COLLEGE of AMERICAN PATHOLOGISTS

Protocol for the Examination of Specimens From Patients With Carcinoma of the Esophagus

Protocol applies to all carcinomas of the esophagus, including esophagogastric junction carcinomas. Well-differentiated neuroendocrine tumors (carcinoid tumors) are not included.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: January 2016

Procedures

- Endoscopic Resection
- Esophagectomy
- Esophagogastrectomy

Authors

Kay Washington, MD, PhD*
Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, TN
Jordan Berlin, MD
Department of Medicine, Vanderbilt University Medical Center, Nashville, TN
Philip Branton, MD
Department of Pathology, Inova Fairfax Hospital, Falls Church, VA
Lawrence J. Burgart, MD
Allina Laboratories, Abbott Northwestern Hospital, Minneapolis, MN
David K. Carter, MD
Department of Pathology, St. Mary's/Duluth Clinic Health System, Duluth, MN
Patrick Fitzgibbons, MD
Department of Pathology, St. Jude Medical Center, Fullerton, CA
Wendy L. Frankel, MD
Department of Pathology, Ohio State University Medical Center, Columbus, OH
John Jessup, MD
Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD
Sanjay Kakar, MD
Department of Pathology, University of California San Francisco and the Veterans Affairs Medical Center, San Francisco, CA
Bruce Minsky, MD
Department of Radiation Oncology, University of Chicago, Chicago, IL
Raouf Nakhleh, MD
Department of Pathology, Mayo Clinic, Jacksonville, FL
Chanjuan Shi, MD, PhD
Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, TN
Laura H. Tang, MD, PhD
Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY
Carolyn C. Compton, MD, PhD†
Critical Path Institute, Tucson, AZ
For the Members of the Cancer Committee, College of American Pathologists

* Denotes primary author. † Denotes senior author. All other contributing authors are listed alphabetically.

Previous contributors: Randall G. Lee, MD; Leslie H. Sobin, MD; Donald Antonioli, MD; Harvey Goldman, MD; Rodger C. Haggitt, MD; Robert V. P. Hutter, MD; Klaus Lewin, MD; Pablo Ross, MD; Heidrun Rotterdam, MD; Stuart Spechler, MD; Christopher Willett, MD; Donald E. Henson, MD

The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the “Surgical Pathology Cancer Case Summary” portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the required data elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

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CAP Esophagus Protocol Revision History

Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: Esophagus 3.2.0.0

Summary of Changes
The following changes have been made since the October 2013 release.

The following data elements have been modified:

- Histologic Type
- Margins: Distal Margin
- Treatment Effect
- Lymph-Vascular Invasion
- Perineural Invasion
- Distant Metastasis (changed to required only if confirmed pathologically)
- Ancillary Studies (added note)

The following data element was added:

- Margins: Mucosal Margin

Surgical Pathology Cancer Case Summary

Protocol web posting date: January 2016

ESOPHAGUS: Endoscopic Resection, Esophagectomy, or Esophagogastrectomy (Note A)

Select a single response unless otherwise indicated.

Specimen (select all that apply)
___ Esophagus
___ Proximal stomach
___ Other (specify): _____
___ Not specified

Procedure
___ Endoscopic resection
___ Esophagectomy
___ Esophagogastrectomy
___ Other (specify): _____
___ Not specified

Tumor Site (select all that apply) (Note B)
___ Cervical (proximal) esophagus
___ Midesophagus
+ ___ Upper thoracic esophagus
+ ___ Midthoracic esophagus
___ Distal esophagus (lower thoracic esophagus)
___ Esophagogastric junction (EGJ)
___ Proximal stomach and esophagogastric junction
___ Other (specify): _____
___ Not specified

Relationship of Tumor to Esophagogastric Junction (Note B)
___ Tumor is entirely located within the tubular esophagus and does not involve the esophagogastric junction
___ Tumor midpoint lies in the distal esophagus *and* tumor involves the esophagogastric junction
___ Tumor midpoint is located at the esophagogastric junction
___ Tumor midpoint lies in the proximal stomach or cardia *and* tumor involves the esophagogastric junction
___ Not specified
___ Cannot be assessed

Distance of tumor center from esophagogastric junction (specify, if applicable): ___ cm

Tumor Size
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (explain): _____

Histologic Type (select all that apply) (Note C)
___ Adenocarcinoma
___ Squamous cell carcinoma
___ Adenosquamous carcinoma
___ High-grade neuroendocrine carcinoma
    ___ Large cell neuroendocrine carcinoma
    ___ Small cell neuroendocrine carcinoma
___ Undifferentiated carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined

Histologic Grade (Note D)
___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ G4: Undifferentiated

Microscopic Tumor Extension (Note E)
___ Cannot be assessed
___ No evidence of primary tumor
___ High-grade dysplasia (carcinoma in situ)
___ Tumor invades lamina propria
___ Tumor invades muscularis mucosae
___ Tumor invades submucosa
___ Tumor invades muscularis propria
___ Tumor invades through the muscularis propria into the periesophageal soft tissue (adventitia)
___ Tumor directly invades adjacent structures (specify): _____

Margins (select all that apply) (Note F)

If all margins uninvolved by invasive carcinoma:
Distance of invasive carcinoma from closest margin: ___ mm *or* ___ cm
    Specify margin: _____

<u>Proximal Margin</u>
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma
___ Uninvolved by dysplasia
___ Involved by dysplasia
    ___ Squamous dysplasia
        ___ Low grade
        ___ High grade
    ___ Intestinal metaplasia (Barrett's esophagus) with dysplasia
        ___ Low grade
        ___ High grade
___ Involved by intestinal metaplasia (Barrett's esophagus) without dysplasia

Distal Margin
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma
___ Uninvolved by dysplasia
___ Involved by dysplasia
    ___ Squamous dysplasia
        ___ Low grade
        ___ High grade
    ___ Intestinal metaplasia (Barrett's esophagus) with dysplasia
        ___ Low grade
        ___ High grade
___ Involved by intestinal metaplasia (Barrett's esophagus) without dysplasia

Circumferential (Adventitial) Margin (esophagectomy or esophagogastrectomy specimens) or
Deep Margin (endoscopic resection specimens)
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma

Mucosal Margin (endoscopic resection specimens)
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
    +Distance of invasive carcinoma from closest mucosal margin: ___ mm *or* ___ cm
___ Involved by invasive carcinoma
___ Uninvolved by dysplasia
___ Involved by dysplasia
    ___ Squamous dysplasia
        ___ Low grade
        ___ High grade
    ___ Intestinal metaplasia (Barrett's esophagus) with dysplasia
        ___ Low grade
        ___ High grade
___ Involved by intestinal metaplasia (Barrett's esophagus) without dysplasia

Other Margin(s) (required only if applicable)
Specify margin(s): _____
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma

Treatment Effect (applicable to carcinomas treated with neoadjuvant therapy) (select all that apply) (Note G)
___ No prior treatment
___ Present
    + ___ No viable cancer cells (complete response, score 0)
    + ___ Single cells or rare small groups of cancer cells (near complete response, score 1)
    + ___ Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response, score 2)
___ Extensive residual cancer with no evident tumor regression (poor or no response, score 3)
___ Treatment history not known

Lymph-Vascular Invasion
___ Not identified
___ Present
___ Cannot be determined

+ Perineural Invasion
+ ___ Not identified
+ ___ Present
+ ___ Cannot be determined

Pathologic Staging (pTNM) (Note H)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: High-grade dysplasia
___ pT1: Tumor invades lamina propria, muscularis mucosae, or submucosa
___ pT1a: Tumor invades lamina propria or muscularis mucosae
___ pT1b: Tumor invades submucosa
___ pT2: Tumor invades muscularis propria
___ pT3: Tumor invades adventitia
___ pT4: Tumor invades adjacent structures (specify): _____
___ pT4a: Resectable tumor invading pleura, pericardium, or diaphragm
___ pT4b: Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc

Regional Lymph Nodes (pN) (Note I)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis involving 1 to 2 nodes
___ pN2: 3 to 6 nodes involved
___ pN3: 7 or more nodes involved

___ No nodes submitted or found

Number of Lymph Nodes Examined
Specify: ____
___ Number cannot be determined (explain): _____

Number of Lymph Nodes Involved
Specify: ____
___ Number cannot be determined (explain): _____

Distant Metastasis (pM) (required only if confirmed pathologically in this case)
___ pM1: Distant metastasis
Specify site(s), if known: _____

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Additional Pathologic Findings (select all that apply) (Note J)
___ None identified
___ Intestinal metaplasia (Barrett's esophagus)
___ Dysplasia
    ___ Low grade
    ___ High grade
+ ___ Esophagitis (type): _____
+ ___ Gastritis (type): _____
+ ___ Other (specify): _____

+ Ancillary Studies

Note: For HER2 reporting, the CAP Gastric HER2 template should be used. Pending biomarker studies should be listed in the Comments section of this report.

+ Specify: _____

+ Clinical History (select all that apply) (Note J)
+ ___ Barrett's esophagus
+ ___ Other (specify): _____
+ ___ Not known

+ Comment(s)

Explanatory Notes

A. Application

This protocol applies to all carcinomas arising in the esophagus and to carcinomas involving the esophagogastric junction (EGJ), including tumors that cross the EGJ but are predominantly located in the proximal stomach. Lymphomas, well-differentiated neuroendocrine tumors (carcinoid tumors), and sarcomas are not included (separate TNM staging systems[1] and CAP protocols apply).

B. Location

The location of the tumor in the esophagus (cervical, upper thoracic, midthoracic, lower thoracic, abdominal) and with respect to the macroscopic EGJ (defined as where the tubular esophagus meets the stomach, as measured from the top of the gastric folds) should be noted whenever possible (Figure 1). The macroscopic EGJ often does not correspond to the junction of esophageal squamous mucosa and columnar mucosa because of the common finding in esophageal resection specimens of glandular mucosa involving the distal esophagus. Because anatomic divisions of the esophagus are defined by anatomic boundaries and relationships to other structures,[1] it may not be possible for the pathologist to determine exact tumor location from the resection specimen.

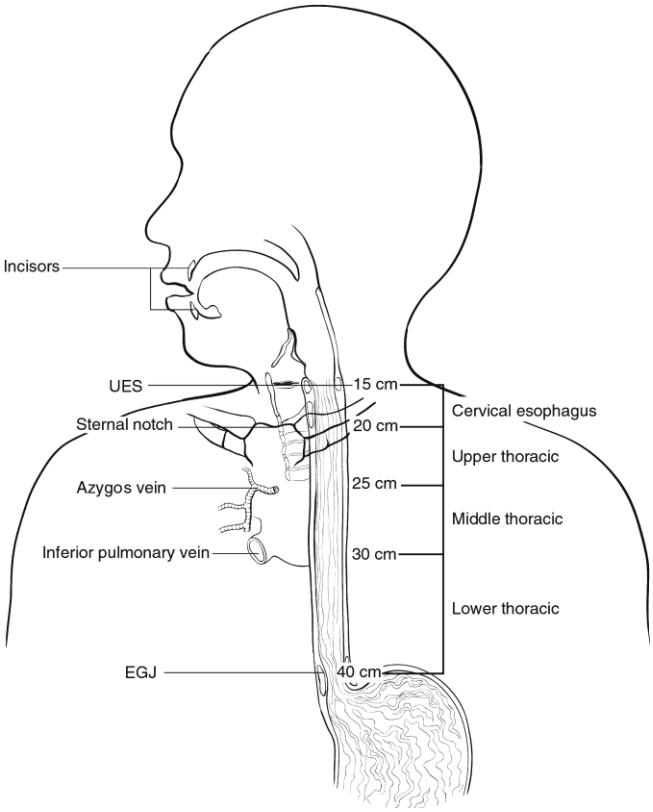

Figure 1. Anatomic subdivisions of the esophagus. From Edge et al.[1] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, 7th edition (2009) published by Springer Science and Business Media LLC, www.springerlink.com.

For tumors involving the esophagogastric junction, specific observations should be recorded in an attempt to establish the exact site of origin of the tumor. The EGJ is defined as the junction of the tubular esophagus and the stomach, irrespective of the type of epithelial lining of the esophagus. The pathologist should record the maximum longitudinal dimension of the tumor mass, the distance of the tumor midpoint from the EGJ, and the relative proportions of the tumor mass located in the esophagus and in the stomach.

Tumors involving the EGJ are classified for purposes of staging as esophageal carcinomas.[1] Although the nature of these tumors (gastric versus esophageal) has been controversial[2,3] (reviewed by Carneiro and Chaves[4]), recent data support their classification as esophageal carcinomas.[1] The World Health Organization (WHO) defines esophageal tumors are those located entirely above the EGJ and proximal gastric tumors as those located entirely below the EGJ.[5] Tumors crossing the EGJ are classified as EGJ tumors. An alternative system proposed by Siewart and colleagues divides adenocarcinomas involving the EGJ into 3 categories, based upon location of the midpoint of the tumor[6]:

Type I: Adenocarcinoma of the distal esophagus, with or without infiltration of the EGJ from above
Type II: True carcinoma of the gastric cardia, arising from the cardiac epithelium or short segments with intestinal metaplasia at the EGJ
Type III: Subcardial gastric carcinoma, which infiltrates the EGJ and distal esophagus from below

Application of the Siewart system is complicated by lack of consensus as to the definition and nature of the gastric cardia, with some investigators regarding it as a normal anatomic finding,[7] and others as a metaplastic response to injury from esophagogastric reflux.[2,4]

C. Histologic Type
For consistency in reporting, the histologic classification proposed by the WHO is recommended.[5] However, this protocol does not preclude the use of other systems of classification or histologic types.

Worldwide, squamous cell carcinoma continues to predominant as the most common histologic type, but numerous population-based studies document the increasing incidence of adenocarcinoma of the esophagus and EGJ in Western countries.[8] More than 50% of esophageal carcinomas diagnosed in the United States since 1900 are adenocarcinomas. Other subtypes, such as adenoid cystic carcinoma and mucoepidermoid carcinoma, which resemble their counterparts arising in salivary gland, are rarely encountered.

The revised TNM staging system for esophageal carcinomas incorporates tumor grade and histologic type in the stage groupings (see Note H). Mixed histologic types, such as adenosquamous carcinomas, are staged using the squamous cell carcinoma stage grouping.[1]

WHO Classification of Carcinoma of the Esophagus
Squamous cell carcinoma
Verrucous (squamous) carcinoma
Spindle cell (squamous) carcinoma
Adenocarcinoma
Adenosquamous carcinoma
Mucoepidermoid carcinoma[#]
Adenoid cystic carcinoma[#]
High-grade neuroendocrine carcinoma
    Large cell neuroendocrine carcinoma[#]
    Small cell neuroendocrine carcinoma[#]
Undifferentiated carcinoma[#]
Others

[#]These types are not generally graded.

The term *carcinoma, NOS (not otherwise specified)* is not part of the WHO classification.

D. Histologic Grade
The histologic grades for esophageal squamous cell carcinomas are as follows:

Grade X Grade cannot be assessed
Grade 1 Well differentiated
Grade 2 Moderately differentiated

Grade 3 Poorly differentiated

If there are variations in the differentiation within the tumor, the highest (least favorable) grade is recorded. In general, mucoepidermoid carcinoma and adenoid cystic carcinoma of the esophagus are not amenable to grading.

For adenocarcinomas, a suggested grading system based on the proportion of the tumor that is composed of glands is as follows:

Grade X Grade cannot be assessed
Grade 1 Well differentiated (greater than 95% of tumor composed of glands)
Grade 2 Moderately differentiated (50% to 95% of tumor composed of glands)
Grade 3 Poorly differentiated (49% or less of tumor composed of glands)

Undifferentiated tumors cannot be categorized as squamous cell carcinoma or adenocarcinoma (or other) type. They are classified as "undifferentiated carcinomas" in the WHO classification of tumor types (see above) and may be assigned grade 4. Small cell carcinomas are not typically graded but are high-grade tumors and would correspond to grade 4.

The revised TNM staging system for esophageal carcinomas incorporates tumor grade and histologic type in the stage groupings (see Note H). For purposes of staging, grade 4 carcinomas (undifferentiated carcinomas) are staged as grade 3 squamous cell carcinomas.[1] Grade X tumors are grouped as grade 1 carcinomas.

E. Tumor Extension
For purposes of data reporting, Barrett's esophagus with high-grade dysplasia in an esophageal resection specimen is reported as "carcinoma in situ." The term *carcinoma in situ* is not widely applied to glandular neoplastic lesions in the gastrointestinal tract but is retained for tumor registry reporting purposes as specified by law in many states. Invasion of the lamina propria may be difficult to assess for glandular neoplasms in the esophagus. The muscularis mucosae (Figure 2) is commonly duplicated and thickened in Barrett's esophagus; invasion of this layer should not be misinterpreted as invasion of the muscularis propria.[9] It should be noted that the muscularis mucosae varies in organization from relatively sparse bundles of smooth muscle in the cervical esophagus to a thickened reticulated network in the distal esophagus.[10]

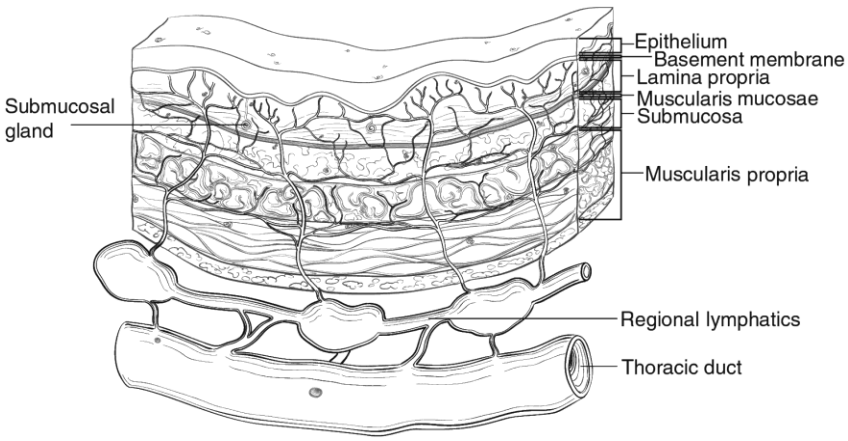

Figure 2. Microscopic anatomy of the esophagus. From Edge et al.[1] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, 7th edition (2009) published by Springer Science and Business Media LLC, www.springerlink.com.

F. Margins
Margins include the proximal, distal, and radial margins. The radial margin represents the adventitial soft tissue margin closest to the deepest penetration of tumor. Sections to evaluate the proximal and distal resections margins can be obtained in 2 orientations: (1) en face sections parallel to the margin or (2) longitudinal sections

perpendicular to the margin. Depending on the closeness of the tumor to the margin, select the orientation(s) that will most clearly demonstrate the status of the margin. The distance from the tumor edge to the closest resection margin(s) should be measured. Proximal and distal resection margins should be evaluated for Barrett's esophagus and for squamous and glandular dysplasia. It may be helpful to mark the margin(s) closest to the tumor with ink. Margins marked by ink should be so designated in the macroscopic description.

G. Treatment Effect

Response of tumor to previous chemotherapy or radiation therapy should be reported. Several systems for tumor response have been advocated, and a modified Ryan scheme is suggested, which has been shown to provide good interobserver reproducibility provide prognostic significance in rectal cancer.[11]

Modified Ryan Scheme for Tumor Regression Score[11]

Description	Tumor Regression Score
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near complete response)	1
Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumor regression (poor or no response)	3

Sizable pools of acellular mucin may be present after chemoradiation but should not be interpreted as representing residual tumor.

This protocol does not preclude the use of other systems for assessment of tumor response.[12-14]

H. TNM and Anatomic Stage/Prognostic Groupings

The TNM staging system for esophageal carcinoma of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended (Figure 3).[1]

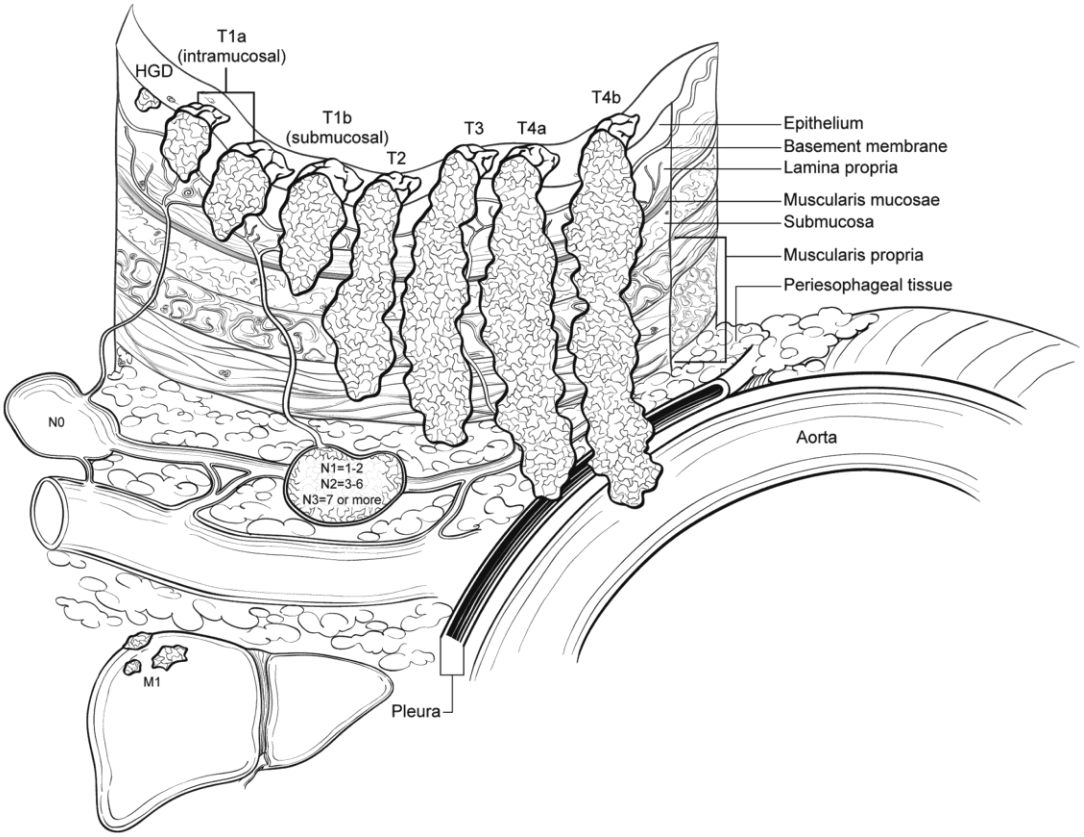

Figure 3. T, N, and M classifications for esophageal carcinoma. From Edge et al.[1] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, 7th edition (2009) published by Springer Science and Business Media LLC, www.springerlink.com.

According to AJCC/UICC convention, the designation "T" refers to a primary tumor that has not been previously treated. The symbol "p" refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically infeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

TNM Descriptors
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The "m" suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The "y" prefix indicates those cases in which classification is performed during or after initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present

at the time of that examination. The "y" categorization is not an estimate of tumor before multimodality therapy (ie, before initiation of neoadjuvant therapy).

The "r" prefix indicates a recurrent tumor when staged after a documented disease-free interval and is identified by the "r" prefix: rTNM.

The "a" prefix designates the stage determined at autopsy: aTNM.

N Category Considerations
A mediastinal lymphadenectomy specimen will ordinarily include 7 or more regional lymph nodes.

Stage Groupings: Squamous Cell Carcinoma

Stage	T	N	M	G	Location
Stage 0	Tis	N0	M0[#]	1	Any
Stage IA	T1	N0	M0	1	Any
Stage IB	T1	N0	M0	2 or 3	Any
	T2 or T3	N0	M0	1	Lower
Stage IIA	T2 or T3	N0	M0	1	Upper, middle
	T2 or T3	N0	M0	2 or 3	Lower
Stage IIB	T2 or T3	N0	M0	2 or 3	Upper, middle
	T1 or T2	N1	M0	Any	Any
Stage IIIA	T1 or T2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
Stage IIIB	T3	N2	M0	Any	Any
Stage IIIC	T4a	N1 or N2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
Stage IV	Any T	Any N	M1	Any	Any

[#] M0 is defined as no distant metastasis.

Stage Grouping: Adenocarcinoma

Stage	T	N	M	G
Stage 0	Tis (HGD[#])	N0	M0	1
Stage IA	T1	N0	M0	1 or 2
Stage IB	T1	N0	M0	3
	T2	N0	M0	1 to 2
Stage IIA	T2	N0	M0	3
Stage IIB	T3	N0	M0	Any
	T1 or T2	N1	M0	Any
Stage IIIA	T1 or T2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
Stage IIIB	T3	N2	M0	Any
Stage IIIC	T4a	N1 or N2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
Stage IV	Any T	Any N	M1	Any

[#] HGD, high-grade dysplasia.

Additional Descriptors

Lymph-Vascular Invasion
Lymph-vascular invasion (LVI) indicates whether microscopic lymph-vascular invasion is identified in the pathology report. LVI includes lymphatic invasion, vascular invasion, or lymph-vascular invasion. By AJCC/UICC convention, LVI does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.

I. Regional Lymph Nodes
Regional lymph nodes (Figure 4) extend from periesophageal cervical nodes for the cervical esophagus to celiac lymph nodes for the distal esophagus.[1] Number of involved lymph nodes has consistently emerged as a prognostic indicator on multivariate analysis.[15,16] Extranodal extension may identify a subset of node-positive patients with a particularly poor prognosis.[17]

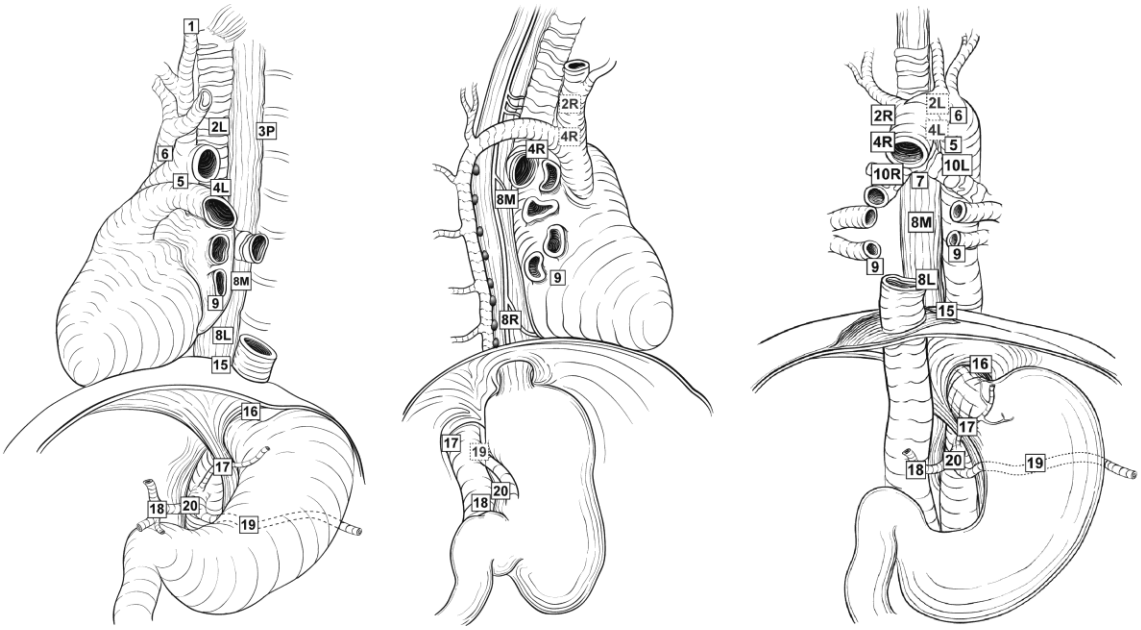

Figure 4. Regional lymph nodes of the esophagus. From Edge et al.[1] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, 7th edition (2009) published by Springer Science and Business Media LLC, www.springerlink.com.

J. Additional Findings
Most esophageal adenocarcinomas develop in the setting of Barrett's esophagus, which is defined as alteration of the mucosal lining of the esophagus from the normal squamous epithelium to metaplastic columnar epithelium in response to esophagogastric reflux. Although in some cases the columnar epithelium may resemble gastric oxyntic or cardiac mucosa, only the specialized columnar epithelium with goblet cells is considered to carry significant risk of cancer and is designated as Barrett's esophagus for diagnostic purposes.

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