

Esophagus

Protocol applies to all invasive carcinomas of the esophagus.

*Protocol revision date: January 2004
Based on AJCC/UICC TNM, 6th edition*

Procedures

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

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Surgical Pathology Cancer Case Summary (Checklist)

Protocol revision date: January 2004
Applies to invasive carcinomas only
Based on AJCC/UICC TNM, 6th edition

*ESOPHAGUS: Biopsy

(Note: Use of checklist for biopsy specimens is optional)

*Patient name:

*Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

*MACROSCOPIC

*Specimen Type

* Incisional biopsy

* Excisional biopsy

*Tumor Site

*Specify, if known: _____

* Not specified

*MICROSCOPIC

*Histologic Type

* Squamous cell carcinoma

* Adenocarcinoma

* Adenosquamous carcinoma

* Small cell carcinoma

* Undifferentiated carcinoma

* Other (specify): _____

* Carcinoma, type cannot be determined

*Histologic Grade

* Not applicable

* GX: Cannot be assessed

* G1: Well differentiated

* G2: Moderately differentiated

* G3: Poorly differentiated

* G4: Undifferentiated

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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.

***Extent of Invasion**

- * Cannot be assessed
- * Epithelium only (no invasion)
- * Lamina propria
- * Submucosa
- * Muscularis propria

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

- * None identified
- * Intestinal metaplasia
- * Dysplasia
- * Esophagitis (type): _____
- * Other (specify): _____

***Comment(s)**

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Surgical Pathology Cancer Case Summary (Checklist)

Protocol revision date: January 2004
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ESOPHAGUS: Resection

Patient name:

Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC

Specimen Type

- Esophageal resection
- Esophagogastrectomy
- Other (specify): _____
- Not specified

Tumor Site

- Specify, if known: _____
- Not specified

Tumor Size

- Greatest dimension: ____ cm
- *Additional dimensions: ____ x ____ cm
- Cannot be determined (see Comment)

MICROSCOPIC

Histologic Type

- Squamous cell carcinoma
- Adenocarcinoma
- Adenosquamous carcinoma
- Small cell carcinoma
- Undifferentiated carcinoma
- Other (specify): _____
- Carcinoma, type cannot be determined

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Histologic Grade

- Not applicable
 GX: Cannot be assessed
 G1: Well differentiated
 G2: Moderately differentiated
 G3: Poorly differentiated
 G4: Undifferentiated

Pathologic Staging (pTNM)Primary Tumor (pT)

- pTX: Cannot be assessed
 pT0: No evidence of primary tumor
 pTis: Carcinoma in situ
 pT1: Tumor invades lamina propria or submucosa
 * pT1a: Tumor invades lamina propria
 * pT1b: Tumor invades submucosa
 pT2: Tumor invades muscularis propria
 pT3: Tumor invades adventitia
 pT4: Tumor invades adjacent structures

Regional Lymph Nodes (pN)

- pNX: Cannot be assessed
 pN0: No regional lymph node metastasis
 pN1: Regional lymph node metastasis
 * pN1a: 1 to 3 nodes involved
 * pN1b: 4 to 7 nodes involved
 * pN1c: More than 7 nodes involved
 Specify: Number examined: ____
 Number involved: ____

Distant Metastasis (pM)

- pMX: Cannot be assessed
 pM1: Distant metastasis, cannot further subclassify
 pM1a: Lower thoracic esophagus: metastasis in celiac lymph nodes;
 Mid-thoracic esophagus: not applicable;
 Upper thoracic esophagus: metastasis in cervical nodes
 pM1b: Lower thoracic esophagus: other distant metastasis;
 Mid-thoracic esophagus: nonregional lymph nodes and/or other
 distant metastasis;
 Upper thoracic esophagus: other distant metastasis
 Specify location of other distant metastases, if possible:

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Margins (check all that apply)

Proximal Margin

- Cannot be assessed
- Uninvolved by invasive carcinoma
- Involved by invasive carcinoma
- Carcinoma in situ absent at proximal margin
- Carcinoma in situ present at proximal margin

Distal Margin

- Cannot be assessed
- Uninvolved by invasive carcinoma
- Involved by invasive carcinoma
- Carcinoma in situ absent at distal margin
- Carcinoma in situ present at distal margin

Circumferential (Adventitial) Margin

- Cannot be assessed
- Uninvolved by invasive carcinoma
- Involved by invasive carcinoma

Distance of invasive carcinoma from closest margin: ____ mm
Specify margin: _____

***Venous (Large Vessel) Invasion (V)**

- * Absent
- * Present
- * Indeterminate

***Lymphatic (Small Vessel) Invasion (L)**

- * Absent
- * Present
- * Indeterminate

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

- * None identified
- * Intestinal metaplasia
- * Dysplasia
- * Esophagitis (type): _____
- * Gastritis (type): _____
- * Other (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. Identification number
 - c. Age (birth date)
 - d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
 - a. Relevant history (eg, previous diagnoses, previous radiotherapy or chemotherapy)
 - b. Relevant findings (eg, endoscopic/imaging studies)
 - c. Clinical diagnosis
 - d. Procedure (eg, brushing, washing, other)
 - e. 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
3. Special studies (specify) (eg, cytochemistry, immunocytochemistry, DNA analysis [specify type], morphometry, cytogenetic analysis)

C. Microscopic Evaluation

1. Adequacy of specimen (if unsatisfactory for evaluation, specify reason)
2. Tumor, if present
 - a. Histologic type, if possible (Note **A**)
 - b. Histologic grade, if possible (Note **B**)
 - c. Other features (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. Incisional or Excisional Biopsy

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 findings (eg, endoscopic/imaging studies)
 - b. Clinical diagnosis
 - c. Procedure (eg, endoscopic biopsy/polypectomy)
 - d. Operative findings
 - e. Anatomic site(s) of specimen(s)

B. Macroscopic Examination

- 1. Specimen
 - a. Unfixed/fixed (specify fixative)
 - b. Number of pieces
 - c. Largest dimension of each piece
 - d. Results of intraoperative consultation
- 2. Tumor, if discernible
 - a. Location
 - b. Descriptive features
 - c. Dimensions
 - d. Configuration
 - e. Relation to margins (excisional biopsy) (Note **C**)
- 3. Tissue submitted for microscopic evaluation
 - a. Incisional biopsy: all
 - b. Excisional biopsy: lesion; margin(s) of excision, if identified
 - c. Frozen section tissue fragment(s) (unless saved for special studies)
- 4. Special studies (specify) (eg, histochemistry, immunohistochemistry, DNA analysis [specify type], morphometry, cytogenetic analysis)

C. Microscopic Evaluation

- 1. Tumor
 - a. Histologic type (Note **A**)
 - b. Histologic grade (Note **B**)
 - c. Extent of invasion, as appropriate
 - d. Venous/lymphatic vessel invasion
- 2. Additional pathologic findings, if present
 - a. Esophagitis
 - b. Intestinal metaplasia
 - c. Squamous dysplasia
 - d. Glandular dysplasia
 - e. Microorganisms
 - f. Other(s)
- 3. Status/results 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. Esophageal Resection

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 (eg, previous diagnoses, previous radiotherapy or chemotherapy)
 - b. Relevant findings (eg, endoscopic and/or imaging studies)
 - c. Clinical diagnosis
 - d. Procedure
 - e. Operative findings
 - f. Anatomic site(s) of specimen(s)

B. Macroscopic Examination

1. Specimen
 - a. Organ(s)/tissue(s) included
 - b. Unfixed/fixed (specify fixative)
 - c. Open/unopened
 - d. Dimensions (measure each piece separately)
 - e. Orientation, if indicated by surgeon
 - f. Results of intraoperative consultation
2. Tumor
 - a. Location (Note **D**)
 - b. Configuration (Note **E**)
 - c. Dimensions (3)
 - d. Descriptive features (eg, color, consistency)
 - e. Ulceration/perforation
 - f. Distance from margins (Note **C**)
 - (1) proximal
 - (2) distal
 - (3) radial (soft tissue margin closest to deepest tumor penetration)
 - g. Estimated depth of invasion
 - h. Extension to other organ(s)/structure(s) (specify)
3. Lesions in noncancerous esophagus
 - a. Intestinal metaplasia
 - b. Ulcer
 - c. Other(s)
4. Regional lymph nodes (Note **F**)
 - a. Number
 - b. Location, if possible
5. Other organs/tissues submitted (eg, nonregional lymph nodes)
6. Tissues submitted for microscopic evaluation
 - a. Carcinoma, including
 - (1) point of deepest penetration
 - (2) interface with adjacent proximal and distal esophagus
 - b. Margins (Note **C**)
 - (1) proximal
 - (2) distal

- (3) radial (soft tissue margin closest to deepest tumor penetration)
- c. All lymph nodes (Note **F**)
- d. Other lesions (eg, ulcers/polyps/Intestinal metaplasia)
- e. Esophagus uninvolved by tumor
- f. Frozen section tissue fragment(s) (unless saved for special studies)
- g. Other organ(s)/tissue(s)
- 7. Special studies (specify) (eg, histochemistry, immunohistochemistry, DNA analysis [specify type], morphometry, cytogenetic analysis)

C. Microscopic Examination

- 1. Tumor
 - a. Histologic type (Note **A**)
 - b. Histologic grade (Note **B**)
 - c. Depth of invasion (pT) (Note **G**)
 - d. Invasion into stomach
 - e. Venous/lymphatic vessel invasion
- 2. Margins (Note **C**)
 - a. Proximal
 - b. Distal
 - c. Radial (soft tissue margin closest to deepest tumor penetration)
 - d. Additional pathologic findings, if present
 - (1) squamous dysplasia
 - (2) intestinal metaplasia
 - (3) glandular dysplasia
 - (4) therapy-related atypia
 - (5) other(s)
- 3. Regional lymph nodes (Note **G**)
 - a. Number (location, if possible)
 - b. Number with metastatic tumor
- 4. Distant metastasis (specify sites) (Note **G**)
- 5. Other organs/tissues submitted
- 6. Results/status of special studies (specify)
- 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

For consistency in reporting, the histologic classification proposed by the World Health Organization (WHO) is recommended.¹ However, this protocol does not preclude the use of other systems of classification or histologic types.

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[#]
 Small cell carcinoma[#]
 Undifferentiated carcinoma[#]
 Others

[#] These types are not generally graded.

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

B. Histologic Grade

The histologic grades for esophageal squamous cell carcinomas are:

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.

C. 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 dysplasia and/or Barrett metaplasia. It may be helpful to mark the margin(s) closest to the tumor with ink. Margins marked by ink should be designated in the macroscopic description.

D. Location

The location of the tumor with respect to the gastroesophageal junction (defined as where the tubular esophagus meets the stomach) should be noted. For tumors involving the gastroesophageal junction (GEJ), specific observations should be recorded in an attempt to establish the exact site of origin of the tumor. GEJ 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:

- proportion of tumor mass located in the esophagus and stomach;
- greatest dimensions of esophageal and gastric portions of the tumor;
- anatomic location of the center of the tumor (cervical, upper thoracic, mid-thoracic, lower thoracic).

For tumors involving the gastroesophageal junction, specific observations should be recorded in an attempt to establish the exact site of origin of the tumor. The gastroesophageal junction is defined as the junction of the tubular esophagus and the stomach irrespective of the type of epithelial lining of the esophagus.

If more than 50% of the tumor involves the esophagus, the tumor is classified as esophageal. If more than 50% of the tumor involves the stomach, the tumor is classified as gastric.² If the tumor is equally located above and below the gastroesophageal junction and/or is designated as being at the junction (anatomic center of the tumor), carcinomas of the squamous, small cell, and undifferentiated types are classified as esophageal, whereas adenocarcinomas and signet-ring cell carcinomas are classified as gastric.³

E. Configuration

Configuration includes exophytic (fungating), endophytic (ulcerative), and diffusely infiltrative, but overlap among these types is common. Reporting of complex configurations may require more than 1 descriptor.

F. Regional Lymph Nodes

Regional lymph nodes comprise the cervical nodes (including the supraclavicular nodes) for the cervical esophagus and the mediastinal nodes for the intrathoracic esophagus.⁴

G. TNM and Stage 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 and shown below.⁴⁻⁵ Category T1 has been expanded according to recommendations published in the *TNM Supplement*.³

By 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 unfeasible) 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.

Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ (including high-grade dysplasia)
- T1 Tumor invades lamina propria or submucosa
- T1a Tumor invades lamina propria[#]
- T1b Tumor invades submucosa[#]
- T2 Tumor invades muscularis propria
- T3 Tumor invades adventitia
- T4 Tumor invades adjacent structures

[#] Separation into T1a and T1b is justified by differences in frequency of lymph node metastasis and subsequent prognosis.^{3,6-8} T1a and T1b correlate with lymph node metastasis and prognosis as follows.⁸

	Lymph Node Metastasis	5-Year Survival Rate
T1a	0%	100%
T1b	47%	86% without nodal metastasis 43% with nodal metastasis

Regional Lymph Nodes (N)[#]

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis^{##}
- N1 Regional lymph node metastasis
- N1a Metastasis in 1 to 3 regional lymph nodes^{###}
- N1b 4 to 7 nodes involved^{##}
- N1c More than 7 nodes involved^{###}

[#] A mediastinal lymphadenectomy specimen will ordinarily include 6 or more regional lymph nodes.

^{##}Regional Lymph Nodes (pN0): Isolated Tumor Cells

Isolated tumor cells (ITCs) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension. Lymph nodes or distant sites with ITCs found by either histologic examination, immunohistochemistry, or nonmorphologic techniques (eg, flow cytometry, DNA analysis, polymerase chain reaction [PCR] amplification of a specific tumor marker) should be classified as N0 or M0, respectively. Specific denotation of the

assigned N category is suggested as follows for cases in which ITCs are the only evidence of possible metastatic disease.^{3,9}

- pN0 No regional lymph node metastasis histologically, no examination for isolated tumor cells (ITCs)
- pN0(i-) No regional lymph node metastasis histologically, negative morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
- pN0(i+) No regional lymph node metastasis histologically, positive morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
- pN0(mol-) No regional lymph node metastasis histologically, negative nonmorphologic (molecular) findings for ITCs
- pN0(mol+) No regional lymph node metastasis histologically, positive nonmorphologic (molecular) findings for ITCs

Separation into N1a, N1b, and N1c is justified by differences in prognosis, as shown below.³ For esophageal carcinoma, survival decreases in a step-wise fashion with increasing number of involved regional lymph nodes. In patients with a limited number of involved nodes, long-term survival is possible with radical resection and extensive lymphadenectomy.¹⁰

	2-Year Survival Rate	5-Year Survival Rate	Median Survival (Months)
N1a	22%	11%	12
N1b	18%	0%	9
N1c	0%	0%	6

Distant Metastasis (M)

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis[#]

[#] For tumors of the lower thoracic esophagus:

- M1a Metastasis in celiac lymph nodes
- M1b Other distant metastasis

[#] For tumors of the mid-thoracic esophagus:

- M1a Not applicable
- M1b Nonregional lymph nodes and/or other distant metastasis

[#] For tumors of the upper thoracic esophagus:

- M1a Metastasis in cervical nodes
- M1b Other distant metastasis

Tumors of the mid-thoracic esophagus are staged only M1b, since tumors with metastasis in nonregional lymph nodes as well as in other sites have an equally poor prognosis.

Stage Groupings

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
Stage III	T3	N1	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

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 following 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 prior to 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.

Additional Descriptors

Residual Tumor (R)

Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

Vessel Invasion

By AJCC/UICC convention, vessel invasion (lymphatic or venous) does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category. In all other cases, lymphatic and venous invasion by tumor are coded separately as follows.

Lymphatic Vessel Invasion (L)

LX	Lymphatic vessel invasion cannot be assessed
L0	No lymphatic vessel invasion
L1	Lymphatic vessel invasion

Venous Invasion (V)

VX	Venous invasion cannot be assessed
V0	No venous invasion
V1	Microscopic venous invasion
V2	Macroscopic venous invasion

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