MFU 9.6 years; 10-year PFS superior with CVP (59% vs. 41%, HR 0.57, $p = .033$), and markedly improved with R-CVP (HR 0.26, $p = .045$). However, 10-year OS was not significantly different (87% vs. 95%, $p = .40$). **Conclusion: Systemic therapy with R-CVP after IFRT significantly improved PFS without benefit in OS.**

What data inform treatment of gastric MALT?

In addition to those summarized previously, few notable series are listed in Table 53.5. Study by Wündisch informs treatment of H. pylori–positive gastric MALT and supports observation when H. pylori is eradicated.

Table 53.5: Summary of Notable RR of Gastric MALT

Institution	Year	*N*	RT Dose	LC
Dana Farber[22]	2007	21	30 Gy	21/21
PMH[23]	2010	25	25–30 Gy	15/15
Japan[24]	2010	8	30 Gy	8/8
MSKCC[25]	1998	17	30 Gy	17/17

Wirth, Multi-Center IELSG Study (*Ann Oncol* 2013, PMID 23293112): Multicenter RR of 102 gastric MALT patients treated with RT to median dose of 40 Gy. MFU 7.9 years; 10 and 15-year FFTF was 88%; 10-year OS 70%. Large cell component and exophytic growth pattern were risk factors for failure.

Wündisch, Germany (*JCO* 2005, PMID 16204012): Prospective trial tracking outcomes of *H. pylori*–positive gastric MALT; 120 patients, all with stage IE disease treated with antibiotics and observed after *H. pylori* eradication. MFU 75 months. Eighty percent achieved pCR, with 80% of those experiencing long-term pCR. Three percent relapsed and were referred for treatment, other 17% were observed, and all entered into CR. Fifteen percent positive for t(11:18). t(11:18) and ongoing monoclonality were associated with failure. **Conclusion: Cure of *H. pylori* results in continuous CR in most patients. Observation is appropriate for most patients when close follow-up is possible.**

What data inform treatment of other MALT NHL?

Tran, Australian Orbital MALT Series (*Leuk Lymphom*a 2013, PMID 23020137): A total of 27 orbits of 24 patients treated to 24 to 25 Gy. MFU 41 months. Fifty-nine percent conjunctival, 26% lacrimal, 4% eyelid, and 11% other; 100% CR, three failures, one local, one contralateral, one distant.

Teckie, MSKCC (*IJROBP* 2015, PMID 25863760): A total of 244 patients with stage IE or IIE MZL treated with RT alone. Ninety-two percent were stage IE. MFU 5.2 years. Stomach (50%), orbit (18%), nonthyroid head and neck (8%), skin (8%), and breast (5%). Median RT dose 30 Gy; 5-year OS 92%, RFS 74%. Most common relapse site was distant. Disease-specific death 1.1% at 5 years. All sites except H&N demonstrated worse RFS compared to gastric. Transformation to aggressive histology was rare (1.6%). **Conclusion: OS and DSS are high in early-stage extranodal MZL. Gastric MALT has improved prognosis compared to other sites.**

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7–30. doi:10.3322/caac.21590
2. Boffetta P. Epidemiology of adult non-Hodgkin lymphoma. *Ann Oncol*. 2011;22(Suppl 4): iv27–iv31. doi:10.1093/annonc/mdr167
3. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's lymphoma classification project. *J Clin Oncol*. 1998;16(8):2780–2795. doi:10.1200/JCO.1998.16.8.2780
4. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375–2390. doi:10.1182/blood-2016-01-643569
5. 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. doi:10.1200/JCO.2006.09.3260
6. Yepes S, Torres MM, Saavedra C, Andrade R. Gastric mucosa-associated lymphoid tissue lymphomas and Helicobacter pylori infection: a Colombian perspective. *World J Gastroenterol*. 2012;18(7):685–691. doi:10.3748/wjg.v18.i7.685
7. Ebie N, Loew JM, Gregory SA. Bilateral trephine bone marrow biopsy for staging non-Hodgkin's lymphoma: a second look. *Hematol Pathol*. 1989;3(1):29–33.

8. Noy A, Schöder H, Gönen M, et al. The majority of transformed lymphomas have high standardized uptake values (SUVs) on positron emission tomography (PET) scanning similar to diffuse large B-cell lymphoma (DLBCL). *Ann Oncol*. 2009;20(3):508–512. doi:10.1093/annonc/mdn657
9. Nooka AK, Nabhan C, Zhou X, et al. Examination of the follicular lymphoma international prognostic index (FLIPI) in the National LymphoCare study (NLCS): a prospective US patient cohort treated predominantly in community practices. *Ann Oncol*. 2013;24(2):441–448. doi:10.1093/annonc/mds429
10. Solal-Céligny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood*. 2004;104(5):1258–1265. doi:10.1182/blood-2003-12-4434
11. 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. doi:10.1200/JCO.2008.21.3991
12. Ferreri AJ, Govi S, Pasini E, et al. Chlamydophila psittaci eradication with doxycycline as first-line targeted therapy for ocular adnexae lymphoma: final results of an international phase II trial. *J Clin Oncol*. 2012;30(24):2988–2994. doi:10.1200/JCO.2011.41.4466
13. NCCN clinical practice guidelines in oncology: B-Cell Lymphomas; 2020. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf
14. Yahalom J, Illidge T, Specht L, et al. Modern radiation therapy for extranodal lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys*. 2015;92(1):11–31. doi:10.1016/j.ijrobp.2015.01.009
15. 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. doi:10.1016/j.ijrobp.2014.01.006
16. Videtic GMM, Woody N, Vassil AD. *Handbook of Treatment Planning in Radiation Oncology* 3rd ed. Demos Medical; 2020. doi:10.1891/9780826168429
17. Monfardini S, Banfi A, Bonadonna G, et al. Improved five-year survival after combined radiotherapy-chemotherapy for stage I–II non-Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys*. 1980;6(2):125–134. doi:10.1016/0360-3016(80)90027-9
18. Nissen NI, Ersbøll J, Hansen HS, et al. A randomized study of radiotherapy versus radiotherapy plus chemotherapy in stage I–II non-Hodgkin's lymphomas. *Cancer*. 1983;52(1):1–7. doi:10.1002/1097-0142(19830701)52:1<1::AID-CNCR2820520102>3.0.CO;2-M
19. Carde P, Burgers JM, van Glabbeke M, et al. Combined radiotherapy-chemotherapy for early stages non-Hodgkin's lymphoma: the 1975–1980 EORTC controlled lymphoma trial. *Radiother Oncol*. 1984;2(4):301–312. doi:10.1016/S0167-8140(84)80072-9
20. 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. doi:10.1007/BF02990087
21. Yahalom J, Varsos G, Fuks Z, et al. Adjuvant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy after radiation therapy in stage I low-grade and intermediate-grade non-Hodgkin lymphoma: results of a prospective randomized study. *Cancer*. 1993;71(7):2342–2350. doi:10.1002/1097-0142(19930401)71:7<2342::AID-CNCR2820710728>3.0.CO;2-I
22. Tsai HK, Li S, Ng AK, et al. Role of radiation therapy in the treatment of stage I/II mucosa-associated lymphoid tissue lymphoma. *Ann Oncol*. 2007;18(4):672–678. doi:10.1093/annonc/mdl468
23. Goda JS, Gospodarowicz M, Pintilie M, et al. Long-term outcome in localized extranodal mucosa-associated lymphoid tissue lymphomas treated with radiotherapy. *Cancer*. 2010;116(16):3815–3824. doi:10.1002/cncr.25226
24. Ono S, Kato M, Takagi K, et al. Long-term treatment of localized gastric marginal zone B-cell mucosa associated lymphoid tissue lymphoma including incidence of metachronous gastric cancer. *J Gastroenterol Hepatol*. 2010;25(4):804–809. doi:10.1111/j.1440-1746.2009.06204.x
25. Schechter NR, Portlock CS, Yahalom J. Treatment of mucosa-associated lymphoid tissue lymphoma of the stomach with radiation alone. *J Clin Oncol*. 1998;16(5):1916–1921. doi:10.1200/JCO.1998.16.5.1916