Introduction to Non-Hodgkin's Lymphoma

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Hasmukh Jain, Abhinav Zawar, and Jayashree Thorat

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1.1 Non-Hodgkin's Lymphoma

Non-Hodgkin's Lymphoma (NHL) arises from the lymphoid system and is grouped as B and T cell lymphomas. They represent 4% of all the cancers in USA [1].

H. Jain (✉) · A. Zawar · J. Thorat
Department of Medical Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India

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1.1.1 Biology of Lymphomas

Lymphomas originate from the lymphocytes at various stages of their development (Table 1.1).

1.1.2 Risk Factors

In more than 90%, the exact cause is unknown. However, in a small subset a specific etiology can be identified (Table 1.2).

The specific diagnosis can be suspected based on

1. The extent of adenopathy, i.e., localized or generalized.
2. Presentation (Table 1.3).

1.1.3 WHO Classification of NHL: (Table 1.4)

1.1.3.1 Clinical Features in NHL

The clinical course can be indolent or aggressive depending on the subtype. Early bone marrow involvement, extra-axial nodes, and extra nodal sites with noncontiguous dissemination characterize NHL. Majority of them present with painless adenopathy and

Table 1.1 The classification of B- and T-cell lymphoma according to the cell of origin

B cell	Normal counterpart	Disease
Bone marrow	Progenitor B cell	B lymphoblastic leukemia/lymphoma
	Precursor B cell	
	Immature B cell	
Lymph node	Naïve B cell	CLL/SLL
	Pre-germinal center	Mantle cell lymphoma
	Germinal center B cell	Follicular lymphoma, Burkitt's lymphoma, DLBCL, Hodgkin's lymphoma
	Marginal zone B cell	Marginal zone and MALT lymphoma Lymphoplasmacytic lymphoma CLL/SLL (some)
	Plasma cell	Plasma cell myeloma
T cell	**Precursor cell**	**Disease**
Thymus	Double negative T cells (No CD4/8 and non-rearranged T cell receptor-TCR)	T lymphoblastic leukemia/lymphoma
	Double positive (CD4, 8 and express complete TCR)	
Lymph node	TH1 cells	Peripheral T-cell lymphoma NOS (subset)
	TH2 cells	Subset of PTCL, NOS
	Follicular helper T cells	Angioimmunoblastic T-cell lymphoma PTCL-FHT cell type
	Regulatory T cells	Adult-T cell leukemia/lymphoma

Table 1.2 Risk factors associated with lymphoma

Viral infection	
EBV	Burkitt's lymphoma, Post-transplant lymphoproliferative disorder
HTLV-1	Adult T-cell leukemia/lymphoma
HHV-8	Kaposi sarcoma, Primary effusion lymphoma
Hepatitis C virus	Splenic marginal zone lymphoma
Hepatitis B virus	Diffuse large B- cell lymphoma
Bacterial infection	
Helicobacter pylori	Gastric Maltoma
Chlamydia psittaci	Orbital Maltoma
Borrelia burgdorferi/afzeliłi	Cutaneous Maltoma
Campylobacter jejuni	Immunoproliferative small intestinal disease
Primary immunodeficiency	
Ataxia-telangiectasia	Both B & T Cell NHL
Wiskott-Aldrich syndrome	DLBCL, NHL of larynx
X-linked lymphoproliferative syndrome	NHL
Severe combined immunodeficiency	NHL, HL, EBV associated Burkitt's lymphoma
Acquired conditions of immunodeficiency	
HIV infections	DLBCL, Burkitt's Łlymphoma, primary CNS Łlymphoma, Plasmablastic lymphoma, primary effusion lymphoma
Organ or stem cell transplantation	Post-transplant lymphoproliferative disorder(PTLD)
Autoimmune and rheumatologic disease	
Rheumatoid arthritis	Hodgkin's lymphoma, PTCL, TLGL
Systemic lupus erythematosus	DLBCL
Sjögren's syndrome	Marginal zone lymphoma, Lymphoplasmacytic lymphoma, DLBCL
Celiac disease	Intestinal T- cell lymphoma
Hashimoto's thyroiditis	Follicular center cell lymphoma
Environmental or occupational	
Herbicides/pesticides	Non- Hodgkin's lymphoma
Anti TNF	B cell NHL, Hepatosplenic γδ T lymphoma
Phenytoin/carbamazepine	Pseudo lymphoma and malignant lymphoma
Breast implant associated	ALCL

extra nodal involvement can be detected in up to 40%. Systemic symptoms occur in approximately 25%. Cytopenias (rare) occur due to marrow involvement, immune mediated, hypersplenism, or hemophagocytic lymphohistiocytosis.

1.1.3.2 Workup for NHL (Table 1.5)

PET using 18-Fluorodeoxyglucose is used to stage and assess response to therapy. It improves accuracy of staging for both nodal and extra nodal compared to CT scan leading to change in stage in 10–30%. Interim PET scan positivity has shown inferior outcome in Hodgkin's lymphoma [3] but failed to predict outcome in DLBCL [4, 5]. 18-FDG uptake varies according to histology and proliferative activity with less uptake in indolent lymphoma than aggressive.

Table 1.3 Differential diagnosis based on pattern of presentation and extra nodal site of involvement

A. Based on pattern of presentation		
Presentation	**Aggressive**	**Indolent**
Extent		
Localized	DLBCL Burkitt's lymphoma ALCL	HL/NLPHL Follicular lymphoma Nodal MZL
Generalized	DLBCL Lymphoblastic lymphoma PTCL ALCL Mantle cell lymphoma Follicular lymphoma grade III	CLL FL Splenic MZL Hairy cell leukemia Lymphoplasmacytic lymphoma Mycosis Fungoides T-cell LGL
B. Based on extra nodal site involvement		
Sl. No	**Site**	**Entities**
1.	Skin	Primary cutaneous lymphoma ALCL AITL ATLL T-PLL
2.	CNS	DLBCL BL Dural marginal zone lymphoma LPL—Bing–Neel syndrome T-cell lymphoma- ATLL,T-PLL
3.	GIT	DLBCL Burkitt's lymphoma Mantle cell lymphoma Maltoma Follicular lymphoma EATL Heavy chain disease
4.	Splenomegaly predominant	Mantle cell lymphoma SMZL Hairy cell leukemia T-PLL Lymphoplasmacytic lymphoma HSTL HCL variant Follicular lymphoma
5.	Ocular and extra ocular	DLBCL PCNSL Maltoma
6.	AIHA	CLL/SLL Follicular lymphoma AITL

Table 1.4 WHO classification of NHL [2]

Mature B cell neoplasms	Mature T cell neoplasms
Aggressive neoplasms	**Leukemic or disseminated**
Diffuse large B-cell lymphoma: Variants, subgroups, and subtypes Diffuse large B-cell lymphoma (DLBCL), NOS Germinal center B-cell type Activated B-cell type	T-cell large granular lymphocytic leukemia Chronic lymphoproliferative disorders of NK cells T-cell T-cell prolymphocytic leukemia Aggressive NK-cell leukemia Adult T-cell leukemia/lymphoma
Diffuse large B-cell lymphoma subtypes	**Extra nodal**
T-cell/ histiocyte-rich large B-cell lymphoma Primary DLBCL of the CNS Primary cutaneous DLBCL, leg type DLBCL associated with chronic inflammation HHV8-positive DLBCL, NOS EBV-positive DLBCL, NOS	Extra nodal NK/T-cell lymphoma, nasal type Enteropathy-type T-cell lymphoma Hepatosplenic T-cell lymphoma Breast implant-associated anaplastic large-cell lymphoma
Other lymphomas of large B cells Primary mediastinal large B-cell lymphoma Intravascular large B-cell lymphoma EBV-positive mucocutaneous ulcer ALK-positive large B-cell lymphoma Plasmablastic lymphoma Multicentric Castleman disease Primary effusion lymphoma	**Cutaneous** Mycosis fungoides Sezary syndrome Primary cutaneous anaplastic large-cell lymphoma Lymphomatoid papulosis Subcutaneous panniculitis-like T-cell lymphoma Primary cutaneous γδ T-cell lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma	**Nodal** Peripheral T-cell lymphoma (PTCL), NOS Angioimmunoblastic T-cell lymphoma (AITL) Follicular T-cell lymphoma Nodal peripheral T-cell lymphoma with TFH phenotype Anaplastic large-cell lymphoma (ALCL), ALK positive Anaplastic large-cell lymphoma, ALK negative
High-grade B-cell lymphoma, with MYC and BCL2 and/ or BCL6 rearrangements	
High-grade B-cell lymphoma, NOS	
Burkitt's lymphoma	
Mantle cell lymphoma	
Indolent lymphomas	

(continued)

Table 1.4 (continued)

Mature B cell neoplasms	Mature T cell neoplasms
Follicular lymphoma Extra nodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) Nodal marginal zone lymphoma Splenic marginal zone lymphoma Lymphoplasmacytic lymphoma Heavy chain disease Plasma cell neoplasms CLL/SLL Monoclonal B-cell lymphocytosis B-cell prolymphocytic leukemia (PLL) Hairy cell leukemia	

Table 1.5 Staging work up

Staging workup for lymphoma
Initial studies
History and physical examination (including B symptoms, any immunosuppression, autoimmune disease, HIV)
Complete blood count with peripheral smear examination
Biochemistry—Renal function with uric acid and liver function tests
Lactate dehydrogenase and/ or $\beta_2$microglobulin
Hepatitis B, C and HIV Serologies
Tumor biopsy preferably excisional with histopathology Site preferred for biopsy—cervical > axillary > inguinal
Immunohistochemistry of tumor specimen
Cytogenetic analysis of tumor specimen (if lymphoma associated translocations suspected)
PET/CT scans for FDG avid lymphomas
Contrast enhanced CT scan of neck, chest, abdomen, and pelvis (FDG non-avid lymphomas)
Cardiac ejection fraction measurement (anthracycline based therapy)
Pregnancy testing in women of child bearing age
Additional studies in selected cases
Bone marrow study with aspiration and biopsy
Lumbar puncture with cytology and flow cytometry
Magnetic resonance imaging of brain if neurologic signs or symptoms
Immunoglobulin and TCR gene rearrangement studies

18-FDG PET scan can be used for staging in FDG-avid lymphomas such as DLBCL, Hodgkin's lymphoma, Follicular lymphoma whereas in non-FDG avid lymphomas, a contrast-enhanced CT scan is preferred.

The current staging system for NHL in adults is the **Lugano classification** [6]. Stage I involves one node or a group of adjacent nodes or single extra nodal lesion without nodal involvement. Stage II involves two or more lymph node regions on the same side of the diaphragm or Stage II by nodal extent with limited contiguous extra nodal extension. Limited stage (I or II) lymphomas that affect an organ outside the lymph system (an extra nodal organ) have an E added (for example, stage IIE). Stage III is involvement of lymph node regions on both sides of the

diaphragm, nodes above the diaphragm with or spleen involvement. Stage IV is widely spread into at least one organ outside the lymph system, such as the bone marrow, liver, or lung.

1.1.4 Prognostic Indices (Table 1.6)

The International prognostic index (IPI) applies for untreated aggressive NHL with 1 point assigned to each factor and score of 1, 2, 3, and 4 to 5 correspond to 5 year survival of 73%, 51%, 43%, and 26%, respectively, in the pre-rituximab era [7]. The Revised IPI(R-IPI) was developed to predict the outcome of individuals receiving rituximab with chemotherapy [8].

Table 1.6 Prognostic indices

R-IPI (1 point each)	NCCN IPI (1 point each)	FLIPI (1 point each)	MIPI (Simplified)
Age > 60 years	Age 41–60 years—1 point	Age > 60 years	Age < 50 years—0 point
	Age > 60–75 years—2 point		Age 50–59 years—1point
	Age > 75 years—3 point		Age 60–69 years—2 point
			Age ≥ 70 years—3 point
Performance status ≥2	Performance status ≥2—1 point	Hemoglobin <12 g/L	Performance status 0–1—0 point
			Performance status 2–4—2 point
LDH above normal	LDH ratio 1–3—1 point	LDH above normal	LDH:ULN ratio <0.67—0 point
			0.67–0.99—1 point
	LDH ratio > 3—2 point		1.00–1.49—2 point
			≥1.50—3 point
Ann Arbor stage III or IV	Ann Arbor stage III or IV	Stage III or IV	Leucocyte count (10^9/L) <6.7—0 point
			06.7–9.9—1 point
			10.0–14.9—2 point
			≥15.0—3 point
Number of extra nodal sites >1	Extra nodal disease involving the bone marrow, central nervous system, liver/gastrointestinal tract, or lung – 1 point	Number of nodal sites >4	
Risk group—3 year OS	**Risk group—5 year OS**	**Risk group—2 year OS**	**Risk group—5 year OS**
0–1—91	0–1—96	0–1—98	0–3—60
2—81	2–3—77	2—94	4–5—35
3—65	4–5—56	≥3—87	6–12—20
4–5—59	>5—35		

The National Comprehensive Cancer Network (NCCN)-IPI incorporates detailed information about the clinical variables used in the original IPI [9]. The Follicular Lymphoma International Prognostic Index (FLIPI) and Mantle Cell Lymphoma International Prognostic Index (MIPI) have been found to reliably predict survival in follicular lymphoma [10] and mantle cell lymphoma [11].

1.1.5 Specific Features of Common Subtypes

1.1.5.1 Follicular Lymphoma

Epidemiology and pathology: The most common indolent lymphoma with a median age of presentation of 64 years, and a female predominance [12]. FLs are derived from germinal center B cell and graded based on centroblasts per high power field: Grade 1–2 (0–15), Grade 3 A(>15) centroblasts present and 3B with sheets of centroblasts [13].

Clinical features: Asymptomatic lymphadenopathy, extra nodal disease is less common, B symptoms present in 20% cases and bone marrow involvement seen in 70% cases.

Immunophenotype: FL cells express CD 10, CD 20, and BCL-6 and anti-apoptotic protein BCL 2. The overexpression of anti-apoptotic BCL2 is mediated by t (14:18) which juxtaposes BCL2 gene to the Ig heavy chain locus in 85% cases.

Evaluation: PET/CT scan is particularly useful to stage or to identify the site for biopsy in suspected transformed disease.

1.1.5.2 DLBCL

Epidemiology: Most common NHL subtype [2] with median age of 65 years and male predominance.

Clinical features: Nodal or extra nodal disease and bone marrow involvement in fewer than 10% cases.

Immunophenotype: B cell markers CD 19, 20, 22 & 79a and germinal B cell markers include CD 10, BCL6. CD5 and BCL2 are variable positive. Rearrangements in the MYC oncogene are found in ~15% of DLBCL and are associated with BCL2 or BCL6 and termed as "double hit" lymphomas or "triple hit" when all three are present.

Evaluation: Bone marrow biopsy is not recommended if bone marrow involvement is indicated by PET and if imaging is negative it is appropriate to consider biopsy. CSF analysis is to be considered with clinical features of CNS disease, high CNS IPI (4–6), 2 or more extra nodal disease sites irrespective of CNS IPI and testicular, renal/adrenal or intravascular involvement, double hit/triple hit lymphoma.

1.1.5.3 Specific Clinicopathologic Entities of DLBCL

Primary mediastinal(thymic) large B-cell Lymphoma—Both clinically and biologically more closely resemble classical HL, with median age of presentation of 35 years and female preponderance [14].

T-cell/ histiocyte–rich large B-cell lymphoma—Uncommon variant (<10%) of DLBCL; mainly in middle-aged males [15].

1.1.6 Primary CNS Lymphoma

Epidemiology: 1% of all NHL, with median age of 65 years and male predominance. Risk factors include immunosuppression, HIV infection, and autoimmune disease.

Clinical features: Neurocognitive symptoms are most common, focal neurodeficits as per site are common presentation.

Immunophenotype: B cell markers CD 19, 20, 22 positive, BCL2 variable, BCL 6 + (50%), CD 10 negative. 95% of PCNSLs are DLBCL [16].

Evaluation: CSF, bone marrow studies, and contrast enhanced MRI Brain & systemic imaging to determine disease extent. Slit lamp examination and stereotactic needle biopsy of brain are indicated in most of cases. Prognostication done using IELSG score (age, PS, LDH, deep seated brain tumors, and elevated CSF proteins) [17].

1.1.7 Marginal Zone Lymphoma

Epidemiology and pathology: Indolent neoplasm of mature post-germinal center B lymphocytes [18]. About 10% of all NHL with three subtypes nodal, extra nodal, and splenic MZL.

MZL arise with chronic antigenic stimulation due to pathogens or autoimmune diseases; or translocations result in Ag independent activation of NF-kB.

Clinical features: They vary as per the site of involvement, for example, lymphadenopathy (Nodal MZL), orbital mass, parotid mass, cough (bronchial MZL), skin nodules (Cutaneous MALT), epigastric pain (Gastric MALT), intestinal obstruction (SI), splenomegaly (splenic MZL), and B symptoms.

Immunophenotype: Cell markers CD19, 20, 22; CD 5, 10, cyclin D1 negative.

Cytogenetics [19]: Most common is t(11;18), other t(1;14), t(14;18).

Evaluation: Baseline evaluation as suggested above with SPEP (paraprotein often present) should be considered. BM aspirate and biopsy in splenic MZL show intrasinusoidal lymphocytic infiltration. Upper GI endoscopy in Gastric MALT for biopsy and H. pylori testing.

Imaging with Contrast CT Chest/abdomen/pelvis; MRI orbits (Ocular MALT). FDG PET scan not considered.

1.1.8 Mantle Cell Lymphoma

Epidemiology and pathology: 6% of all NHL with male predominance and median age of 70 years.

Clinical features: Clinical behavior is intermediate between indolent and aggressive with strong tendency to present in advanced stage. Lymphadenopathy with extra nodal involvement is common including bone marrow involvement.

Immunophenotype: CD 19, 20 (B cell markers), CD5 (aberrant expression of T cell) but negative for CD200/23 (CLL) or CD 10(FL).

Cytogenetics: t(11; 14) which juxtaposes cyclin D1 with Ig heavy chain locus is the hallmark (overexpression of cyclinD1).

Evaluation: Peripheral blood flow/bone marrow biopsy as leukemic phase disease is common, and pan-endoscopy as GI tract is commonly involved. Ki67 (>30% or <30%), p53 abnormality, and SOX 11 expression are prognostic factors and predict for aggressive disease.

1.1.9 Burkitt's Lymphoma

Among the most aggressive of all human malignancies with acute onset, rapid doubling time <24 h, and B symptoms.

Epidemiology and pathology: Arise from germinal center B cell, with translocations that dysregulate MYC expression by placing it under control of Ig gene enhancer. Histology shows monotonous sheet of medium sized atypical B cells, extensive necrosis, frequent mitosis (Ki67 95%), and classic starry sky pattern (Sky—Burkitt's cells with lipid droplets and starry—macrophages with apoptotic debris within).

Distinct clinical forms:

Endemic—In equatorial Africa with strong association for EBV, male predominance and commonly presents as jaw mass.

Sporadic—30% of pediatric lymphoma and <1% of adult NHL with peak age 11 years and 30 years, respectively. Commonly extra nodal presentation as abdominal lump.

Immunodeficiency associated—In HIV positive & EBV negative, CD4 independent, HAART has no impact on incidence and usually present in adult with both nodal and extra nodal disease.

Immunophenotype: CD19, 20, 22 positive (B cell markers), CD 10 & Bcl-6 positive (germinal center).

Characterized by MYC translocation t(8;14) in 85% cases or t(2;8) or t(8;22).

Evaluation: Bone marrow study and lumbar puncture to rule out CNS involvement. Imaging with contrast enhanced thorax, abdomen, and pelvis to determine disease extent.

1.1.10 Hairy Cell Leukemia

Epidemiology and pathology: 2% of all leukemia with median age of presentation of 50 years and male predominance.

Clinical features: Constitutional symptoms with massive splenomegaly and symptomatic cytopenias. *Immunophenotype*: Mature B cell markers present are CD19, 20, 22 with CD25; aberrant expression of CD 11c, CD103, CD123.

Evaluation: Peripheral smear shows small–medium size mononuclear cells with finger like projections (hairy cells), BM biopsy is hypercellular within filtrating hairy cells; abundant cytoplasm surrounding the nuclei give the appearance of fried egg. Often the bone marrow aspirate is dry tap.

1.1.11 Peripheral T-Cell Lymphoma

10% of all NHL, male predominance and median age of 65 years.

Aggressive neoplasms arising from mature T lymphocytes and NK Cells with poor response to chemotherapy and OS relative to B cell, exception ALCL, skin limited mycosis fungoides have excellent prognosis. Presentation is prominent B symptoms with pruritus, generalized lymphadenopathy, hepatosplenomegaly; extra nodal disease and 70% have advanced disease.

Investigations: Baseline NHL workup and other tests to be considered are coombs test (if AIHA suspected), HTLV 1 serology (ATLL), Serum EBV PCR (NK/T-cell Lymphoma). Imaging with PET CT scan for disease extent.

1.1.11.1 Types

PTCL NOS: MC subtype of PTCLs, accounting for 30% of cases.

AITL (Angioimmunoblastic T-Cell Lymphoma): Account for 15–20% of cases with median age of 65 years.

ALCL (Anaplastic Large-Cell Lymphoma): CD 30 positive subtype of PTCL with two biologically distinct diseases; ALK positive ALCL that overexpresses ALK due to t(2;5) and ALK negative ALCL.

ALK positive usually present in young age group and has better prognosis compared to ALK negative ALCL.

Primary cutaneous ALCL: Indolent behavior, predominant dermatologic involvement. Second most common type of CTCL with median age of presentation is 60 years but favorable outcomes.

Breast implant associated ALCL: ALCL associated with implants (silicone and saline) with CD30 + and ALK negative. Typical localized presentation with unexplained seroma or capsular thickening.

Extra nodal NK/T-cell lymphoma: Mainly seen in Asian males aged 40–50 years and associated with EBV. Typically involves midline sinus/palate but involvement of other sites can occur.

ATLL (Adult T-Cell Lymphoma & Leukemia): Endemic in Southwestern Japan, Caribbean basin where HTLV-1 prevalence is high. There are four clinical variants: Acute, lymphoma type, chronic, and smoldering. The most common is the acute form with elevated white blood count, skin rash, lymphadenopathy, hepatosplenomegaly, pulmonary infiltrates, and hypercalcemia with or without lytic bone lesions.

1.1.12 Cutaneous T-Cell Lymphoma (CTCL)

5% of NHL with primary involvement of skin.

1.1.12.1 Types

Mycosis fungoides (MF): Most common CTCL (50%) with indolent clinical course and primary involvement of skin. In early stage appears as plaques or patches with pruritus and gradually evolves to diffuse erythroderma or tumor usually associated with adenopathy. Extra cutaneous involvement occurs in advanced stage of disease with histologic transformation.

Sezary Syndrome (SS): Characterized by erythroderma, generalized lymphadenopathy, presence of Sezary cells in skin, lymph nodes, and peripheral blood.

1.2 Summary and Conclusions

Non-Hodgkin lymphomas encompass several subtypes with unique clinical, biological characteristics. A multidisciplinary approach is essential for correct diagnosis, staging, and management.

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References

1. Lymphoma—Non-Hodgkin: Statistics|Cancer.Net. https://www.cancer.net/cancer-types/lymphoma-non-hodgkin/statistics. Accessed 22 Nov 2020.
2. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375–90.
3. Hutchings M, Loft A, Hansen M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood. 2006;107:52–9.
4. 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;30:184–90.
5. Pregno P, Chiappella A, Bellò 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;119:2066–73.
6. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32:3059–67.
7. Fisher RI. The New England Journal of Medicine. No other uses without permission. Copyright © 1993 Massachusetts Medical Society. All rights reserved. N Engl J Med. 1993;29:1230–5.
8. Ziepert M, Hasenclever D, Kuhnt E, Glass B, Schmitz N, Pfreundschuh M, Loeffler M. 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;28:2373–80.
9. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood. 2014;123:837–42.

10. Solal-Céligny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood. 2004;104:1258–65.
11. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood. 2008;111:558–65.
12. Junlén HR, Peterson S, Kimby E, et al. Follicular lymphoma in Sweden: nationwide improved survival in the rituximab era, particularly in elderly women: a Swedish Lymphoma Registry Study. Leukemia. 2015;29:668–76.
13. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, Lister TA, Bloomfield CD. World health organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the clinical advisory committee meeting—Airlie house, Virginia, November 1997. J Clin Oncol. 1999;17:3835–49.
14. Nguyen LN, Ha CS, Hess M, Romaguera JE, Manning JT, Cabanillas F, Cox JD. The outcome of combined-modality treatments for stage I and II primary large B-cell lymphoma of the mediastinum. Int J Radiat Oncol Biol Phys. 2000;47:1281–5.
15. Achten R, Verhoef G, Vanuytsel L, De Wolf-Peeters C. T-cell/Histiocyte–rich large B-cell lymphoma: a distinct Clinicopathologic entity. J Clin Oncol. 2002;20:1269–77.
16. Bhagavathi S, Wilson JD. Primary central nervous system lymphoma. Arch Pathol Lab Med. 2008;132(11):1830–4. https://doi.org/10.1043/1543-2165-132.11.1830.
17. Ferreri AJM, Blay JY, Reni M, et al. Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. J Clin Oncol. 2003;21:266–72.
18. Novak U, Basso K, Pasqualucci L, Dalla-Favera R, Bhagat G. Genomic analysis of non-splenic marginal zone lymphomas (MZL) indicates similarities between nodal and extranodal MZL and supports their derivation from memory B-cells. Br J Haematol. 2011;155:362–5.
19. Sagaert X, De Wolf-Peeters C, Noels H, Baens M. The pathogenesis of MALT lymphomas: where do we stand? Leukemia. 2007;21:389–96.