Chapter 36
Non-Hodgkin's Lymphoma

Anna K. Paulsson and Adam Garsa

PEARLS

EPIDEMIOLOGY

- Rising in incidence, but decreased rate of death (2016 estimated US incidence 72,580 and mortality 20,150); median age 60–65 years.
- Causative conditions:
  - Immunodeficiency – congenital (SCID, ataxia telangiectasia), acquired (HIV, organ transplant).
  - Autoimmune (Sjogren's, Hashimoto's disease, rheumatoid arthritis, systemic lupus erythematosus).
  - Environmental – chemicals (pesticides and solvents).
  - Viral – EBV (Burkitt's lymphoma and NK/T cell), HTLV-1 (human lymphotrophic virus, type I; adult T-cell leukemia in southern Japan and Caribbean, spread by breastfeeding, sex, and blood products), HHV-8 (Kaposi's sarcoma), HCV (extranodal B-cell NHL).
  - Bacterial – *Helicobacter pylori* (gastric MALT), *Chlamydia Psittaci* (orbital MALT).
  - Radiation – weak association.
  - Chemo – alkylating agents.

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HISTOLOGY

- *WHO classification*: B-cell neoplasms vs. T-cell and natural killer (NK) cell neoplasms.
- B cell (85) = DLBCL (33%), follicular (20%), MALT (5–10%), B-cell CLL (5–10%), and mantle cell (5%).
- T cell (15%) = T/NK cell, peripheral T-cell lymphoma (6%), mycosis fungoides (<1%), anaplastic large cell (2%).
- *Low grade*: follicular (grade 1–2), CLL, MALT, mycosis fungoides.
- *Intermediate grade*: follicular (grade 3), mantle cell, DLBCL, T/NK cell, peripheral T-cell lymphoma, anaplastic large cell.
- *High grade*: Burkitt's lymphoma, lymphoblastic.
- Follicular presentation = stage I–II (21%), III (19%), IV (60%). Histologic grade: 1 = follicular small cleaved, 2 = follicular mixed, 3 = follicular large.
- MALT (or extranodal marginal zone B-cell lymphoma) commonly involves stomach, ocular adnexae, skin, thyroid, parotid gland, lung, and breast. Most present as stage I–II (65–70%).
- DLBCL: 30–40% present with stage I–II disease. Extranodal disease is common.
  - Double hit: translocations in MYC and BCL-2 and/or BCL-6. Poor outcomes with R-CHOP chemotherapy (Johnson *JCO* 2012).
- Mantle cell: commonly presents with disseminated disease with spleen, bone marrow, and gastrointestinal involvement.
  - Associated with t(11;14)(q13;q32) translocation with overexpression of cyclin D1.
  - M:F 4:1, median age 60 years.
  - Associated with poor prognosis; median survival time 3 years.

WORKUP

- H&P. Performance status. B symptoms. Thorough node examination, including Waldeyer's ring, and attention to liver and spleen. ENT examination if suprahyoid cervical LN involvement. Ophthalmologic examination for CNS lymphoma.
- Excisional LN biopsy with H&E, immunophenotyping, genotyping, and molecular profiling with microarrays.
- Labs: CBC, LFTs, creatinine, alkaline phosphatase, uric acid, LDH, HBsAg, HCV Ab, and HIV.

- Imaging: FDG-PET/CT scan. MRI or CT if clinically indicated. MUGA scan or echocardiogram if considering anthracycline-based chemotherapy.
- Bone marrow biopsy.
- CSF cytology if indicated (CNS, epidural or testicular lymphoma).
- Pregnancy testing, if indicated.
- Discuss fertility issues and sperm banking if pertinent.

STAGING

- *AJCC Ann Arbor staging system used* (see Chap. 35). Note: in the Lugano Classification, B symptoms were removed from the staging system for NHL (Cheson *JCO* 2014).
- Sites that are extranodal, but not extralymphatic (therefore, not classified as E): Waldeyer's ring, thymus, and spleen.

International Prognostic Index (NEJM 1993).

- For intermediate- and high-grade NHL.
- Adverse factors: age ≥60 years, stage III/IV, elevated LDH, reduced performance status (e.g., ECOG ≥2), and more than one site of extranodal involvement.
- Five-year OS by number adverse factors: 0–1 (73%), 2 (51%), 3 (43%), 4–5 (26%).

Follicular Lymphoma International Prognostic Index-2 (Federico *JCO* 2009)

- Adverse factors: beta-2 microglobulin > upper limit of normal, bone marrow involvement, nodes >6 cm in greatest diameter, number of involved nodal and extra nodal sites, B-symptoms, age (>60 years), stage III/IV, hemoglobin level (<120 g/L), number of nodal areas (>4), and elevated LDH.
- Five-year OS for low-risk, intermediate-risk, and high-risk patients was 98%, 88%, and 77%, respectively.

Mantle Cell Lymphoma International Prognostic Index (MIPI) (Hoster *Blood* 2008).

- For advanced-stage mantle cell lymphoma.
- Adverse factors: age (<50 = 0, 50–59 = 1, 60–69 = 2, ≥70 = 1), performance status (ECOG ≥2 = 2), lactate dehydrogenase (<0.67*upper limit of normal (ULN) = 0, 0.67–0.99*ULN = 1, 1–1.49*ULN = 2, ≥1.5*ULN = 3), and leukocyte count (<6.7 = 0, 6.7–9.9 = 1, 10–14.9 = 2, ≥15 = 3).
- Five-year OS by risk: low risk = 0–3 (70%), intermediate risk = 4–5 (45%), high risk = 6–11 (10%).

International staging and response criteria for lymphoma (Barrington *JCO* 2014): Standardized FDG-PET/CT staging and response criteria for clinical trials using a 5-point scale.

1. No uptake
2. Uptake ≤ mediastinum
3. Uptake > mediastinum but ≤ liver
4. Uptake moderately higher than liver
5. Uptake markedly higher than liver and/or new lesions

X. New areas of uptake unlikely to be related to lymphoma

TREATMENT RECOMMENDATIONS

Table 36.1 LOW-GRADE B-CELL NHL

Stage	Recommended Treatment
I–II	ISRT (24–30 Gy at 1.5–2 Gy/fx) Median survival 10–15 years. 10-year DFS 40–50%. LC 90–100% Transformation to DLBCL occurs in 10–15%
III–IV	Asymptomatic: observation Symptomatic: decision to treat based on international criteria (GELF or FLIPI), which consider symptoms, threatened end-organ dysfunction, cytopenias, bulky disease at presentation, steady progression of disease, or patient preference. Treatment options include rituximab (R) ± chemotherapy (CHOP, CVP, or bendamustine), radioimmunotherapy (RIT), or palliative local RT (ex. 4 Gy × 1 or 2 Gy × 2; Haas *JCO* 2003) Median survival 8–9 years (among <60 years, 10–12 years)
Relapse	Rituximab ± chemotherapy, radioimmunotherapy, or high-dose chemotherapy plus stem cell transplant
Transformed disease	Treat as per intermediate-grade disease Radioimmunotherapy Transplant is investigational

Table 36.2 GASTRIC MALT

Stage	Recommended Treatment
Stage I–II	For *H. pylori* positive patients, 3–4 drug current antibiotic regimen with proton pump inhibitor for 2 weeks. CR 97–99%, but median time to CR is 6–8 months. t(11:18) is a predictor for lack of response to antibiotic therapy and these patients should be considered for RT. If disease persists despite antibiotic therapy or if *H. pylori* negative, RT to entire stomach and perigastric nodes (30 Gy in 20 fractions). Local control >95%. If RT contraindicated, rituximab may be considered
Stage III–IV	Induction chemoimmunotherapy or ISRT indicated for symptoms, GI bleeding, threatened end-organ dysfunction, bulky disease, steady progression, or patient preference

RADIOIMMUNOTHERAPY

- Indications:
  - Relapsed or refractory low-grade, follicular, or transformed B-cell NHL, CD20+
  - Sixty to eighty percent response rate with 20–40% CR
- Contraindications:
  - Known hypersensitivity to murine proteins
  - ≥25% marrow involvement by lymphoma
  - Platelets <100,000
  - Pregnancy, nursing mothers

Table 36.3

Name	Decay	Half-Life, Dose	Dosimetry	Toxicity
Y-90 Ibritumomab (Zevalin)	Pure beta (2.3 MeV, 1.1 cm tissue range)	2.7 days 0.3-0.4 mCi/kg	Pretreatment with rituximab on day 1, then treat on day 7 to 9. Biodistribution improved with pretreatment nonlabeled rituximab	85% grade 3–4 cytopenia nadir 8 weeks. MDS/AML 2%

INTERMEDIATE-GRADE B-CELL NHL

Table 36.4

Stage	Recommended Treatment
I–II (30% of cases)	Favorable (nonbulky <7.5 cm; stage I; <60 years, PS 0–1, normal LDH) R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) × 3c, then ISRT (30–36 Gy) R-CHOP × 6c Unfavorable (bulky; stage II; >60 years; PS ≥2; elevated LDH) R-CHOP × 6 ± ISRT (30–36 Gy) Alternative: R-CHOP × 3c + ISRT (30–36 Gy)
III–IV (70%)	R-CHOP × 6–8 Consider ISRT to initially bulky sites Upfront transplant is investigational Mantle cell lymphoma – R-CHOP or hyperCVAD ± R
Relapse/Refractory	Second-line chemo +/– high-dose chemo plus stem cell transplant If not a candidate for further chemo, RT alone (40–55 Gy)

*In testicular lymphoma, after completion of chemotherapy, RT (25–30 Gy) should be given to the scrotum (Vitolo U et al. 2011)

HIGH-GRADE NHL

Table 36.5

Stage	Recommended Treatment
All cases	Combination chemo or clinical trial. Palliative RT as needed.

STUDIES

- *UK multicenter trial* (Lowry *Radiother Oncol* 2011): Prospective randomized trial comparing RT to 40–45 Gy in 20–23 fx vs. 24 Gy in 12 fx (indolent) or 30 Gy in 15 fx (aggressive). 361 sites of indolent lymphoma, 640 sites of aggressive lymphoma treated. Indications for RT included definitive RT alone, consolidative RT following chemo, or palliation. Indolent group – no difference in LC at 5 yrs. (79% high dose vs. 76% low dose). Aggressive group – no difference in LC at 5 yrs. (84% high dose vs. 82% low dose). No significant difference was detected in PFS or OS at 5 years for both indolent and aggressive NHL.

LOW-GRADE LYMPHOMA

- *British Columbia* (Campbell *Cancer* 2010): 237 patients with stage I–II FL treated with RT alone. Ten-year PFS/OS were 49% and 66%. Comparing involved nodal radiation therapy (INRT) using up to 5 cm margins to regional radiation therapy, there was no difference in PFS or OS and only 1% developed regional-only recurrence.
- *UK FORT* (Hoskin *Lancet Oncol* 2014): Prospective randomized noninferiority study comparing 4 Gy in 2 fx vs. 24 Gy in 12 fx for patients with follicular or marginal zone lymphoma. 614 sites randomized. Higher response rate with 24 Gy (overall 91% vs. 81%; CR 68% vs. 49%). Shorter time to progression with 4 Gy (HR 3.42). No difference in survival.
- *NCDB* (Vargo, Cancer 2015). 35,961 pts. with follicular lymphoma in National Cancer Database (NCDB). Pts who received RT had improved 5/10-yr OS vs. those who did not (86%/68% vs. 74%/54%). Upfront RT was independently associated with OS on multivariate analysis.

LIMITED STAGE INTERMEDIATE-GRADE LYMPHOMA

- *SWOG 8736* (Miller *NEJM* 1998; Spier *ASH abstract* 2004; Stephens, JCO 2016): 401 patients with intermediate-grade, stage I/IE/II/IIE, or bulky stage I lymphoma were randomized to CHOP × 3 + IFRT (40–50 Gy) or CHOP × 8 alone. Five-year results showed improved OS and FFS with CHOP-IFRT, but 7-, 10-, and 12-year results no longer show any difference in OS or FFS.
- *ECOG E1484* (Horning *JCO* 2004): 352 patients with intermediate-grade, bulky or extranodal stage I, nonbulky stage II/IIE disease received CHOP × 8, then randomized to observation or IFRT (30–40 Gy). IFRT improved 6-year DFS (73 vs. 56%), but no OS difference.
- *GELA LNH93-1* (Reyes *NEJM* 2005): 647 patients ≤60 years, stage I–II, IPI = 0 intermediate-grade NHL were randomized to ACVBP × 3 followed by consolidation chemo (no RT) or CHOP × 3 + IFRT (40 Gy). ACVBP significantly improved 5-year EFS and OS, regardless of bulky disease or not.
- *GELA LNH93-4* (Bonnet *JCO* 2007): 576 patients >60 years, stage I–II, IPI = 0 randomized to CHOPx4 + IFRT (40 Gy) vs. CHOP × 4. Median follow-up 7 years. Five-year EFS (64 vs. 61%) and OS (68 vs. 72%) showed no difference between the groups.
- *Lysa/Goelams Group 02-03 Trial* (Lamy *ASH Abstract* 2014): 301 patients with nonbulky, limited-stage DLBCL randomized to R-CHOP x 4–6 +/– RT. No difference in EFS or OS was found between the two groups. However, RT was recommended for all patients with residual PET-avid disease PR after 4 cycles R-CHOP, regardless of randomization, and these pts. achieved similarly favorable outcome, suggesting a role for RT for pts. who achieve only a PR to chemotherapy.
- Retrospective series from several institutions and large database analyses report improved local control and PFS by adding radiotherapy in the rituximab era, and abbreviated course R-CHOP with RT reduces short-term toxicity compared to 6–8 cycles R-CHOP alone. For example:
  - MDACC (Phan, JCO 2010). 469 pts. with DLBCL treated with R-CHOP +/– RT. 41% stage I/II, 59% stage

III/IV. RT improved 5-yr OS/PFS for stage I/II pts. (92%/82% vs. 73%/68%) and stage III/IV pts. (89%/76% vs. 66%/55%).

- NCDB database (Vargo, JCO 2015). 59,255 pts. with stage I-II DLBCL in NCDB. Adding RT improved 5/10-yr OS (82%/64% vs. 75%/55%).
- SEER-Medicare database (Odejide, Leuk Lymphoma 2015). 874 pts. with stage I–II DLBCL. Pts. treated with abbreviated R-CHOP with radiation had similar OS, but lower risk of second-line therapy and febrile neutropenia than 6–8 cycles R-CHOP.

ADVANCED-STAGE INTERMEDIATE-GRADE LYMPHOMA

- *MiNT* (Pfreundschuh *Lancet Oncol* 2006, 2011): 824 patients ≤60 years with IPI 0–1, stage II–IV or bulky stage I DLBCL randomized to CHOP-like × 6 or CHOP-like + rituximab × 6. CHOP-like + R improved 6-year EFS (74.3 vs. 55.8%) and 6-year OS (90.1 vs. 80%).
- *RICOVER-60* (Pfreundschuh *Lancet Oncol* 2008; Held, JCO 2014): 1222 patients 61–80 years with stage I–IV DLBCL (50% stage III/IV) randomized to 6 vs. 8 cycles of CHOP-14 (given at 2-week intervals) ± rituximab. Patients with initial bulky disease (diameter ≥ 7.5 cm) or extranodal involvement received 36 Gy RT. 6-cycle R-CHOP improved 3-year EFS (47 → 66%) and OS (68 → 78%) vs. CHOP alone, and there was no benefit of increasing to 8 cycles of R-CHOP even for patients with only a PR after 4 cycles of chemo. In post-hoc subgroup analysis, pts. who received RT for bulky or extranodal involvement had improved 3-yr EFS (80% vs. 54%), PFS (88% vs. 62%), and OS (90% vs. 65%).
- *UNFOLDER* (final results pending). Randomized pts. to R-CHOP-21 or R-CHOP-14 with or without RT. After 2nd planned interim analysis of 285 pts., 2 arms without RT were closed early due to inferior EFS for pts. with bulky (>7.5 cm) or extralymphatic sites.
- *DSHNHL* (Held, JCO 2013). Post-hoc analysis of 161 pts. with skeletal. involvement in MiNT and RICOVER-60 trials. Adding RT improved 3-yr EFS for these pts. (75% vs. 36%) with trend for improved OS (86% vs. 71%).

RELAPSED INTERMEDIATE-GRADE LYMPHOMA

- About 50–75% of failures after autologous stem cell transplant occur at initial sites of disease. IFRT may improve LC and PFS.
  - MSKCC (Hoppe, Bone Marrow Transplantation 2009). 83 pts. with chemosensitive relapsed or primary refractory DLBCL treated with high-dose therapy and autologous stem cell rescue. 57% received IFRT. IFRT improved LC (94% vs. 69%), PFS (HR 2.7), and DFS (HR 2.8), but not OS.
- University of Rochester (Biswas, IJROBP 2010). 176 pts. treated with high-dose therapy and autologous stem cell transplant for recurrent or refractory DLBCL. 48% received IFRT. IFRT improved LC by 10% and OS on multivariate analysis.

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Follow ILROG guidelines (Illidge, IJROBP 2014).
- ISRT fields are used. Similar to descriptions in Chap. 35.
- Contour pre-chemo and post-chemo GTV.
- For early-stage disease, CTV includes original GTV, but normal tissues previously displaced should be excluded from CTV according to clinical judgment.
- In advanced-stage disease, for consolidative RT to isolated or solitary residual PET+ disease, CTV may include only the post-chemotherapy residual disease.
- If involved nodal volumes are <5 cm apart, they can potentially be included in the same CTV, but nodal volumes >5 cm apart are treated separately.
- 4DCT and ITV may be considered to account for respiratory motion.
- Add PTV to account for setup error. When RT is the primary treatment (without chemotherapy), larger margins are used to encompass subclinical disease.
- 3D planning is indicated for all pts. IMRT planning may be considered for selected pts. with more extensive mediastinal involvement for improved cardiac and/or pulmonary sparing.

- Large-field RT is limited to salvage treatment of pts. who fail chemotherapy and are unable to have more intensive salvage treatment regimens.

DOSE PRESCRIPTIONS

- See treatment algorithm
- Low-grade NHL (follicular): 24–30 Gy in 12–15 fx
- Intermediate-grade NHL (DLBCL): 30–36 Gy in 15–18 fx
- Refractory disease
  - CR to salvage therapy: 30–40 Gy
  - PR to salvage therapy: 40–50 Gy
  - RT alone: 40–55 Gy
- Palliation: 4 Gy in 2 fx or 24–30 Gy in 12–15 fx

DOSE LIMITATIONS

- Same as in Chap. 35

COMPLICATIONS

- Same as in Chap. 35

FOLLOW-UP

- Same as in Chap. 35

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