

Gastrointestinal Lymphoma

Protocol applies to Hodgkin and non-Hodgkin lymphomas of the gastrointestinal tract.

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

Procedures

- **Cytology** (No Accompanying Checklist)
- **Incisional Biopsy** (No Accompanying Checklist)
- **Resection**

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Surgical Pathology Cancer Case Summary (Checklist)

*Protocol revision date: January 2004
Applies to Hodgkin and non-Hodgkin lymphomas
of the gastrointestinal tract only
No AJCC/UICC TNM staging system*

GASTROINTESTINAL LYMPHOMA: Resection

Patient name:

Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC**Tumor Site(s)**

Specify, if known: _____

 Not specified***Tumor Size (largest single mass)**

*Greatest dimension: ___ cm

*Additional dimensions: ___ x ___ cm

* ___ Cannot be determined (see Comment)

MICROSCOPIC**Tumor**

Immunophenotyping

 Performed Not performed**Histologic Type (WHO Classification)**Hodgkin Lymphoma Nodular lymphocyte predominance Hodgkin lymphoma (NLPHL) Classical Hodgkin lymphoma (CHL) CHL, nodular sclerosis Hodgkin lymphoma (NSHL) CHL, mixed cellularity Hodgkin lymphoma (MCHL) CHL, lymphocyte-rich classical Hodgkin lymphoma (LRCHL) CHL, lymphocyte depletion Hodgkin lymphoma (LDHL)

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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.

Non-Hodgkin Lymphoma Histologic type cannot be assessed*B-cell lymphoma* B-cell lymphoma, subtype cannot be determined Precursor B-lymphoblastic lymphoma/leukemia Mature B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma B-cell prolymphocytic leukemia Lymphoplasmacytic lymphoma Hairy cell leukemia Plasma cell myeloma/ Plasmacytoma Extranodal marginal zone B-cell lymphoma of MALT type Follicular lymphoma , grade 1 (0 to 5 centroblasts per HPF) Follicular lymphoma , grade 2 (6 to 15 centroblasts per HPF) Follicular lymphoma , grade 3 (greater than 15 centroblasts per HPF) Follicular lymphoma , cutaneous follicle center lymphoma Follicular lymphoma , diffuse follicle center cell lymphoma Mantle cell lymphoma Diffuse large B-cell lymphoma Burkitt lymphoma/ Burkitt cell leukemia Other (specify): _____*T-cell Lymphoma* T-cell lymphoma, subtype cannot be determined Precursor T-lymphoblastic lymphoma/leukemia T-cell prolymphocytic leukemia T-cell granular lymphocytic leukemia Aggressive NK-cell leukemia Adult T-cell lymphoma/leukemia (HTLV1+) Enteropathy-type T-cell lymphoma Anaplastic large cell lymphoma Peripheral T-cell lymphoma, not otherwise characterized Angioimmunoblastic T-cell lymphoma Other (specify): _____**Extent of Involvement** Cannot be assessed Confined to mucosa/submucosa Involvement of muscular wall/subserosa Penetration of serosa, perforation present Penetration of serosa, perforation absent Direct extension to other organ(s) or structure(s)

(specify): _____

 Noncontiguous tumor involvement of other organ(s) or structure(s) absent Noncontiguous tumor involvement of other organ(s) or structure(s) present

(specify site[s]): _____

* 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.

Margins (check all that apply)

- Cannot be assessed
- Uninvolved by lymphoma
- Proximal margin involved by lymphoma
- Distal margin involved by lymphoma
- Circumferential (radial or mesenteric) margin involved by lymphoma

Regional Lymph Nodes

- Cannot be assessed
- No regional lymph node involvement
- Regional lymph node involvement

Specify: Number examined: ____
 Number involved: ____

Nonregional Lymph Nodes

- Cannot be assessed
- No nonregional lymph node involvement
 Number present in specimen: ____
- Nonregional lymph node involvement
 Number present in specimen: ____
 Number involved: ____

***Additional Pathologic Findings (check all that apply)**

- * None identified
- * *Helicobacter pylori* gastritis
- * Celiac disease (sprue)
- * Inflammatory bowel disease
- * Other (specify): _____

***Comment(s)**

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.

Background Documentation

Protocol revision date: January 2004

I. Cytologic Material

A. Clinical Information

1. Patient identification
 - a. Name
 - b. Identification number
 - c. Age (birth date)
 - d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
 - a. Relevant history
 - (1) *Helicobacter pylori* gastritis
 - (2) gluten enteropathy (celiac disease)
 - (3) inflammatory bowel disease
 - (4) heavy chain disease
 - (5) AIDS
 - (6) previous diagnosis and treatment for lymphoma
 - (7) prior solid organ or bone marrow transplantation
 - b. Relevant findings (eg, endoscopic and/or imaging studies)
 - c. Clinical diagnosis
 - d. Procedure (eg, brushing, washing, other)
 - e. Operative findings
 - f. Anatomic site(s) of specimen(s)

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, smear of fluid, cell block)
3. Special studies (specify) (eg, flow cytometry for immunophenotyping, cytochemistry, immunocytochemistry, cytogenetic analysis)

C. Microscopic Examination

1. Adequacy of specimen (if unsatisfactory for evaluation, specify reason)
2. Tumor, if present
 - a. Histologic type, if possible (Note **A**)
 - b. Other characteristics (eg, nuclear grade, necrosis)
3. Additional pathologic findings, if present (specify)
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. Incisional Biopsy (Endoscopic or Other)

A. Clinical Information

1. Patient identification
 - a. Name
 - b. Identification number
 - c. Age (birth date)
 - d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
 - a. Relevant history
 - (1) *Helicobacter pylori* gastritis
 - (2) gluten enteropathy (celiac disease)
 - (3) inflammatory bowel disease
 - (4) heavy chain disease
 - (5) AIDS
 - (6) previous diagnosis and treatment for lymphoma
 - b. Relevant findings (eg, endoscopic and/or imaging studies)
 - c. Clinical diagnosis
 - d. Procedure (eg, endoscopic biopsy)
 - e. Operative findings
 - f. Anatomic site(s) of specimen(s)

B. Macroscopic Examination

1. Specimen
 - a. Fixed/unfixed (specify fixative) (Note: Fresh frozen tissue should be saved, if possible, for immunophenotyping and molecular genetic studies)
 - b. Orientation
 - c. Number of pieces
 - d. Dimensions
 - e. Obstruction
 - f. Description of other tissues, as appropriate
 - g. Results of intraoperative consultation
2. Submit all nonfrozen tissue for microscopic evaluation
3. Special studies (specify) (eg, flow cytometry for immunophenotyping, histochemistry, immunohistochemistry, cytogenetic analysis)

C. Microscopic Evaluation

1. Tumor
 - a. Histologic type (Note **A**)
 - b. Histologic grade
 - c. Extent of invasion
2. Additional pathologic findings, if present
3. Results/status of special studies (specify)
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 Stomach, Small Intestine, Colon, Rectum**A. Clinical Information**

1. Patient identification
 - a. Name
 - b. Identification number
 - c. Age (birth date)
 - d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
 - a. Relevant history
 - (1) *Helicobacter pylori* gastritis
 - (2) gluten enteropathy (celiac disease)
 - (3) inflammatory bowel disease
 - (4) heavy chain disease
 - (5) AIDS
 - (6) previous diagnosis and treatment for lymphoma
 - b. Relevant findings (eg, endoscopic and/or imaging studies)
 - c. Clinical diagnosis
 - d. Procedure (eg, partial gastrectomy, total gastrectomy, ileal resection)
 - e. Operative findings
 - f. Anatomic site(s) of specimen(s)

B. Macroscopic Examination

1. Specimen
 - a. Organ(s)/tissue(s) (specify)
 - b. Unfixed/fixed (specify fixative) (Note: Fresh frozen tissue should be saved, if possible, 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
 - b. Location
 - c. Configuration
 - d. Dimensions (Note **B**)
 - e. Descriptive characteristics (eg, color, consistency)
 - f. Ulceration/perforation
 - g. Estimated extent of invasion
 - h. Penetration of serosa (Note **C**)
 - i. Distance from margins (Note **D**)
 - (1) proximal
 - (2) distal
 - (3) radial (soft tissue or mesenteric margin closest to deepest tumor penetration)
 - j. Direct extension to other organ(s) or structure(s) (Note **E**)
 - k. Noncontiguous tumor involvement of other organ(s) or structure(s) (Note **E**)
3. Additional pathologic findings, if present
4. Regional lymph nodes (Note **F**)

5. Tissues submitted for microscopic evaluation
 - a. Lymphoma, representative sections, including:
 - (1) point of deepest penetration
 - (2) interface with adjacent mucosa
 - (3) visceral serosa overlying tumor
 - (4) soft tissue or mesenteric margin closest to deepest tumor penetration (radial margin) (Note **D**)
 - b. Proximal and distal resection margins
 - c. Regional lymph nodes
 - d. Other specific nodes, when marked by surgeon
 - e. Other lesions (eg, polyps, ulcers)
 - f. Section(s) of viscus uninvolved by tumor
 - g. Other tissue(s)/organ(s)
6. Special studies (specify) (eg, flow cytometry for immunophenotyping, histochemistry, immunohistochemistry, cytogenetic analysis)

C. Microscopic Evaluation

1. Tumor
 - a. Histologic type (Note **A**)
 - b. Histologic grade
 - c. Extent of invasion
 - d. Penetration of serosa (Note **C**)
 - e. Margins (Note **D**)
 - f. Direct extension to other organ(s) or structure(s) (Note **E**)
2. Regional lymph nodes (Note **F**)
 - a. Number
 - b. Number involved by tumor (Note **G**)
3. Extraregional lymph nodes
 - a. Number
 - b. Number involved by tumor (Note **G**)
4. Other tissues submitted (if distant involvement by lymphoma, specify site) (Note **G**)
5. Additional pathologic findings, if present
 - a. Chronic gastritis with or without *Helicobacter pylori* infection
 - b. Celiac disease
 - c. Inflammatory bowel disease
 - d. Lymphoid hyperplasia
6. Results/status of special studies
7. 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. Histologic Type

Hodgkin Lymphoma

Hodgkin lymphoma is traditionally categorized histologically by the Rye Classification, which recognizes 4 major histologic types. The current classification has been revised

by the World Health Organization (WHO)^{1,2} and is recommended by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC).^{3,4}

WHO Classification of Hodgkin Lymphoma³

Nodular lymphocyte predominance Hodgkin lymphoma (NLPHL)

Classical Hodgkin lymphoma (CHL)

 Nodular sclerosis Hodgkin lymphoma (Grades 1 and 2) (NSHL)

 Mixed cellularity Hodgkin lymphoma (MCHL)

 Lymphocyte-rich classical Hodgkin lymphoma (LRCHL)

 Lymphocyte depletion Hodgkin lymphoma (LDHL)

Histologic classification is based on paraffin-embedded, hematoxylin and eosin-stained sections. The histologic types should be recorded because they may have prognostic significance, but, overall, prognosis appears to be determined more strongly by the stage of disease than the histologic subtype. Primary Hodgkin lymphoma of the gastrointestinal tract is exceptionally rare. Immunophenotyping and, if necessary, genetic studies (ie, gene rearrangement) should be performed to confirm the diagnosis and to exclude non-Hodgkin lymphoma.

Non-Hodgkin Lymphoma

Controversy currently exists as to whether the spectrum of lymphomas found in the gut can be adequately accommodated within the conventional classifications (see below), or whether a site-specific classification of gastrointestinal lymphomas is needed. In contrast to nodal lymphomas, many lymphomas of the gastrointestinal tract are derived from mucosa-associated lymphoid tissue (MALT), which they resemble histologically. In further contrast to nodal lymphomas, they tend to be localized at the time of diagnosis and may be effectively treated with local therapy. MALT-derived lymphomas are sometimes referred to by the unscientific and imprecise term of “MALToma.” Some of these tumors have unique etiologic associations (eg, marginal zone lymphoma of MALT type of the stomach and infection by *Helicobacter pylori*). Unique etiologic associations also exist between gluten enteropathy and primary T-cell lymphomas of the gastrointestinal tract. In addition, nodal-type lymphomas (eg, Burkitt, mantle cell, follicular lymphomas) may also present in the gastrointestinal tract.

The protocol recommends the most recent World Health Organization (WHO) classification of non-Hodgkin lymphoma,^{1,2} which incorporates the B-cell lymphomas of the MALT type and the enteropathy-associated T-cell lymphomas as well as other types of gastrointestinal lymphomas with unique clinical associations. The WHO classification encompasses both nodal and extranodal lymphomas and outlines the immunobiologic features of the defined entities that aid in the diagnosis.^{1,2,5,6} These concepts have also been incorporated into the classification of primary gastrointestinal lymphoma proposed by Isaacson.⁷ Both of these classifications are shown below in modified form.

Prognostic information necessary to determine treatment of gastrointestinal lymphomas is provided by the histologic type. Further sorting of these diseases into broad histologic grades or clinical prognostic groups provides little additional useful information.

WHO Classification of Non-Hodgkin LymphomaB-Cell Neoplasms

Precursor B-lymphoblastic lymphoma/leukemia

Mature B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma

Variant: with plasmacytoid differentiation or monoclonal gammopathy

B-cell prolymphocytic leukemia

Lymphoplasmacytic lymphoma

Hairy cell leukemia

Plasma cell myeloma / plasmacytoma

Extranodal marginal zone B-cell lymphoma of MALT type[#]

Follicular lymphoma

Grading:

Grade 1: 0-5 centroblasts per high power field

Grade 2: 6-15 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

Mantle cell lymphoma^{##}Diffuse large B-cell lymphoma^{###}

Morphologic variants:

Centroblastic

Immunoblastic

Anaplastic large B-cell

T-cell/histiocyte-rich

Plasmablastic

Lymphomatoid granulomatosis-type

Burkitt lymphoma/Burkitt cell leukemia[^]

Morphologic variants:

Classical

Burkitt-like

With plasmacytoid differentiation (AIDS-associated)

T-Cell Neoplasms

Precursor T-cell Neoplasm

Precursor T-lymphoblastic lymphoma/leukemia

Mature (peripheral) T-cell neoplasms

T-cell prolymphocytic leukemia

Morphologic variants:

Small cell

Cerebriform cell

T-cell granular lymphocytic leukemia

Aggressive NK-cell leukemia

Adult T-cell lymphoma/leukemia (HTLV1+)

Clinical variants:

Acute

Lymphomatous

Chronic

Smoldering

Hodgkin-like

Enteropathy-type T-cell lymphoma^^

Peripheral T-cell lymphoma, not otherwise characterized

Morphologic variants: lymphoepithelial (Lennert's), T-zone

Angioimmunoblastic T-cell lymphoma

Extranodal marginal zone B-cell lymphoma of MALT type. Typical immunophenotype: slg+ (IgM or IgA or IgG), slgD-, clg-/+, Pan B+, CD5-, CD10-, CD23-, CD43-/+, CD79a+, cyclin D1-, bcl2+. Genetics: IgH and IgL genes rearranged; BCL1 and BCL2 germline; Trisomy 3 or t(11;18)(q21;q21) may be seen.

Primary gastrointestinal mantle cell lymphoma is associated with a growth pattern of lymphomatous polyposis. Typical immunophenotype: slgM+, slgD+, lambda>kappa, Pan B+, cyclin D1+, CD5+, CD10-/+, CD23-, CD43+, CD11c-, CD25-, bcl2+, bcl6-, ill-defined loose or expanded follicular dendritic cell meshworks in 80%. Genetics: IgH and IgL genes rearranged: t(11;14); rearranged BCL1 gene (CCND1/cyclin D1/PRAD1) common.

Diffuse large B-cell lymphoma. Extranodal occurrence (eg, gastrointestinal tract) in 40% of cases overall. Typical immunophenotype: slg+/-, clg+, Pan B+, CD19+, CD20+, CD22+, CD30+/-, CD45+/-, CD5-/+, CD10-/+(weak), cyclin D1-, bcl2-/+, bcl6+, CD138-. Genetics: IgH and IgL genes rearranged: BCL2 gene rearranged in 30%; BCL6/LAZ3 gene (chromosome 3q27) rearranged in 30%, rearranged c-myc gene uncommon. About 25% of gastric large B-cell lymphomas have associated low-grade MALToma.

^ Burkitt lymphoma/Burkitt cell leukemia. Typical immunophenotype: slgM+, pan B+, CD5-, CD10+(strong), CD21-/+, CD23-, CD34-, bcl2-, bcl6+, TdT-, Ki-67 high. Genetics: IgH and IgL genes rearranged; t(8;14) and variations including t(2;8) and t(8;22); rearranged c-myc gene. EBV common (95%) in endemic cases, infrequent (15% to 20%) in sporadic cases, intermediate occurrence (30% to 40%) in HIV-positive cases.

^^ Enteropathy-type T-cell lymphoma. Typical immunophenotype: TdT-, CD2+, CD3+, CD5-, CD7+, CD4-, CD8+/-, CD30+, CD103+ (mucosal lymphocyte antigen as detected by HML-1). Genetics: TCR genes rearranged.

Histological Classification of Primary Gastrointestinal Lymphoma

B-Cell

MALT type

Low-grade#

High-grade with or without a low-grade component#

Immunoproliferative small intestinal disease (IPSID)

Low-grade

High-grade with or without a low-grade component

Mantle cell (lymphomatous polyposis)

Burkitt and Burkitt-like

Other types of low- or high-grade lymphoma corresponding to lymph node equivalents

T-Cell

Enteropathy-associated T-cell lymphoma (EATL)

Other types unassociated with enteropathy

Rare Types

(Including conditions that may simulate lymphoma such as histiocytic neoplasms and granulocytic sarcoma)

Equivalent entity within the WHO classification (see above): extranodal marginal zone B-cell lymphoma of MALT type. The term MALT lymphoma (“MALToma”) is discouraged but, if used, should be restricted to histologically low-grade extranodal marginal zone B-cell lymphoma of MALT type. High-grade B-cell lymphoma of the gastrointestinal tract should be referred to as diffuse-B large- cell lymphoma (with or without a residual low-grade component).

B. Tumor Dimensions

The largest tumor dimension has been shown to have independent prognostic significance, with size less than 5 cm constituting a favorable prognostic factor.⁸⁻¹⁰

C. Serosal Penetration by Tumor

The serosal penetration by tumor has been shown to be an adverse prognostic factor.¹¹⁻¹⁴

D. Resection Margins

Includes the proximal, distal, and radial margins. The radial margin represents the nonperitoneal soft tissue or mesenteric margin closest to the deepest penetration of tumor.

Although controversial, involvement of surgical margins by tumor may correlate with decreased survival.^{9,15} In some institutions, adjuvant radiation and/or chemotherapy may be used in those cases in which tumor is found to be present at the surgical resection margins.^{9,16}

In low-grade gastric extranodal marginal zone B-cell lymphomas of MALT type, small foci of lymphoma consisting of 1 to 4 lymphoid follicles surrounded by neoplastic marginal zone B-cells may be found throughout the gastric mucosa at various distances from the main confluent tumor mass and from each other.¹⁷ This phenomenon may contribute to local relapse within the gastric stump in cases in which the resection margins are negative by microscopic examination.

E. Involvement of Adjacent Structures by Tumor

Direct penetration of adjacent structures by tumor has been shown to have independent adverse prognostic significance.⁹

F. Regional Lymph Nodes by Site

Stomach: perigastric nodes along the lesser and greater curvature, nodes located along the left gastric, common hepatic, splenic, and celiac arteries.

Duodenum: duodenal, hepatic, pancreaticoduodenal, infrapyloric, gastroduodenal, ampulla of Vater, pyloric, cystic, superior mesenteric, hilar, pericholedochal.

Jejunum/Ileum: superior mesenteric, mesenteric, posterior cecal (terminal ileum only), ileocolic (terminal ileum only).

Large Intestine:

Cecum and appendix — anterior cecal, posterior cecal, ileocolic, right colic

Ascending colon — ileocolic, right colic, middle colic

Hepatic flexure — middle colic, right colic

Transverse colon — middle colic

Splenic flexure — middle colic, left colic, inferior mesenteric

Descending colon — left colic, inferior mesenteric, sigmoid

Sigmoid colon — inferior mesenteric, superior rectal sigmoidal, sigmoid mesenteric

Rectosigmoid — perirectal, left colic, sigmoid mesenteric, sigmoidal, inferior mesenteric, superior rectal, middle rectal

Rectum — perirectal, sigmoid mesenteric, inferior mesenteric, lateral sacral, presacral, internal iliac, sacral promontory, superior rectal, middle rectal, inferior rectal

G. Stage

In general, the TNM classification has not been used for staging the malignant lymphomas because the site of origin of the tumor is often unclear and there is no way to differentiate among T, N, and M category. Thus, a special staging system (Ann Arbor System) is used for both Hodgkin lymphoma and non-Hodgkin lymphoma. The Ann Arbor classification for lymphomas has been applied to extranodal lymphomas by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) (see below)^{3,4,18} The Ann Arbor System has also been modified specifically for primary gastrointestinal lymphomas by Musshoff.¹⁹ Both systems are shown below.

Pathologic staging depends on biopsy or resection of the primary mucosal site, biopsy or resection of 1 or more regional lymph nodes, splenectomy, wedge liver biopsy, bone marrow biopsy, and 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, progressing sequentially from less invasive to more invasive, and includes medical history, physical examination, laboratory tests (eg, urinalysis, complete venous examination, and venous chemistry studies), imaging studies (eg, CAT scans, GI series) and biopsy to determine diagnosis and histologic type of tumor (initial diagnosis is almost always made on biopsy).

There is almost universal agreement that staging of gastrointestinal lymphoma is prognostically significant.^{8,9,11-15,20-23}

Staging for Primary Extralymphatic Lymphomas

Stage I Localized involvement of a single extralymphatic organ or site (IE)*

Stage II Localized involvement of a single extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm (IIE) #, ##

Stage III Localized involvement of a single extralymphatic organ or site with involvement of lymph node regions on both sides of the diaphragm (IIIE) or involvement of the spleen (IIIS) or both (IIIE+S) #, ##

Stage IV Disseminated (multifocal) involvement of 1 or more extralymphatic organs with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement^{#,##}

[#] Direct spread of a lymphoma into adjacent tissues or organs does not influence stage. Multifocal involvement of a single extralymphatic organ is classified as stage IE and not stage IV. Involvement of 2 or more segments of the gastrointestinal tract, isolated and not in continuity, is classified as stage IV (disseminated involvement of 1 or more extralymphatic organs).

^{##} The definitions of regional lymph nodes for individual sites of extranodal lymphomas are identical to the definitions of regional lymph nodes for individual sites of gastrointestinal carcinomas. For example, the regional lymph nodes for a primary gastric lymphoma are the perigastric nodes along the lesser and greater curvatures and the nodes located along the left gastric, common hepatic, splenic, and celiac arteries.

Modified Ann Arbor Staging System for Gastrointestinal Lymphoma^{3,19}

Stage I Tumor confined to the gastrointestinal tract (IE)[#]
 Stage II Tumor with spread to regional lymph nodes (IIE1) or tumor with nodal involvement beyond regional lymph nodes (IIE2)^{#,##}
 Stage III Tumor with spread to other organs within the abdomen (liver, spleen) or beyond the abdomen (chest, bone marrow)^{#,##}

[#] Direct spread of a lymphoma into adjacent tissues or organs does not influence stage. Multifocal involvement of a single extralymphatic organ is classified as stage IE and not stage IV. Involvement of 2 or more segments of the gastrointestinal tract, isolated and not in continuity, is classified as stage IV (disseminated involvement of 1 or more extralymphatic organs).

^{##} The definitions of regional lymph nodes for individual sites of extranodal lymphomas are identical to the definitions of regional lymph nodes for individual sites of gastrointestinal carcinomas. For example, the regional lymph nodes for a primary gastric lymphoma are the perigastric nodes along the lesser and greater curvatures and the nodes located along the left gastric, common hepatic, splenic, and celiac arteries.

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