Cancer of the Esophagus and Esophagogastric Junction—Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual

1. Summarize major changes in the American Joint Committee on Cancer system for staging of cancers of the esophagus and esophagogastric junction.

2. Highlight how findings from the Worldwide Esophageal Cancer Collaboration, with data from 33 institutions spanning 6 continents, have helped to guide improvements in prognostication.

3. Describe clinical implications for esophageal and esophagogastric cancer treatment decision making based on the eighth edition of the American Joint Committee on Cancer manual.

SCORING:
A score of 70% or better is needed to pass a quiz containing 10 questions (7 correct answers), or 80% or better for 5 questions (4 correct answers).

INSTRUCTIONS ON RECEIVING CME CREDIT:
This activity is intended for physicians. For information concerning the applicability and acceptance of CME credit for this activity, please consult your professional licensing board.

This activity is designed to be completed within 1.25 hours; physicians should claim only those credits that reflect the time actually spent in the activity. To successfully earn credit, participants must complete the activity during the valid credit period, which is up to 2 years from the time of initial publication.

INSTRUCTIONS ON RECEIVING CNE CREDIT:
This activity is intended for nurses. For information concerning the applicability and acceptance of CNE credit for this activity, please consult your professional licensing board.

This activity is designed to be completed within 1.25 hours; nurses should claim only those credits that reflect the time actually spent in the activity. To successfully earn credit, participants must complete the activity during the valid credit period, which is up to 2 years from the time of initial publication.

FOLLOW THESE STEPS TO EARN CREDIT:
- Log on to acsjournals.com/ce.
- Read the target audience, educational objectives, and activity disclosures.
- Read the activity contents in print or online format.
- Reflect on the activity contents.
- Access the examination, and choose the best answer to each question.
- Complete the required evaluation component of the activity.
- Claim your certificate.

This activity will be available for CME/CNE credit for 1 year following its launch date. At that time, it will be reviewed and potentially updated and extended for an additional 12 months.

All CME/CNE quizzes are offered online FREE OF CHARGE. Please log in at acsjournals.com/ce. New users can register for a FREE account. Registration will allow you to track your past and ongoing activities. After successfully completing each quiz, you may instantly print a certificate, and your online record of completed courses will be updated automatically.
Cancer of the Esophagus and Esophagogastric Junction—Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual

Thomas W. Rice, MD1; Donna M. Gress, RHIT, CTR2; Deepa T. Patil, MD3; Wayne L. Hofstetter, MD4; David P. Kelsen, MD5; Eugene H. Blackstone, MD6

Abstract: New to the eighth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual for epithelial cancers of the esophagus and esophagogastric junction are separate, temporally related cancer classifications: 1) before treatment decision (clinical); 2) after esophagectomy alone (pathologic); and 3) after preresection therapy followed by esophagectomy (postneoadjuvant pathologic). The addition of clinical and postneoadjuvant pathologic stage groupings was driven by a lack of correspondence of survival, and thus prognosis, between both clinical and postneoadjuvant pathologic cancer categories (facts about the cancer) and pathologic categories. This was revealed by a machine-learning analysis of 6-continent data from the Worldwide Esophageal Cancer Collaboration, with consensus of the AJCC Upper GI Expert Panel. Survival is markedly affected by histopathologic cell type (squamous cell carcinoma and adenocarcinoma) in clinically and pathologically staged patients, requiring separate stage grouping for each cell type. However, postneoadjuvant pathologic stage groups are identical. For the future, more refined and granular data are needed. This requires: 1) more accurate clinical staging; 2) innovative solutions to pathologic staging challenges in endoscopically resected cancers; 3) integration of genomics into staging; and 4) precision cancer care with targeted therapy. It is the responsibility of the oncology team to accurately determine and record registry data, which requires eliminating both common errors and those related to incompleteness and inconsistency. Despite the new complexity of eighth edition staging of cancers of the esophagus and esophagogastric junction, these key concepts and new directions will facilitate precision cancer care.

CA Cancer J Clin 2017;67:304-317. © 2017 American Cancer Society.

Keywords: American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) eighth edition staging, esophageal cancer, esophagogastric cancer, staging

Practical Implications for Continuing Education

> In the eighth edition staging of cancers of the esophagus and esophagogastric junction, classifications are no longer shared. There are separate classifications for the clinical (cTNM), pathologic (pTNM), and postneoadjuvant pathologic (ypTNM) stage groups.

> Separate stage groupings for squamous cell carcinoma and adenocarcinoma are necessary for clinical (cTNM) and pathologic (pTNM) classifications but not for postneoadjuvant pathologic (ypTNM) classifications.

> Except for the addition of peritoneal invasion to the criteria for T4a, T, N, and M categories and subcategories remain unchanged for the eighth edition. Subgrouping of pT1N0M0 cancers requires subcategorization by pT1a and pT1b. Furthermore, the nonanatomic category grade (G) is necessary for pathologic staging of pT1-T2N0M0 cancers, and grade (G) and location (L) are necessary for pathologic staging of pT3N0M0 squamous cell carcinomas.
Introduction

Esophageal and esophagogastric junction (EGJ) cancers are rare, rapidly lethal, and primarily seen in elderly men. There are 2 major histopathologic cell types, squamous cell carcinoma and adenocarcinoma, with marked geographic distributions. In the past, prognostication has been based on pathologic findings after esophagectomy alone. However, this is inadequate for decision making, which is based on clinical findings before treatment, and it is inadequate for prognostication in: 1) patients who have not yet been treated or 2) those not treated with esophagectomy alone. These inadequacies are addressed in the eighth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual using data on outcomes of treating 22,654 patients. The Worldwide Esophageal Cancer Collaboration (WECC) collected this information from 33 institutions spanning 6 continents.2-7

Important findings were, first, that clinical staging, currently based largely on imaging with minimal histologic and biomarker information, remains coarse and inaccurate. Therefore, clinical staging for decision making and prognostication, which has relied on corresponding pathologic stage groups, required it own stage groupings and cannot be based on post-treatment staging as it has been in the past. Second, pathologic staging based on esophagectomy alone is losing its relevance for advanced-stage cancer. However, it remains relevant for early-stage cancers and as a staging and survival reference point. Third, because neoadjuvant therapy affects depth of cancer invasion (T), lymph node metastases (N), and distant metastases (M) differently, the treatment produces unique combinations of these cancer characteristics and their survival profiles compared with esophagectomy alone. Therefore, separate cancer staging had to be developed for patients after neoadjuvant therapy (which includes esophagectomy).

Key Concepts and New Directions

Key Concepts: Esophagus and EGJ

Cancer classification: a temporal definition

For all cancers in the eighth edition, their individual facts or characteristics are now named categories. For esophageal and esophagogastric cancers, anatomic categories are primary tumor (T), regional lymph node (N), and distant metastases (M). Nonanatomic cancer categories include histopathologic cell type, histologic grade (G), and location (L). A cancer stage is a grouping of cancer categories that reflects prognosis. Stages may be defined at various points in the life history and care of a patient with cancer and are designated as cancer classifications. Temporally related cancer classifications were an advance conceived by the AJCC and originally included clinical–diagnostic, surgical–evaluative, postsurgical treatment–pathologic, and retreatment classifications. These have evolved primarily into clinical (c) (before treatment decision), pathologic (p) (after esophagectomy alone), and post-neoadjuvant pathologic therapy (yp) classifications.

Stage grouping by classification

The dual purposes of staging, as outlined in the initial Union for International Cancer Control manual, are that TNM categories are “a means of recording facts observed by the clinician [about the cancer], whereas staging implies interpretation of these facts regarding prognosis.”9

Stage groups are arrangements of cancer categories that are monotonically decreasing in survival with increasing stage group, have distinctive survival between stage groups, and have homogeneous survival within each stage group. Therefore, ideally, cancer stage grouping and survival should be connected. However, early on in esophageal cancer staging, the lack of accurate clinical staging modalities and the novelty of neoadjuvant therapy, contrasted with the conclusion of pathologic assessment of resection specimens, led to the practice of sharing pathologic stage groups (pTNM) with the corresponding cTNM or ypTNM groups. The AJCC Upper Gastrointestinal Expert Panel, in preparing the eighth edition AJCC Cancer Staging Manual for esophageal and esophagogastric cancer, examined this practice of sharing stage groups among classifications. Because of survival differences among classifications, a need for separate stage groups for each classification was identified. Although these new stage groups can be linked according to equivalent survival across classifications, the panel decided against this strategy.

Pathologic stage groups (p). Pathologic stage groups (Figs. 1A and 2A) have the most widely separated and completely distributed survival. Although pathologic tumor in situ (pTis) and pT1aN0M0 have similar survival, the AJCC definition of stage group 0 is limited to pTis; consequently, pT1aN0M0 is forced into stage group IA. Subgrouping maximizes distinctiveness of survival between groups and subgroups. Homogeneity of survival within groups is excellent in all but the advanced groups. Separation among advanced subgroups might be improved by adding more N subcategories, but such additions are clinically irrelevant, because survival is so poor in patients with more than 7 regional lymph node metastases (N3).

Clinical stage groups (c). Clinical staging is based on physical examination, esophagoscopy, and imaging, and rarely on microscopic examination of biopsy specimens. Because of the limitations of current imaging modalities, clinical stage group composition and survival profiles (Figs. 1B and 2B) differ from those of pathologic stage groups (see Figs. 1A and 2A). This necessitates separating clinical stage groups from pathologic stage groups.
Compared with pathologic stage groups, survival is less distinctive between groups, and survival curves are compressed from above and below, with poorer survival of early-stage groups and better survival of advanced-stage groups compared with the corresponding pathologic stage groups. Some of this heterogeneity may be caused by data limitations and different clinical staging practices around the world. Goals for future clinical staging are more uniform use of available clinical staging tools, improved modalities to acquire more accurate data, and documentation of all clinical cancer categories and the modality used to define them.

**Postneoadjuvant pathologic stage groups (yp).** New to the eighth edition is postneoadjuvant pathologic (yp) staging. This means preoperative treatment—chemotherapy, radiotherapy, or combined chemoradiotherapy—followed by esophagectomy. Postneoadjuvant pathologic categories are determined by pathologic assessment of esophagectomy specimens.

Variable effects of neoadjuvant therapy on T, N, and M produce unique postneoadjuvant pathologic categories (ypTisN0-N3M0 and ypT0N0-N3M0) and dissimilar stage group compositions and survival profiles compared with pathologic categories. This necessitated a unique set of stage groups for patients who received neoadjuvant therapy. Survival for postneoadjuvant pathologic stage groups (Figs. 1C and 2C) \(^{1,4,7}\) differs from that for comparable pathologic stage groups (see Figs. 1A and 2A) \(^{1,4,7}\): Postneoadjuvant pathologic stage group survival is less distinctive between groups, and the survival curves are greatly depressed from above, with much poorer survival of early-stage groups compared with the corresponding pathologic stage groups and dismal survival of advanced-stage groups, no better or worse than that of the corresponding pathologic stage groups (see Figs. 1C and 2C). \(^{1,4,7}\) This has been characterized as the hysteresis effect of downstaging by neoadjuvant therapy. \(^{11}\)

**Stage grouping by histopathologic cell type**

The 2 main cell types of esophageal cancer are squamous cell carcinoma and adenocarcinoma. Although they occur in the same organ, the epidemiology, potential driving factors, and spectrum of genomic alterations are markedly different between the 2 cell types.

Histopathologic cell type markedly affects the survival of clinically and pathologically staged patients, but less so in postneoadjuvant pathologically staged patients. The survival of patients with early-stage and intermediate-stage disease was worse for those who had squamous cell carcinomas than for those who had similarly staged adenocarcinomas for all classifications.

**Pathologic stage groups. Squamous cell carcinoma.** Consensus agreement restricts pathologic stage 0 to high-grade squamous dysplasia, pTis (Table 1). This is defined in the eighth edition as malignant cells confined to the epithelium by the basement membrane.

---

**FIGURE 1.** Risk-Adjusted Survival for Squamous Cell Carcinoma of the Esophagus Based on Worldwide Esophageal Cancer Collaboration Data. \(^{2-7}\) (A) Pathologic (p) stage groups, (B) clinical (c) stage groups, and (C) postneoadjuvant pathologic (yp) stage groups.

**FIGURE 2.** Risk-Adjusted Survival for Adenocarcinoma of the Esophagus Based on Worldwide Esophageal Cancer Collaboration Data. \(^{2-7}\) (A) Pathologic (p) stage groups, (B) clinical (c) stage groups, and (C) postneoadjuvant pathologic (yp) stage groups.
Subcategorization of pT1 and the addition of grade (G1–G3) of differentiation by histopathologic review for pT1–T2 cancers allow pathologic subgrouping of stage I (see subsequent text for a description of histologic grade). This produces 2 pathologic stage I subgroups: stage IA (pT1aN0M0G1) and stage IB (pT1aN0M0G2-G3, pT1bN0M0, and pT2N0M0G1). In addition to the grade of the primary cancer, the location of a squamous cell cancer within the upper and middle esophagus is important for subgrouping pathologic stage II (see subsequent text for description of location [L]). pT2N0M0G2-G3 cancers, pT3N0M0 cancers of the lower thoracic esophagus and EGJ, and pT3N0M0G1 cancers of the upper and middle thoracic esophagus are included in stage IIA. pT3N0M0G2-G3 cancers of the upper and middle thoracic esophagus and pT1N1M0 cancers are included in stage IIB.

Advanced cancers with relatively good survival are stage IIIA, pT2N1M0 and pT1N2M0. pT2N2M0, pT3N1-N2M0, and pT4aN0-1N0M0 cancers are stage IIIB. Pathologic stage IV is subgrouped, because most locoregional advanced cancers (pT4aN2M0, pT4bN0-N2M0, and pTanyN3M0) have survival distinctly worse than stage III and are stage IVA. Cancers with metastasis to distant sites (M1) are isolated into stage IVB.

Adenocarcinoma. Similar to squamous cell carcinoma, pathologic stage 0 is restricted to high-grade glandular dysplasia, pTis (Table 2). pT1 subcategorization combined with grade produces 3 pathologic subgroups for stage I: stage IA (pT1aN0M0G1), stage IB (pT1aN0M0G2 and pT1bN0M0G1-G2), and stage IC (pT1N0M0G3 and pT2N0M0G1-G2). Only pT2N0M0G3 defines stage IIA.

### TABLE 1. American Joint Committee on Cancer Pathologic Stage Groups for Squamous Cell Carcinoma of the Esophagus and Esophagogastric Junction

| WHEN pT IS... | AND pN IS... | AND M IS | AND GRADE IS... | AND LOCATION IS... | THEN THE STAGE GROUP IS... |
|---------------|---------------|----------|-----------------|-------------------|-----------------------------|
| Ta            | N0            | M0       | NA              | Any               | 0                           |
| T1a           | N0            | M0       | G1              | Any               | IA                          |
| T1a           | N0            | M0       | G2-G3           | Any               | IB                          |
| T1a           | N0            | M0       | GX              | Any               | IA                          |
| T1b           | N0            | M0       | G1-G3           | Any               | IB                          |
| T1b           | N0            | M0       | GX              | Any               | IB                          |
| T2            | N0            | M0       | G1              | Any               | IB                          |
| T2            | N0            | M0       | G2-G3           | Any               | IA                          |
| T2            | N0            | M0       | GX              | Any               | IA                          |
| T3            | N0            | M0       | G1              | Upper/middle      | IA                          |
| T2            | N0            | M0       | G2-G3           | Upper/middle      | IIA                         |
| T3            | N0            | M0       | GX              | Any               | IIB                         |
| T3            | N0            | M0       | Any             | Location X        | IIB                         |
| T1            | N1            | M0       | Any             | Any               | IIB                         |
| T1            | N2            | M0       | Any             | Any               | IIIA                        |
| T2            | N1            | M0       | Any             | Any               | IIIA                        |
| T2            | N2            | M0       | Any             | Any               | IIIA                        |
| T3            | N1-N2         | M0       | Any             | Any               | IIB                         |
| T4a           | N0-N1         | M0       | Any             | Any               | IIB                         |
| T4b           | N2            | M0       | Any             | Any               | IVA                         |
| Any T         | N3            | M0       | Any             | Any               | IVA                         |
| Any T         | Any N         | M1       | Any             | Any               | IVB                         |

Abbreviations: G, histologic grade; M, metastasis classification; NA, not applicable; pN, pathologic lymph node classification; pT, pathologic tumor classification; Tis, tumor in situ. *Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017), published by Springer International Publishing.
T3N0M0 and pT1N1M0 constitute stage IIB. Pathologic stages III and IV are identical for both squamous cell carcinoma and adenocarcinoma.

**Clinical stage grouping.** Stage grouping for squamous cell carcinoma follows a much different pattern from that for adenocarcinoma.

**Squamous cell carcinoma.** Clinical stage 0 comprises cTis (Table 3). Stage I has a mix of cT1N0-N1M0 cancers. cT2N0-N1M0 and cT3N0M0 cancers comprise stage II. cT3N1M0 and cT1-T3N2M0 cancers define stage III. Only stage IV requires subgrouping: cT4a-T4bN0-N2M0 and all cN3M0 cancers define stage IVA, and cM1 cancers define stage IVB.

**Adenocarcinoma.** Clinical stage 0 comprises cTis (Table 4). Stage I is solely cT1N0M0. Stage II is subgrouped as stage IIA (cT1N1M0) and stage IIB (cT2N0M0). Stage III comprises cT2N1 and cT3-T4aN0-N1M0. T4bN0-N1M0 and all cN2-N3M0 cancers are included in stage IVA. Stage IVB solely contains all cM1 cancers.

**Postneoadjuvant pathologic stage grouping.** Unlike pathologic and clinical stage groupings, postneoadjuvant pathologic groupings are identical for both histopathologic cell types (Table 5). There are unique combinations of categories and single-category cancers in postneoadjuvant pathologic groupings: ypT0-T2 cancers are always grouped together, and staging these cancers depends on ypN category. ypT3N0M0 is the sole component of stage II, and ypM1 is the sole component of stage IVB.

Therefore, stage I contains ypT0-T2N0M0 cancers. Stage II contains the single entity ypT3N0M0. Stage IIIA comprises cancers confined to the esophageal wall, with ypN1 regional lymph node category (ypT0-T2N1M1). ypT1-T3N2M0 plus ypT3N1M0 and ypT4aN0M0 cancers are stage IIIB. Stage IVA includes ypT4aN1-N2M0, ypT4bN0-N2M0, and ypTanyN3M0. ypM1 cancers define stage IVB.

**Anatomic (TNM) categories**

Except for the addition of direct peritoneal invasion categorized as T4a, TNM categories remain unchanged from the
seventh edition of the AJCC Cancer Staging Manual. Subcategorization of pT1, new in the seventh edition, is refined and improved in eighth edition stage I subgrouping. Regional lymph nodes (N), which are found in the periesophageal tissue from the upper esophageal sphincter to the celiac artery, are clarified in a simplified esophageal-specific map (Fig. 3).

Nonanatomic (non-TNM) categories

**Histologic grade.** The nonanatomic cancer category “grade” is distinctive in pathologic stage grouping of early-stage cancers (Tables 1 and 2) and has moved to a 3-grade subcategorization (G1-G3). Undifferentiated (formerly G4) cancers require additional pathologic analyses to expose histopathologic cell type. If glandular origin can be determined, then the cancer is staged as a grade 3 adenocarcinoma; if a squamous origin can be determined or if the cancer remains undifferentiated after full analysis, then it is a grade 3 squamous cell carcinoma (Tables 1 and 2).

**Location.** Consensus changed the definition of location from the position of the upper edge of the cancer in the esophagus (seventh edition) to the epicenter of the cancer (eighth edition), both referenced to distance from the incisor teeth. Clinically, the epicenter is determined from upper and lower border measurements, which also provide

| Table 3. American Joint Committee on Cancer Clinical Stage Groups for Squamous Cell Carcinoma of the Esophagus and Esophagogastric Junction |
| --- |
| **WHEN cT IS . . .** | **AND cN IS . . .** | **AND M IS . . .** | **THEN THE STAGE GROUP IS . . .** |
| Tis | N0 | M0 | 0 |
| T1 | N0-N1 | M0 | I |
| T2 | N0-N1 | M0 | II |
| T3 | N0 | M0 | II |
| T3 | N1 | M0 | III |
| T1-T3 | N2 | M0 | III |
| T4 | N0-N2 | M0 | IVA |
| Any T | N3 | M0 | IVA |
| Any T | Any N | M1 | IVB |

Abbreviations: M, metastasis classification; cN, clinical lymph node classification; cT, clinical tumor classification; Tis, tumor in situ. *Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017), published by Springer International Publishing.

| Table 4. American Joint Committee on Cancer Clinical Stage Groups for Adenocarcinoma of the Esophagus and Esophagogastric Junction |
| --- |
| **WHEN cT IS . . .** | **AND cN IS . . .** | **AND M IS . . .** | **THEN THE STAGE GROUP IS . . .** |
| Tis | N0 | M0 | 0 |
| T1 | N0 | M0 | I |
| T1 | N1 | M0 | IIA |
| T2 | N0 | M0 | IIB |
| T2 | N1 | M0 | III |
| T3 | N0-N1 | M0 | III |
| T4a | N0-N1 | M0 | III |
| T1-T4a | N2 | M0 | IVA |
| T4b | N0-N2 | M0 | IVA |
| Any T | N3 | M0 | IVA |
| Any T | Any N | M1 | IVB |

Abbreviations: cN, clinical lymph node classification; cT, clinical tumor classification; M, metastasis classification; Tis, tumor in situ. *Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017), published by Springer International Publishing.
cancer length. For treatment planning, it is especially important to know the upper border for cancers of the upper thoracic and cervical esophagus and the lower border for cancers of the lower esophagus and EGJ. Although location is distinctive for both pT2-T3N0M0 cancers, the consensus process chose to limit use of this nonanatomic cancer category to subgrouping pT3N0M0 squamous cell carcinoma (Fig. 4) (Table 1).

**Esophagogastric junction**

Consensus review by the Upper GI Expert Panel of the EGJ led to a change in the definition. Cancers with epicenters no more than 2 cm into the gastric cardia are staged as adenocarcinomas of the esophagus, while those with more than 2-cm involvement of the gastric cardia are staged as stomach cancers (Fig. 4).

**New Directions**

**Registry data**

Registry data requested in the eighth edition have been refined and expanded from the data requested in the seventh edition of the AJCC Cancer Staging Manual (Table 6). This expanded list will aid cancer registrars, support data managers, help maximize eighth edition data collection, and potentially increase the accuracy of assigning eighth edition stage. Capturing data from the different modalities used in clinical staging is critical to understanding inherent inaccuracies and deficiencies and thus to direct future clinical staging projects. For example, information regarding accuracy of clinical staging of regional lymph nodes may inform future clinical staging. Augmenting pathologic and postneoadjuvant pathologic cancer elements collected and recording of specific therapies will potentially refine prognostication and may direct future adjuvant therapy. This prospective data collection will assist in development of the ninth edition esophageal cancer staging.

### TABLE 5. American Joint Committee on Cancer Postneoadjuvant Pathologic Stage Groups for Squamous Cell Carcinoma and Adenocarcinoma of the Esophagus and Esophagogastric Junction

| WHEN ypT IS . . . | AND ypN IS . . . | AND M IS . . . | THEN THE STAGE GROUP IS . . . |
|------------------|-----------------|---------------|-----------------------------|
| T0-T2            | N0              | M0            | I                           |
| T3               | N0              | M0            | II                          |
| T0-T2            | N1              | M0            | IIIA                        |
| T3               | N1              | M0            | IIIB                        |
| T0-T3            | N2              | M0            | IIIB                        |
| T4a              | N0              | M0            | IIIB                        |
| T4a              | N1-N2           | M0            | IVA                         |
| T4a              | NX              | M0            | IVA                         |
| T4b              | N0-N2           | M0            | IVA                         |
| Any T            | N3              | M0            | IVA                         |
| Any T            | Any N           | M1            | IVB                         |

Abbreviations: M, metastasis classification; ypN, postneoadjuvant pathologic lymph node classification; ypT, postneoadjuvant pathologic tumor classification.

*Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017), published by Springer International Publishing.*

### TABLE 6. Registry Data Collection Variables

1. Clinical staging modalities (endoscopy and biopsy, EUS, EUS-FNA, CT, PET/CT)
2. Tumor length
3. Depth of invasion
4. No. of lymph nodes involved, clinical
5. No. of lymph nodes involved, pathologic
6. Location of lymph node disease, clinical
7. Location of lymph node disease, pathologic
8. Sites of metastasis, if applicable
9. Presence of skip lesions: T(m)
10. Perineural invasion
11. LVI (lymphatic, vascular, both)
12. Extranodal extension
13. Type of surgery
14. Chemotherapy
15. Chemoradiation therapy (for ypTNM)
16. Surgical margin (negative, R0; microscopic positive, R1; macroscopic positive, R2)
17. HER2 status (positive or negative) for adenocarcinoma

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; HER2, human epidermal growth factor receptor 2; LVI, lymphovascular invasion; PET, positron emission tomography; ypTNM, postneoadjuvant pathologic TNM classification.
Pathologic stage

With the increasing use of neoadjuvant therapy for the majority of advanced-stage esophageal and EGJ cancers, pathologic staging will likely be most germane to early-stage cancers. The eighth edition analysis has demonstrated similar survival for pTis and T1N0M0G1 cancers. Current definitions do not allow pTis to be grouped with stage pIA cancers and restrict it to stage p0. An alternative solution is to move T1N0M0G1 cancers into stage p0. Regardless of the choice, these 2 entities have similar survival and “travel together.”

The decision to remove location for grouping pT2N0M0 cancers as a criterion was by consensus in the eighth edition, and this non–data-driven decision should be readdressed in the ninth edition.

With the use of endoscopic therapies to treat T1 cancers, the presence or absence of metastatic disease to regional lymph nodes is determined on the basis of clinical assessment (cN), usually by imaging modalities and not by pathologic assessment (pN) of resected lymph nodes. Improvement in imaging assessment of regional lymph nodes, or potentially biopsies of suspicious lymph nodes in these patients, is critical for decision making and prognostication, because it implies the possibility of using additional therapy for pN1-N3 cancers in patients who initially receive endoscopic therapy.

Extranodal extension present in lymph node metastases (pN1M0 cancers) should be evaluated and should direct adjuvant therapy for these poor-prognosis patients.12

A new regional lymph node map (Fig. 3) will permit lymph node location data to be collected on all patients. This will aid in investigating the prognostic importance of location of those uncommon positive lymph nodes in patients with one or two regional lymph node metastases that are well removed from the primary cancer. This may confirm whether these isolated, remote lymph node metastases should be classified as regional lymph nodes, as they now are, or redefined as distant lymph node metastases.

Testing to identify the genetic signature of esophageal and esophagogastric cancers and liquid “biopsy” molecular staging may impact cancer care at some time in the future. This may augment or replace current staging.

Clinical staging

Clinical staging based chiefly on imaging is limited by the resolution and accuracy of each technique. The shortcoming of each staging method should be taken into account during...
interpretation of clinical staging. Because current data reveal that clinical staging is still relatively inaccurate, histologic confirmation of any imaging abnormality is advisable, particularly of suspicious regional lymph nodes and oligometastatic disease. This may be the last time unaltered cancer is available for histologic review.

Current recommendations for clinical staging include esophagogastroduodenoscopy and biopsy or endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (for cancers suspected to be pT1) to determine location, histopathologic cell type, and histologic grade; endoscopic ultrasound (EUS) for cT; EUS–fine-needle aspiration for cN; and computed tomography-positron emission tomography for cM and cN, supplemented by ancillary imaging, aspiration, or biopsy. Although it is inclusive, the current standard of care for clinical staging is problematic because of various cost limitations in some areas of the world and various use of available staging modalities. Minimal standards for clinical staging must be set with worldwide adherence. Recording how clinical stage was obtained is necessary to determine the quality of clinical staging. More accurate and precise clinical staging modalities are needed.

Although histologic grading from biopsy specimens may be challenging, it should be assessed in all patients. Despite its importance in data-driven stage grouping, by consensus, grade was eliminated from clinical staging. However, this does not remove histologic grade as a factor in treatment decision making and pretreatment prognostication.

**Postneoadjuvant pathologic staging**

Patients with clinical, locoregional advanced esophageal or esophagogastric cancers are likely to be offered neoadjuvant therapy in hopes of improving survival over that expected with esophagectomy alone. However, because it is currently not possible to predict which patient will respond to neoadjuvant therapy and which will not, many patients do not realize a meaningful survival benefit. Adequate pretreatment biopsy specimens are crucial to facilitate the development of accurate biomarkers to predict response to therapy.

With introduction of the eighth edition Cancer Staging Manual, prognostication is specific for patients undergoing neoadjuvant therapy. The role of these recommendations in additional treatment planning is currently limited. However, to realize precision cancer care, advances are necessary in both targeted neoadjuvant and adjuvant therapies.

**Esophagogastric junction**

The use of a simple measurement to define whether a cancer should be considered esophageal or gastric has hobbled esophagogastric cancer staging since the 1980s. Not surprisingly, conflicting statistical analyses necessitated a “place card” consensus decision. Recent studies suggest that the spectrum of genomic alterations may be helpful in assessing the similarities and differences among subsets of patients with adenocarcinomas of the tubular esophagus, gastroesophageal junction, and stomach. Hopefully, these data will inform the ninth edition staging of esophagogastric cancers.

**Harmonization**

Use of worldwide data to develop eighth edition esophageal cancer staging was an important step in harmonizing and reporting cancer care around the world. The common language will assist in current cancer care and direct future projects, including the ninth edition.

**Etiology**

It is evident that stage-by-stage survival of esophageal and esophagogastric cancers is similar worldwide. The WECC has demonstrated that there are no special geographic areas where esophageal and EGJ cancers defy survival prognostication, as revealed by eighth edition staging. However, distribution of histopathologic cell type and cancer location within the esophagus and EGJ varies around the world, suggesting different genomic and etiologic drivers. Hopefully, this worldwide collaboration will permit the unraveling of these etiologies as peculiarities of regions around the world.

---

**FIGURE 4. Anatomy of Esophageal and Esophagogastric Junction Cancer Primary Site, Including Typical Endoscopic Measurements of Each Region Measured From the Incisors.**

Exact measurements depend on body size and height. Location of the primary cancer site is defined by the cancer epicenter. EGJ indicates esophagogastric junction; LES, lower esophageal sphincter; UES, upper esophageal sphincter.
reveal the secrets of the cause of esophageal and esophagogastric cancer.

Differences Between the Seventh and Eighth Editions

The major difference between the seventh and eighth editions is the introduction of separate stage groups among classifications. Direct comparison of these editions is possible only for pathologic staging.

Squamous Cell Carcinoma

Although there was no net change in the number of staging subgroups in the eighth edition compared with the seventh edition, there were significant rearrangements of categories and subgroups. Eighth edition consensus was to maintain the definition of stage p0, restricting this group to pTis. Subcategorizing pT1 allowed stage pIA to be more distinct in the eighth edition and was restricted to pT1aN0M0G1. This change placed all other T1N0M0 squamous cell carcinomas into stage pIB. pT2N0M0 and pT3N0M0 cancers, which were grouped identically in the seventh edition, were more accurately grouped in the eighth edition. In the seventh edition, pT2–T3N0M0 cancers occupied 3 subgroups: pIB, pIIA, and pIIIB. In the eighth edition, location was removed as a category for pT2N0M0 cancers, thus limiting pT2N0M0 cancers to either stage pIB (pT2N0M0G1) or stage pIIA (pT2N0M0G2–G3). pT3N0M0 cancers were restricted to either stage pIIA or stage pIIIB in the eighth edition. All but pT3N0M0G2–G3 upper/middle (stage pIIIB) thoracic esophageal cancers were placed into stage pIIA. Eighth edition stage pIIIB was limited to pT3N0M0G2–G3 upper/middle thoracic esophageal cancers and pT1N1M0 cancers. pT2N1M0 cancers were moved from stage pIIA in the seventh edition to form stage pIIIA in the eighth edition, improving homogeneity. Seventh edition stage pIIIA pT3N1M0 and pT4aN0M0 cancers, stage pIIIB pT3N2M0 cancers, and stage pIIIC pT4aN1M0 cancers, all with similar survival, were placed into stage pIIIB in the eighth edition. All other stage pIIIC cancers of the seventh edition (pT4aN2M0, pT4b, and pN3) became stage pIVA in the eighth edition. pM1 cancers, which were stage pIV in the seventh edition, were placed into stage pIVB in the eighth edition.

Adenocarcinoma

Staging subgroups increased by one in the eighth edition. Similar to squamous cell carcinoma, eighth edition consensus was to maintain the definition of stage p0, restricting this group to pTis. Subcategorizing pT1 required an increase from 2 subgroups of stage p1 in the seventh edition to 7 in the eighth edition, improving the distinctiveness of survival between subgroups. Seventh edition stage pIA pT1N0M0G1–G2 cancers are now stage pIA (pT1aN0M0G1) and stage pIB (pT1aN0M0G2 and pT1bN0M0G1–G2) in the eighth edition. Seventh edition stage pIIB became eighth edition stage pIC (pT1N0M0G3 and pT2N0M0G1–G2), and stage pIIIA is unchanged (pT2N0M0G3). pT2N1M0 cancers were moved from stage pIIIB in the seventh edition to join pT1N2M0 to form stage pIIIA in the eighth edition, improving homogeneity. All eighth edition changes from stage pIIIA and higher are identical to those reported for squamous cell carcinoma.

Common Errors in Staging

Errors in staging are not restricted to any one person responsible for determining or recording the staging categories or assigning stage groups. Awareness of individual staging responsibilities and attention to detail will minimize errors.

Pathologic Staging

Adequate resection requires obtaining satisfactory and preserved margins, particularly radial margins, in the esophagectomy specimen. The definition of a positive margin depends on the system used. The College of American Pathologists defines R1 as microscopic involvement of the margin; the Royal College of Pathologists defines an R1 (microscopically positive) margin as one in which there is cancer within 1 mm of the margin. The WECC data did not distinguish between these definitions. In practice, the pathologist should state the definition used. In addition to sampling the proximal and distal margins, inking the adventitial aspect of the specimen is a routine practice that facilitates microscopic assessment of pT as well as status of the radial margin. Separating periesophageal soft tissue for lymph node harvest should be performed only after sampling the full thickness of the cancer with an intact, inked adventitial surface.

An adequate lymphadenectomy to determine pN is very different from that necessary to maximize survival, and a balance is necessary. More lymph nodes are required to identify the uncommon early-stage cancer with regional lymph node metastases, but fewer are required to adequately assess pN in patients with advanced-stage cancers, which are likely to have regional lymph node metastases. However, greater lymphadenectomy is required to provide a possible therapeutic (survival) benefit for advanced cancers. 10 lymph nodes for pT1, 20 for pT2, and 30 or more for pT3.

The periesophageal soft tissue should be thoroughly dissected to maximize lymph node yield. For cases in which lymph nodes are submitted as separate specimens, the number of nodes should be documented in the pathology report. If the specimen is received in multiple fragments, then an accurate lymph node count is not possible, and this finding
should be documented. This problem can be overcome by the surgeon reporting lymph node numbers for fragmented specimens. In addition to documenting the presence or absence of lymph node metastasis, the eighth edition requires documentation of extracapsular extension, defined as extension of cancer cells into perinodal soft tissue. This feature has been associated with significantly worse long-term survival. To aid registrars, pathologic categories and pathologic stages should be completely recorded in the medical records.

Clinical Staging

Clinical evaluation may provide the only assessment of staging categories of an esophageal or esophagogastric cancer, because nonresective or obliterative neoadjuvant therapy may prohibit future assessment. Every attempt should be made to define the clinical staging categories and to obtain complete registry data during the pretreatment evaluation of the patient.

Esophagoscopy should be used to determine clinical cancer location within the esophagus or the EGJ. Eighth edition location is defined by the epicenter of the cancer. A common error relates to location of the cancer with respect to the EGJ and stomach. Registrars must understand that the criterion is not whether the cancer is in the proximal stomach but whether these new criteria are met: “Cancers involving the EGJ that have their epicenter within the proximal 2 cm of the cardia [Siewert types I/II] are to be staged as esophageal cancers. Cancers whose epicenter is more than 2 cm distal from the EGJ [Siewert type III], even if the EGJ is involved, will be staged using the stomach cancer TNM and stage groupings.”

Biopsy is mandatory and provides the tissue needed to determine histopathologic cell type of the cancer. In most instances, classifying cancers as either squamous cell carcinoma or adenocarcinoma is relatively simple, relying on the identifying features of squamous differentiation (keratin pearl formation; intercellular bridges; and cells with abundant, glassy, eosinophilic cytoplasm) for the former and gland formation for the latter. However, in specimens with limited diagnostic material and in higher grade cancers, this distinction can be challenging. Application of ancillary markers, such as p63, p40, and cytokeratin 5/6 for squamous differentiation, and performing an Alcian blue-periodic acid–Schiff stain to demonstrate subtle intracellular mucin can be helpful in this regard.

Although histologic grade is an important predictor of clinical outcome, it is inconsistently reported in biopsy specimens, in part because superficial biopsy samples may provide limited material to accurately grade the cancer. In addition, reporting the grade of cancer has not been a previously required element for biopsy specimens. Because preoperative biopsy may be the only histologic material available in patients who have a complete pathologic response after neoadjuvant therapy, every attempt should be made to grade cancers using criteria outlined by the World Health Organization. Low-grade (G1) and moderately differentiated cancers (G2) are likely to suffer from significant interobserver variability. However, poor differentiation and signet-ring cell morphology are known to be predictors of poor outcome and thus should be mentioned in pathology reports.

EUS assessment of T is necessary to adequately estimate the cT category, except when histologic assessment of EMR or endoscopic submucosal dissection of superficial cancers is available. Lesions that appear to be amenable to endoscopic resection, including some cT2 cancers, are more accurately staged by EMR. EUS (and, when possible, EUS–fine-needle aspiration) is optimal for determining cT and cN. To the best of their ability, endosonographers using EUS, radiologists using computed tomography, and nuclear radiologists using positron emission tomography must provide a count of regional lymph nodes containing metastases. Simply categorizing a cancer as cN+ is inadequate and is a common staging error. It has been demonstrated in eighth edition staging and the literature that the clinical lymph node count is prognostic. Histo logic confirmation of cN1-N3 and cM1 should be attempted. Positive confirmation will not change the classification of the N category, because diagnostic biopsy of lymph nodes is part of the clinical staging criteria. Positive confirmation will change the classification of the M category from cM1 to pM1, because it is critical to differentiate the method of evaluation for distant metastasis according to Chapter 1 in the AJCC eighth edition, “Principles of Cancer Staging.” To aid registrars, clinical categories and clinical stage should be completely recorded in the medical records before commencing therapy and in any subsequent operative or treatment report.

Postneoadjuvant Pathologic Staging

As for pathologic staging, adequate resection with preservation of margins and adequate lymphadenectomy is essential. That lymphadenectomy has not been demonstrated to affect survival in patients undergoing resection after preoperative therapy should not influence whether an adequate lymphadenectomy is performed in these patients.

Although postchemotherapy/chemoradiotherapy biopsy specimens may seem an attractive option for assessing residual cancer, there is significant discrepancy between biopsy samples and resection specimens. Studies have shown that from 38% to 41% of post-therapy biopsy specimens harbor residual cancer in the subsequent resection specimen.
Thus, ypT is most accurately evaluated on resection specimens. Estimation of residual cancer is performed after thorough evaluation of grossly visible foci of mucosal irregularity or ulcer as well as sampling of the adjacent esophageal wall. The obliteration of anatomic landmarks after preoperative therapy can pose significant diagnostic challenges in assigning ypT, especially for esophagogastric cancers. In some institutions, for esophagogastric cancers, the esophageal adventitial surface and gastric serosa are inked with different colors to determine the exact anatomic location and depth of cancer.

Preoperative therapy induces several histologic changes that include the presence of ulceration, mural fibrosis, acellular mucin pools, and dystrophic calcification. Cancer cells need to be distinguished from reactive stromal cells and macrophages. Regardless of the histologic subtype, residual neoplastic cells usually demonstrate enlarged, irregular, and hyperchromatic nuclei with a dense, homogeneous nuclear chromatin pattern and abundant cytoplasm. Occasionally, residual cancer cells have a neuroendocrine phenotype or squamous features. These foci should be considered when determining ypT stage.

Chemotherapy or chemoradiation therapy-induced histopathologic changes may preclude the accurate grading of cancer, especially in patients with minimal residual cancer. This underscores the importance of grading cancers on preoperative biopsy samples. Acellular mucin pools should not be used to stage cancer or to determine margin status.

The cancer regression grading system described by Mandar et al seems to be the most widely used system for assessing response to therapy. The 3-tiered cancer regression grading system outlined by Ryan et al for assessing treated rectal cancer has shown good interobserver reproducibility among pathologists and is endorsed by the College of American Pathologists.

In patients who have received neoadjuvant therapy, lymph nodes can undergo atrophy and may be difficult to recognize macroscopically. In these patients, histologic assessment of the majority of the periesophageal soft tissue is helpful to retrieve impalpable lymph nodes. After treatment, the lymph node parenchyma shows fibrosis, lymphoid depletion, and acellular mucin lakes. Lymph nodes with these changes, and with no viable cancer cells, should be considered negative for metastasis. Immunohistochemical stains, such as cytokeratin AE1/AE3, may be used to confirm the presence of rare residual cancer cells. However, because false-positive results may occur, they should be interpreted in conjunction with morphologic findings. To aid registrars, postneoadjuvant pathologic categories and postneoadjuvant pathologic stage should be completely recorded in medical records.

Conclusions

Despite the new complexity of eighth edition staging of cancers of the esophagus and EGJ, these key concepts and new directions will facilitate precision cancer care.

Author Contributions: Thomas W. Rice: Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing—review and editing, and visualization. Deepa T. Patil: Conceptualization, methodology, data curation, writing—review and editing, and visualization. Wayne L. Hofstetter: Conceptualization, methodology, data curation, writing—review and editing, and visualization. Eugene H. Blackstone: Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing—original draft, writing—review and editing, visualization, supervision, project administration, and funding acquisition.

References

1. Rice TW, Kelsen D, Blackstone EH, et al. Esophagus and esophagogastric junction. In: Amin MB, Edge S, Greene F, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017:185-202.
2. Rice TW, Chen LQ, Hofstetter WL, et al. Worldwide Esophageal Cancer Collaboration: pathologic staging data. Dis Esophagus. 2016;29:724-733.
3. Rice TW, Apperson-Hansen C, DiPaola LM, et al. Worldwide Esophageal Cancer Collaboration: clinical staging data. Dis Esophagus. 2016;29:707-714.
4. Rice TW, Lerut TE, Orringer MB, et al. Worldwide Esophageal Cancer Collaboration: neoadjuvant pathologic staging data. Dis Esophagus. 2016;29:715-723.
5. Rice TW, Ishwaran H, Hofstetter WL, Kelsen DP, Apperson-Hansen C, Blackstone EH; for the Worldwide Esophageal Cancer Collaboration Investigators. Recommendations for pathologic staging (pTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. Dis Esophagus. 2016;29:907-908.
6. Rice TW, Ishwaran H, Blackstone EH, Hofstetter WL, Kelsen DP, Apperson-Hansen C; for the Worldwide Esophageal Cancer Collaboration Investigators. Recommendations for clinical staging (cTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. Dis Esophagus. 2016;29:913-919.
7. Rice TW, Ishwaran H, Kelsen DP, Hofstetter WL, Apperson-Hansen C, Blackstone EH; for the Worldwide Esophageal Cancer Collaboration Investigators. Recommendations for neoadjuvant pathologic staging (ypTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. Dis Esophagus. 2016;29:906-912.
8. American Joint Committee for Cancer Staging and End-Results Reporting (AJCC). Manual for Staging of Cancer. 1st ed. Chicago, IL: ASC; 1977.
9. International Union Against Cancer (UICC), Committee on TNM Classification. TNM Classification of Malignant Tumors. Geneva, Switzerland: UICC; 1968.
10. Rice TW, Blackstone EH. A brief history of esophageal cancer TNM and stage grouping. In: Rami-Porta R, ed. Staging Manual in Thoracic Oncology. North Fort Meyers, FL: Editorial Rx Press; 2016:185-196.
11. Rice TW, Blackstone EH, Adelstein DJ, et al. N1 esophageal carcinoma: the importance of staging and downstaging. J Thorac Cardiovasc Surg. 2001;121:454-464.
12. Nafteu PR, Lerut AM, Moons J, et al. International multicenter study on the impact of extracapsular lymph node involvement in primary surgery adenocarcinoma of the esophagus on overall survival and staging systems. Ann Surg. 2015;262:809-816.
13. Shapiro J, van Lanschot JJ, Hulshof MC, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16:1090-1098.
14. Cancer Genome Atlas Research Network. Integrated genomic characterization of oesophageal carcinoma. *Nature*. 2017;541:169-175.

15. Hayakawa Y, Sethi N, Sepulveda AR, Bass AJ, Wang TC. Oesophageal adenocarcinoma and gastric cancer: should we mind the gap? *Nat Rev Cancer*. 2016;16:305-318.

16. College of American Pathologists. Protocol for the Examination of Specimens From Patients With Carcinoma of the Oesophagus. Northfield, IL: College of American Pathologists; 2009.

17. The Royal College of Pathologists. Dataset for the Histopathological Reporting of Oesophageal Carcinoma. 2nd ed. London: The Royal College of Pathologists; 2007.

18. Rice TW, Ishwaran H, Hofstetter WL, et al. Esophageal cancer: associations with (pN1) lymph node metastases. *Ann Surg*. 2017;265:122-129.

19. Rizk NP, Ishwaran H, Rice TW, et al. Optimum lymphadenectomy for esophageal cancer. *Ann Surg*. 2010;251:46-50.

20. Lagarde SM, ten Kate FJ, de Boer DJ, Busch OR, Obertop H, van Lanschot JJ. Extracapsular lymph node involvement in node-positive patients with adenocarcinoma of the distal esophagus or gastroesophageal junction. *Am J Surg Pathol*. 2006;30:171-176.

21. Montgomery E, Field JK, Boffetta P. Squamous cell carcinoma of the esophagus. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, eds. WHO Classification of Tumors of the Digestive System. 4th ed. Lyon, France: IARC Press; 2010:18-24.

22. Flejou JF, Odze RD, Montgomery E. Adenocarcinoma of the esophagus. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, eds. WHO Classification of Tumors of the Digestive System. 4th ed. Lyon, France: IARC Press; 2010:25-31.

23. Chirieac LR, Swisher SG, Correa AM, et al. Signet-ring cell or mucinous histology after preoperative chemoradiation and survival in patients with esophageal or esophagogastric junction adenocarcinoma. *Clin Cancer Res*. 2005;11:2229-2236.

24. Natsugoe S, Yoshinaka H, Shimada M, et al. Number of lymph node metastases determined by presurgical ultrasound and endoscopic ultrasound is related to prognosis in patients with esophageal carcinoma. *Ann Surg*. 2001;234:613-618.

25. Chen J, Xu R, Hunt GC, Krinsky ML, Savides TJ. Influence of the number of malignant regional lymph nodes detected by endoscopic ultrasonography on survival stratification in esophageal adenocarcinoma. *Clin Gastroenterol Hepatol*. 2006;4:573-579.

26. Twine CP, Roberts SA, Rawlinson CE, et al. Prognostic significance of the endoscopic ultrasound defined lymph node metastasis count in esophageal cancer. *Dis Esophagus*. 2010;23:652-659.

27. Gress DM, Edge SB, Greene FL. Principles of cancer staging. In: Amin MB, Edge S, Greene F, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2016:3-30.

28. Hornick JL, Farraye FA, Odze RD. Prevalence and significance of prominent mucin pools in the esophagus post neoadjuvant chemoradiotherapy for Barrett’s-associated adenocarcinoma. *Am J Surg Pathol*. 2006;30:28-35.

29. Ryan R, Gibbons D, Hyland JM, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. *Clinico-pathologic correlations. Cancer*. 1994;73:2680-2686.