

Non-Hodgkin Lymphoma

Protocol applies to non-Hodgkin lymphoma involving any organ system except the gastrointestinal tract.

*Protocol revision date: January 2004
No AJCC/UICC staging system*

Procedures

- **Cytology** (No Accompanying Checklist)
- **Biopsy**
- **Resection of Lymph Node or Other Organ**

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Surgical Pathology Cancer Case Summary (Checklist)

Protocol revision date: January 2004

Applies to non-gastrointestinal, non-Hodgkin lymphoma only

No AJCC/UICC staging system

NON-HODGKIN LYMPHOMA: Biopsy/Resection

Patient name:

Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC

Specimen Type

Lymphadenectomy

Other (specify): _____

Not specified

Tumor Site (check all that apply)

Lymph node(s), site not specified

Lymph node(s)

Specify site(s): _____

Other tissue(s) or organ(s)

Specify site(s): _____

Not specified

MICROSCOPIC

Histologic Type (WHO Classification)

Histologic type cannot be assessed

B-cell Lymphoma

B-cell lymphoma, subtype cannot be determined

Precursor B-lymphoblastic leukemia/lymphoma

Chronic lymphocytic leukemia/small lymphocytic lymphoma

B-cell prolymphocytic leukemia

Lymphoplasmacytic lymphoma

Splenic marginal zone lymphoma

Hairy cell leukemia

Plasma cell myeloma/ Plasmacytoma

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* Data elements **with asterisks** are **not required** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

___ Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue
(MALT lymphoma)

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- Nodal marginal zone B-cell lymphoma
- Follicular lymphoma, grade 1 (0-5 centroblasts per HPF)
- Follicular lymphoma, grade 2 (6-15 centroblasts per HPF)
- Follicular lymphoma, grade 3 (greater than 15 centroblasts per HPF)
- Follicular lymphoma, cutaneous follicle center sub-type
- Follicular lymphoma, diffuse follicle center sub-type, grade 1 (0-5 centroblasts per HPF)
- Follicular lymphoma, diffuse follicle center cell sub-type, grade 2 (6-15 centroblasts per HPF)
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
- Mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- Primary effusion lymphoma
- Burkitt lymphoma/leukemia
- Lymphomatoid granulomatosis
- Other (specify): _____

T-cell Lymphoma

- T-cell lymphoma, subtype cannot be determined
- Precursor T-lymphoblastic leukemia/lymphoma
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Aggressive NK-cell leukemia
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-type T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides / Sézary syndrome
- Primary cutaneous anaplastic large cell lymphoma
- Peripheral T-cell lymphoma, unspecified
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma
- Lymphomatoid papulosis
- Other (specify): _____

Extent of Pathologically Examined Tumor (check all that apply)

- Involvement of a single lymph node region
Specify site: _____
- Involvement of multiple lymph node regions
Specify: _____
- Splenic involvement
- Liver involvement
- Bone marrow involvement
- Other organ involvement
Specify: _____

4 * Data elements **with asterisks** are **not required** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

CAP Approved

Hematologic System • Non-Hodgkin Lymphoma

___Not specified

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Phenotyping

Performed, see separate report

Performed

Specify method and results: _____

Not performed

***Additional Pathologic Findings**

*Specify: _____

***Comment(s)**

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Background Documentation

Protocol revision date: January 2004

I. Cytologic Material

A. Clinical Information

1. Patient identification
 - a. Name
 - b. Patient identification number
 - c. Age (birth date) (Note **A**)
 - d. Sex (Note **B**)
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
 - a. Relevant history (eg, duration of lymphadenopathy or other mass; previous diagnosis and treatment for lymphoma, Hodgkin lymphoma, or other malignancy; immunosuppression; AIDS; bone marrow or solid organ transplantation)
 - b. Relevant findings (eg, distribution of lymphadenopathy, signs and symptoms, imaging studies, serum lactate dehydrogenase [LDH] level) (Note **C**)
 - c. Clinical diagnosis
 - d. Clinical stage, if known
 - e. Specific procedure (fine-needle aspiration [FNA], tap of effusion, other)
 - f. Operative findings
 - g. Anatomic site(s) of specimen(s) (Note **D**)

B. Macroscopic Examination

1. Specimen
 - a. Unfixed/fixed (specify fixative)
 - b. Number of slides received, if appropriate
 - c. Quantity and appearance of fluid specimen, if appropriate
 - d. Other (eg, cytologic preparation from tissue)
 - e. Results of intraprocedural consultation
2. Material submitted for microscopic evaluation (eg, FNA, cytospin of fluid, other)
3. Special studies, specify (eg, flow cytometry for immunophenotyping, cytochemistry, immunohistochemistry, cytogenetic analysis)

C. Microscopic Evaluation

1. Adequacy of specimen (if unsatisfactory for evaluation, specify reason)
2. Lymphoma, if present
 - a. Histologic type, if possible (Note **E**)
 - b. Other characteristics (eg, necrosis)
3. Additional pathologic findings, if present
4. Results /status of special studies (specify)
5. Comments
 - a. Correlation with intraprocedural consultation, as appropriate
 - b. Correlation with other specimens, as appropriate
 - c. Correlation with clinical information, as appropriate

II. Biopsy

A. Clinical Information

1. Patient identification
 - a. Name
 - b. Patient identification number
 - c. Age (birth date) (Note **A**)
 - d. Sex (Note **B**)
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
 - a. Relevant history (eg, duration of lymphadenopathy or other mass; previous diagnosis and treatment for lymphoma, Hodgkin lymphoma, or other malignancy; immunosuppression; AIDS; bone marrow or solid organ transplantation)
 - b. Relevant findings (eg, distribution of lymphadenopathy, signs and symptoms, imaging studies, serum LDH level) (Note **C**)
 - c. Clinical diagnosis
 - d. Clinical stage, if known
 - e. Specific procedure (eg, lymph node biopsy, liver biopsy)
 - f. Operative findings
 - g. Anatomic site(s) of specimen(s) (Note **D**)

B. Macroscopic Examination

1. Specimen
 - a. Unfixed/fixed (specify fixative) (Note: When appropriate, fresh sterile tissue should be sent for culture, and fresh frozen tissue should be saved, if possible, for immunophenotyping and molecular genetic studies)
 - b. Number of pieces
 - c. Largest dimension of each piece
 - d. Results of intraoperative consultation
2. Submit nonfrozen tissue for microscopic evaluation
3. Special studies, specify (eg, flow cytometry for immunophenotyping, cytochemistry, immunohistochemistry, cytogenetic analysis) (Note **F**)

C. Microscopic Evaluation

1. Tumor
 - a. Histologic type (Note **E**)
 - b. Other characteristics (eg, necrosis)
2. Additional pathologic findings, if present
3. Results/status of special studies
4. Comments
 - a. Correlation with intraoperative consultation, as appropriate
 - b. Correlation with other specimens, as appropriate
 - c. Correlation with clinical information, as appropriate

III. Resection of Lymph Node or Other Organ

A. Clinical Information

1. Patient identification
 - a. Name
 - b. Patient identification number
 - c. Age (birth date) (Note **A**)

- d. Sex (Note **B**)
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
 - a. Relevant history (eg, duration of lymphadenopathy or other mass; previous diagnosis and treatment for lymphoma, Hodgkin disease, or other malignancy; immunosuppression; AIDS; bone marrow or solid organ transplantation)
 - b. Relevant findings (eg, distribution of lymphadenopathy, signs and symptoms, imaging studies, serum LDH level) (Note **C**)
 - c. Clinical diagnosis
 - d. Clinical stage, if known
 - e. Specific procedure (eg, lymph node excision, splenectomy, other)
 - f. Operative findings
 - g. Anatomic site(s) of specimen(s) (Note **D**)

B. Macroscopic Examination

1. Specimen
 - a. Organ(s)/tissue(s) (Note **D**)
 - b. Unfixed/fixed (specify fixative) (Note: When appropriate, fresh sterile tissue should be sent for culture and fresh frozen tissue should be saved for immunophenotyping and molecular genetic studies)
 - c. Number of pieces
 - d. Dimensions
 - e. Orientation of specimen, if indicated by surgeon
 - f. Results of intraoperative consultation
2. Tumor
 - a. Number of lesions (Note **G**)
 - b. Location (Note **G**)
 - c. Configuration
 - d. Dimensions
 - e. Descriptive characteristics (eg, color, consistency)
 - f. Direct extension to other organ(s) or structure(s) (Note **H**)
 - g. Noncontiguous tumor involvement of other organ(s) or structure(s) (Note **G**)
3. Other lesions
4. Tissues submitted for microscopic evaluation
 - a. Lymphoma, representative sections
 - b. Other specific nodes, when marked by surgeon
 - c. Other lesions
 - d. Section(s) of tissue uninvolved by tumor
 - e. Other tissue(s)/organ(s)
5. Special studies, specify (eg, flow cytometry for immunophenotyping, cytochemistry, immunohistochemistry, cytogenetic analysis) (Note **F**)

C. Microscopic Evaluation

1. Tumor
 - a. Histologic type (Note **E**)
 - b. Direct extension to other organ(s) or structure(s)
2. Additional pathologic findings, if present (eg, reactive follicular hyperplasia)
3. Other tissues submitted (if distant involvement by lymphoma, specify site) (Note **G**)

4. Results/status of special studies (specify)
5. Comments
 - a. Correlation with intraoperative consultation, as appropriate
 - b. Correlation with other specimens, as appropriate
 - c. Correlation with clinical information, as appropriate

Explanatory Notes

A. Patient Age

Age is a risk factor independently associated with survival in non-Hodgkin lymphoma (NHL). Age above 60 years has been shown to be associated with decreased survival compared to age 60 or less.¹⁻⁴ In some series of patients with low grade NHL, age greater than 40 has been associated with decreased survival.⁵ Across all grades and stages of NHL, a decreased ability of patients greater than 60 years of age to tolerate treatment may be the major effect of age.³ However, even among patients treated equivalently for low stage disease (ie, stage I and II, see below), older patients are at greater risk for relapse than younger patients.^{3,6-16}

B. Sex

Across all grades and stages of NHL, male sex has been shown to correlate with other adverse prognostic factors such as histologic type, stage, and symptoms (see below). However, it has also been demonstrated to have independent adverse prognostic significance in patients with low grade NHL.^{5,14,17}

C. Clinical Findings

Although not always provided to the pathologist by the physician submitting the specimen, certain specific clinical findings are known to be of prognostic value in NHL (across all stages). In particular, systemic symptoms of fever (greater than 38.5°C), unexplained weight loss (more than 10% body weight) in the 6 months before diagnosis, and drenching night sweats are used to define 2 categories for each stage of NHL: A (symptoms absent), and B (symptoms present). The presence of B symptoms is known to correlate with extent of disease (stage and tumor bulk), but symptoms also have been shown to have prognostic significance for cause-specific survival that is independent of stage.^{3,4,6,13,18,19}

Poor patient “performance status” has also been shown by several multivariate analyses to have independent adverse prognostic significance.^{1,6,10,17} Performance status refers to the overall activity level of the patient ranging from fully active to completely bed-ridden, and a poor performance status is usually defined as any degree of activity less than fully active or fully ambulatory (ie, bed-ridden for varying proportions of time).^{1,2}

Elevated serum lactate dehydrogenase (LDH) level is an adverse prognostic factor that correlates with tumor burden (stage and bulk).³ It has also been shown to have independent prognostic significance in both early and late stage NHL in many studies.^{8,12,16,20-25}

Tumor bulk, usually defined by clinical and/or imaging studies, is a predictive factor in various settings.³ A tumor greater than 5 to 10 cm in diameter is associated with higher

rates of relapse of stage I and II NHL treated with radiotherapy.¹³ A tumor greater than 10 cm in diameter is associated with poor outcome in patients with stage III and IV NHL treated with chemotherapy.³ Other definitions of bulky disease associated with poor outcome in stage II to IV NHL include a large mediastinal mass (greater than one-third of chest diameter), a palpable abdominal mass, and a combination of para-aortic and pelvic node involvement.^{3,4,7,13,16,17,23,26}

D. Anatomic Sites

The anatomic sites that constitute the major structures of the lymphatic system include groups and chains of lymph nodes, the spleen, the thymus, Waldeyer's ring (a circular band of lymphoid tissue that surrounds the oropharynx consisting of the palatine, lingual, and pharyngeal tonsils), the vermiform appendix, and the Peyer's patches of the ileum. Minor sites of lymphoid tissue include the bone marrow, liver, skin, lung, pleura, and gonads. Involvement of extranodal sites is more common in NHL than in Hodgkin lymphoma.

E. Histologic Type

The protocol recommends the World Health Organization (WHO) Classification of Lymphoid Neoplasms, which is shown below.^{27,28} This classification encompasses both nodal and extranodal lymphomas and outlines the immunobiologic features of the defined entities that aid in the diagnosis. The prognostic information necessary to determine treatment of lymphoma is, in general, provided by the histologic type.

WHO Classification of Lymphoid Neoplasms

B-cell Neoplasms

Precursor B-cell neoplasms

Precursor B-lymphoblastic lymphoma/leukemia

Mature B-cell neoplasms

Chronic lymphocytic leukemia/small lymphocytic lymphoma

Variant: Mu heavy chain disease

B-cell prolymphocytic leukemia

Lymphoplasmacytic lymphoma / Waldenström macroglobulinemia

Variant: Gamma heavy chain disease

Splenic marginal zone lymphoma

Hairy cell leukemia

Variant: Hairy cell variant

Plasma cell myeloma

Solitary plasmacytoma of bone

Extraosseous plasmacytoma

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

Nodal marginal zone B-cell lymphoma

Follicular lymphoma

Grading:

Grade 1: 0 to 5 centroblasts per high power field[#]

Grade 2: 6 to 15 centroblasts per high power field[#]

Grade 3: greater than 15 centroblasts per high power field[#]

Grade 3a: centrocytes are still present

Grade 3b: centroblasts form solid sheets with no residual centrocytes

Reporting of pattern:

Follicular: greater than 75% follicular

Follicular and diffuse: 25% to 75% follicular

Focally follicular: less than 25% follicular

Variants:

Cutaneous follicle center lymphoma

Diffuse follicle center lymphoma

Grade 1: 0 to 5 centroblasts per high power field[#]

Grade 2: 6 to 15 centroblasts per high power field[#]

Mantle cell lymphoma

Variants: Blastoid (classic or pleomorphic), others

Diffuse large B-cell lymphoma

Mediastinal (thymic) B-cell lymphoma

Intravascular large B-cell lymphoma

Primary effusion lymphoma

Morphologic variants:

Centroblastic

Immunoblastic

T-cell/histiocyte-rich

Anaplastic

Burkitt lymphoma

Variants:

Burkitt lymphoma with plasmacytoid differentiation

Atypical Burkitt/Burkitt-like

B-cell proliferations of uncertain malignant potential

Lymphomatoid granulosis

Post-transplant lymphoproliferative disorder, polymorphic

[#] WHO guideline²⁷ for high powered field (HPF) = high powered field of 0.159mm² (40X objective, 18mm field of view ocular; count 10 HPF and divide by 10). If using a 10mm field of view ocular, count 8 HPF and divide by 10, or count 10 HPF and divide by 12 to get the number of centroblasts/0.159mm² HPF. If using a 22-mm field of view ocular, count 7 HPF and divide by 10, or count 10 HPF and divide by 15 to get the number of centroblasts/0.159mm² HPF.

T-cell Neoplasms

Precursor T-cell neoplasms

Precursor T lymphoblastic lymphoma/leukemia

Blastic NK-cell lymphoma

Mature T-cell and NK-cell neoplasms

T-cell prolymphocytic leukemia

Variants: small cell, cerebriform cell (Sézary cell-like)

T-cell granular lymphocyte leukemia

Aggressive NK-cell leukemia

Adult T-cell lymphoma/leukemia (HTLV1+)

Clinical variants:

Acute

Lymphomatous

Chronic
Smoldering
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Hepatosplenic T-cell lymphoma
Variants: gamma-delta T-cell lymphoma in other anatomic sites
(eg, skin, intestine)
Subcutaneous panniculitic-like T-cell lymphoma
Blastic NK-cell lymphoma
Mycosis fungoides (MF) and Sézary syndrome
Variants:
Pagetoid reticulosis
MF-associated follicular mucinosis
Granulomatous slack skin disease
Primary cutaneous anaplastic large cell lymphoma (C-ALCL)
Peripheral T-cell lymphoma, unspecified
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma
T-cell proliferation of uncertain malignant potential
Lymphomatoid papulosis

Immunophenotypes and Genetics²⁶⁻²⁹

Precursor B lymphoblastic leukemia/lymphoma: SIg-, cytoplasmic μ chain 30%, CD19+, CD20-/+, CD22+, CD79a+, TdT+, HLA-DR+, CD10+/-, CD34+/-, CD13-/+, CD33-/+, IgH gene rearrangement +/-, IgL gene rearrangement -/+, TCR gene rearrangement -/+, variable cytogenetic abnormalities

B-cell chronic lymphocytic leukemia (B-CLL): Faint SIgM+, SIgD+/-, CIg+/-, panB+ (CD19+, CD20+), CD5+, CD10-, CD23+, CD43+, CD11c-/+, IgH and IgL gene rearrangements; trisomy 12-/+, 13q abnormalities-/+

Lymphoplasmacytic lymphoma: SIgM+, SIgD-/+, CIg+, PanB+, CD5-, CD10-, CD43+/-, CD25-/+, IgH and IgL gene rearrangements

Splenic marginal zone lymphoma: SIgM+, SIgD+, CD20+, CD79a+, CD5-, CD10-, CD23-, CD43-, nuclear cyclin D1-, CD103-, allelic loss at 7q21-32 (40% of cases)

Hairy cell leukemia: SIg+ (IgM, IgD, IgG, or IgA), PanB+, CD79a+, CD79b-, DBA.44+, CD5-, CD10-, CD23-, CD11c+, CD25+, FMC7+, CD103+ (mucosal lymphocyte antigen as detected by B-ly7), tartrate resistant acid phosphatase (TRAP)+; IgH and IgL gene rearrangements

Plasma cell myeloma: CIg+ (IgG, IgA, rare IgD, IgM, or IgE or light chain only), PanB-, (CD19-, CD20-, CD22-), CD79a+/-, CD45-/+, HLA-DR-/+, CD38+, CD56+/-, EMA-/+, CD43+/-; IgH and IgL gene rearrangements; deletions most commonly 13q, and occasional translocations, in particular t(11;14)(q13;q32)

Extranodal marginal zone B-cell lymphoma of MALT (MALT lymphoma): SIg+ (IgM or IgA or IgG), SIgD-, CIg-/+, PanB+, CD5-, CD10-, CD23-, CD43-/++; IgH and IgL gene rearrangements, bcl-1 and bcl-2 germline, trisomy 3 or t(11;18)(q21;q21) may be seen

Nodal marginal zone B-cell lymphoma : SIgM+, SIgD-, CIg-/+, PanB+, CD5-, CD10-, CD23-, CD43-/++; IgH and IgL gene rearrangements, bcl-1 and bcl-2 germline

Follicular lymphoma: SIg+ (usually IgM +/- IgD, IgG, IgA), PanB+, CD10+/-, CD5-, CD23-/+, CD43-, CD11c-, CD25-; overexpression of BCL-2+ (useful to distinguish from reactive follicles); BCL6+ IgH and IgL gene rearrangements, t(14;18) with rearranged BCL-2 gene in 70-95% of cases

Mantle cell lymphoma: SIgM+, SIgD+, lambda>kappa, PanB+, CD5+, CD10-/+, CD23-, CD43+, CD11c-, CD25-; IgH and IgL gene rearrangements, t(11;14); bcl-1 gene rearrangements (CCND1/cyclinD1/PRAD1) common

Diffuse large B-cell lymphoma: SIg+/-, CIg-/+, PanB+, CD45+/-, CD5-/+, CD10-/ (weak); IgH and IgL gene rearrangements; bcl-2 gene rearranged in 30% of cases, bcl-6/LAZ3 gene (chromosome 3q27) rearranged in 30% of cases, c-myc gene rearrangement uncommon

Mediastinal (thymic) large B-cell lymphoma: SIg-/+, PanB+, (especially CD20, CD79a), CD45+/-, CD15-, CD30-/ (weak); IgH and IgL gene rearrangements

Burkitt lymphoma: SIgM+, PanB+, CD5-, CD10+, CD23-; IgH and IgL gene rearrangements, t(8;14) and variants t(2;8) and t(8;22); rearranged c-myc gene. EBV common (95%) in endemic cases and infrequent (15-20%) in sporadic cases, intermediate incidence (30-40%) in HIV-positive cases

Atypical Burkitt/ Burkitt-like lymphoma: SIg+/- (IgM or IgG), CIg-/+, PanB+, CD5-, CD10-/++; IgH and IgL gene rearrangements, infrequent rearrangement of c-myc gene, bcl-2 gene rearranged in 30% of cases

Precursor T-lymphoblastic lymphoma/leukemia: TdT+, CD7+, CD3+/-, variable expression of other PanT antigens, CD1a+/-, often CD4 and CD8 double positive or negative, Ig-, PanB-; variable rearrangement of TCR genes; IgH gene rearrangement -/+, most common chromosomal abnormalities involve 14q11-14 or 7q35; variable cytogenetic abnormalities reported

T-cell prolymphocytic leukemia: TdT-, PanT+, (CD2, CD3, CD5, CD7) CD25-, CD4+/CD8->CD4+/CD8+>CD4-/CD8-; TCR gene rearrangements, 75% of cases show inv 14(q11;q32)

T-cell large granular lymphocytic leukemia, T-cell type: TdT-, PanT+ (CD2, CD3+, CD5+/-, CD7-), TCR+, CD4-, CD8+, CD16+, CD56-, CD57+, CD25-; most cases show clonal rearrangements of TCR genes

T- cell large granular lymphocytic leukemia, NK-cell type: TdT-, CD2+, CD3-, TCR-, CD4-, CD8+/-, CD16+/-, CD56+/-, CD57+/-, CD25-; TCR and Ig genes are germline

Adult T-cell lymphoma/leukemia (HTLV1+): TdT-, PanT+ (CD2+, CD3+, CD5+, CD7-) CD4+, CD8-, CD25+; TCR gene rearrangements, clonally integrated HTLV1

Extranodal NK/T-cell lymphoma, nasal type: TdT-, CD2+, CD5-/+, CD7-/+, CD3-/+, may be CD4+ or CD8+, CD56+/-; usually no rearranged TCR or Ig genes; often EBV positive

Enteropathy-type T-cell lymphoma: TdT-, CD3+, CD7+, CD4-, CD8+/-, CD103+ (mucosal lymphocyte antigen, such as detection by HML-1) (see gastrointestinal lymphoma protocol)

Hepatosplenic T-cell lymphoma: CD2+, CD3+, TCR gamma-delta+, TCRab-, CD5-, CD7+, CD4-, CD8-/+, CD56+/-, CD25-; TCR- gene rearrangements, variable TCR-gene rearrangements

Mycosis fungoides/Sézary syndrome: TdT-, PanT+ (CD2+, CD3+, CD5+, CD7-/+) , most cases CD4+/CD8-, CD25-/+, TCR gene rearrangements

Angioimmunoblastic T-cell lymphoma: TdT-, PanT+ (often with variable loss of some PanT antigens), usually CD4+; TCR gene rearrangements in 75%; IgH gene rearrangements in 10%, EBV often positive, but usually only in isolated neoplastic or reactive cells

Peripheral T-cell lymphomas, unspecified: TdT-, PanT variable (CD2+/-, CD3+/-, CD5+/-, CD7-/+) , most cases CD4+, some cases CD8+, CD4-/CD8-, or CD4+/CD8+; TCR gene rearrangements usual

Anaplastic large cell lymphoma: TdT-, CD30+, EMA+/-, PanT-/+, CD45+/-, CD25+/-, CD15-/+, CD68-, lysozyme-, BNH9+/-; primary cutaneous form is EMA- and cutaneous lymphocyte antigen+; TCR gene rearrangements > germline, 12-50% of adult cases show t(2;5) resulting in a fusion on NPM gene (5q35) with ALK gene (2q23)

F. Special Studies: Specimen Handling

Specimens for the diagnosis of lymphoma require special handling in order to optimize the histologic diagnosis and to prepare the tissue for performance of molecular and other special studies. The guidelines detailed below are suggested for specimen handling in cases of suspected lymphoma.

- Tissue should be received fresh. Unsectioned lymph nodes should not be immersed in fixative.
- The fresh specimen size, color and consistency should be recorded, as should the presence or absence of any visible nodularity, hemorrhage, or necrosis after serial sectioning at 2-mm intervals perpendicular to the long axis of a lymph node.
- Touch imprints may be made from the freshly cut surface, and the imprints fixed in alcohol or air dried.
- For cytogenetic studies or culture of microorganisms: submit a portion of the node sterilely in appropriate medium.
- Fixation (record fixative[s] used for individual slices of the specimen):
 - B5 produces superior cytologic detail but is not suitable for DNA extraction and may impair some immunostains (eg, CD30).

- Over-fixation (ie, more than 24 hours in formalin, more than 4 hours in B5) should be avoided.
- Snap-frozen tissue is optimal for some immunostains and for DNA and RNA extractions.
 - Cover tissue samples (cut to approximately 1x1x0.3 cm) in OCT.
 - Immerse in dry ice/isopentane slush or liquid nitrogen.
 - Store at -80°C until needed.

G. Stage

In general, the TNM classification has not been used for staging of lymphomas because the site of origin of the tumor is often unclear and there is no way to differentiate among T, N, and M. Thus, a special staging system (Ann Arbor System) is used for both Hodgkin lymphoma and NHL. The Ann Arbor classification for lymphomas has been applied to NHL by the American Joint Committee (AJCC) on Cancer and the International Union Against Cancer (UICC) (see below).^{30,31} For multiple myeloma, the Durie-Salmon staging system is recommended by the AJCC. Both staging systems are shown below.

Pathologic staging depends on biopsy or resection of one or more regional lymph nodes, splenectomy, wedge liver biopsy, bone marrow biopsy, and biopsy of multiple lymph nodes on both sides of the diaphragm to assess distribution of disease. Clinical staging generally involves a combination of clinical, radiologic, and surgical procedures and includes medical history, physical examination, laboratory tests (eg, complete blood examination, and blood chemistry studies), imaging studies (eg, computed tomography [CAT] scans, magnetic resonance imaging [MRI] studies, and nuclear medicine studies), biopsy to determine diagnosis, extent of disease, and histologic type of tumor (initial diagnosis is almost always made on biopsy), and often bone marrow biopsy. Most commonly, staging of NHL is clinical rather than pathologic.

There is almost universal agreement that the stage of NHL is prognostically significant.^{1-3,6,8,13,17,21}

AJCC/UICC Staging for Non-Hodgkin Lymphomas^{30,31}

- Stage I Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE)[#], ^{##}
- Stage II Involvement of 2 or more lymph node regions on the same side of the diaphragm (II), or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE)^{##} ^{###}
- Stage III Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen (IIIS) or both (IIIE+S)^{##}, ^{###}, [^]
- Stage IV Diffuse or disseminated involvement of 1 or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant

site(s). Any involvement of the liver or bone marrow, or nodular involvement of the lung(s).^{##,###,^}

Multifocal involvement of a single extralymphatic organ is classified as stage IE and not stage IV.

For all stages, tumor bulk greater than 10 to 15 cm is an unfavorable prognostic factor.³

The number of lymph node regions involved may be indicated by a subscript: eg, II₃. For stages II to IV, involvement of more than 2 sites is an unfavorable prognostic factor.³

^ For stages III to IV, a large mediastinal mass is an unfavorable prognostic factor.³

AJCC/UICC Staging for Plasma Cell Myeloma^{30,31}

Stage I	Hemoglobin greater than 10.0 g/dL Serum calcium 12 mg/dL or less Normal bone x-rays or a solitary bone lesion IgG less than 5 g/dL IgA less than 3 g/dL Urine M-protein less than 4 g/24 hours
Stage III	One or more of the following are included: Hemoglobin greater than 8.5 g/dL Serum calcium greater than 12 mg/dL Advanced lytic bone lesions IgG greater than 7 g/dL IgA greater than 5 g/dL Urine M-protein less than 12 g/24 hours
Stage II	Disease fitting neither stage I nor stage III

Note: Patients are further classified as (A) serum creatinine less than 2.0 mg/dL, or (B) serum creatinine 2.0 mg/dL or greater. The median survival for stage IA disease is about 5 years, and that for stage IIIB disease is 15 months.³⁰

H. Direct Spread into Adjacent Tissues or Organs

Direct spread of a lymphoma into adjacent tissues or organs does not influence classification of stage.

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