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: October 2013

Procedures
• Endoscopic Resection
• Esophagectomy
• Esophagogastrectomy

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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 3.1.1.2

Summary of Changes
The following changes have been made since the June 2012 release.

Endoscopic Resection, Esophagectomy, or Esophagogastrectomy

Pathologic Staging (pTNM)
Primary Tumor (pT)
pT4b was changed from an optional to a required data element.
Surgical Pathology Cancer Case Summary

Protocol web posting date: October 2013

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 (see “Comment”)

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.
Histologic Type (Note C)
___ Squamous cell carcinoma
___ Adenocarcinoma
___ 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: __________________________

Proximal 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

+ 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.
**Distal Margin**
- Cannot be assessed
- Uninvolved by invasive carcinoma or dysplasia
- Involved by invasive carcinoma
- 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

**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 residual tumor (complete response, grade 0)
  + Marked response (grade 1, minimal residual cancer)
  + Moderate response (grade 2)
- No definite response identified (grade 3, poor or no response)
- Treatment history not known

**Lymph-Vascular Invasion**
- Not identified
- Present
- Indeterminate

**Perineural Invasion**
- Not identified
- Present
- Indeterminate

**Pathologic Staging (pTNM) (Note H)**

<table>
<thead>
<tr>
<th>TNM Descriptors</th>
<th>(required only if applicable) (select all that apply)</th>
</tr>
</thead>
<tbody>
<tr>
<td>m (multiple primary tumors)</td>
<td></td>
</tr>
<tr>
<td>r (recurrent)</td>
<td></td>
</tr>
<tr>
<td>y (posttreatment)</td>
<td></td>
</tr>
</tbody>
</table>

+ 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.
### 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

### 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)
- **Not applicable**
- **pM1:** Distant metastasis
  + Specify site(s), if known: ____________________________

### 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
+ Specify: ____________________________

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+ 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.
+ 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 also not included (separate TNM staging systems 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, 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. 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. Although the nature of these tumors (gastric versus esophageal) has been controversial (reviewed by Carneiro and Chaves), recent data support their classification as esophageal carcinomas. The World Health Organization (WHO) defines esophageal tumors as those located entirely above the EGJ and proximal gastric tumors as those located entirely below the EGJ. Tumors crossing the EGJ are classified as EGJ tumors. An alternative system proposed by Siewert and colleagues divides adenocarcinomas involving the EGJ into three categories, based upon location of the midpoint of the tumor:

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 Siewert 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, and others as a metaplastic response to injury from esophagogastric reflux.

C. Histologic Type
For consistency in reporting, the histologic classification proposed by the WHO is recommended. 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. 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.

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. 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. 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.
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. Although grading systems for tumor response have not been established, in general, three-category systems provide good interobserver reproducibility. The following system is suggested:

<table>
<thead>
<tr>
<th>Description</th>
<th>Tumor Regression Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>No viable cancer cells</td>
<td>0 (Complete response)</td>
</tr>
<tr>
<td>Single cells or small groups of cancer cells</td>
<td>1 (Moderate response)</td>
</tr>
<tr>
<td>Residual cancer outgrown by fibrosis</td>
<td>2 (Minimal response)</td>
</tr>
<tr>
<td>Minimal or no tumor kill; extensive residual cancer</td>
<td>3 (Poor response)</td>
</tr>
</tbody>
</table>

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.

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).
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 (i.e., 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 (i.e., 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

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>G</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>1</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>1</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>2 or 3</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>T2 or T3</td>
<td>N0</td>
<td>M0</td>
<td>1</td>
<td>Lower</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2 or T3</td>
<td>N0</td>
<td>M0</td>
<td>1</td>
<td>Upper, middle</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2 or T3</td>
<td>N0</td>
<td>M0</td>
<td>2 or 3</td>
<td>Lower</td>
</tr>
<tr>
<td></td>
<td>T1 or T2</td>
<td>N0</td>
<td>M0</td>
<td>2 or 3</td>
<td>Upper, middle</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1 or T2</td>
<td>N2</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>Any</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>N3</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>

* M0 is defined as no distant metastasis.

### Stage Grouping: Adenocarcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>G</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis (HGD#)</td>
<td>N0</td>
<td>M0</td>
<td>1</td>
<td>Any</td>
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<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>1 or 2</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>3</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>1 to 2</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>3</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1 or T2</td>
<td>N1</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
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<tr>
<td></td>
<td>T3</td>
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<td>N0</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
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<td>Any</td>
<td>M0</td>
<td>Any</td>
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<td>M0</td>
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<td>Stage IIIB</td>
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<td>Any</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>N3</td>
<td>M0</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>
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. Number of involved lymph nodes has consistently emerged as a prognostic indicator on multivariate analysis. Extranodal extension may identify a subset of node-positive patients with a particularly poor prognosis.

Figure 4. Regional lymph nodes of the esophagus. From Edge et al. 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.
References