



Cancer of the Esophagus and Esophagogastric Junction: An Eighth Edition Staging Primer



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ABSTRACT

This primer for eighth edition staging of esophageal and esophagogastric epithelial cancers presents separate classifications for the clinical (cTNM), pathologic (pTNM), and postneoadjuvant pathologic (ypTNM) stage groups, which are no longer shared. For pTNM, pT1 has been subcategorized as pT1a and pT1b for the subgrouping pStage I adenocarcinoma and squamous cell carcinoma. A new, simplified esophagus-specific regional lymph node map has been introduced. Undifferentiated histologic grade (G4) has been eliminated; additional analysis is required to expose histopathologic cell type. Location has been removed as a category for pT2N0M0 squamous cell cancer. The definition of the esophagogastric junction has been revised. ypTNM stage groups are identical for both histopathologic cell types, unlike those for cTNM and pTNM.

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Introduction

Staging of cancer of the esophagus and esophagogastric junction for the eighth edition of the AJCC/UICC cancer staging manuals^{1,2} was built on a strong seventh edition foundation.^{3,4} A greatly expanded Worldwide Esophageal Cancer Collaboration database, with a substantial increase in both numbers of patients entered and variables collected,⁵⁻⁷ permitted a more robust and reliable random forest-based machine learning analysis. Random forest techniques provided risk-adjusted survival estimates for all patients, from which distinctive and homogeneous stage groups with

monotonically decreasing survival were identified. This primer presents three classifications separately for both adenocarcinoma and squamous cell carcinoma: the classic reference pathologic (pTNM) stage groups, the newly introduced postneoadjuvant pathologic (ypTNM) stage groups, and clinical (cTNM) stage groups.⁸⁻¹⁰

Cancer Categories

What used to be called classifications are now termed *categories* and *subcategories* in the AJCC eighth edition. Criteria (Table 1) define the elements of categories. Esophageal anatomic cancer categories include primary tumor (T), regional lymph node (N), and distant site (M) (Table 1 and Fig. 1). Subcategorization of pT1 into pT1a and pT1b has refined and improved stage I grouping.

Regional lymph nodes (N), which are found in the adventitia (periesophageal tissue) from the upper esophageal sphincter to the celiac artery, are clarified in a new map (Fig. 2). The seventh edition map was problematic because it included lung lymph node stations, some of which were not regional esophageal nodes.

The nonanatomic cancer category *grade* is important for pathologic staging (pTNM) of early-stage cancers (see Table 1). Undifferentiated cancers require additional

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Table 1. Cancer Staging Categories for Cancer of the Esophagus and Esophagogastric Junction

Category	Criteria
T category	
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a ^a	Tumor invades the lamina propria or muscularis mucosae
T1b ^a	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades the adventitia
T4	Tumor invades adjacent structures
T4a ^a	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b ^a	Tumor invades other adjacent structures, such as the aorta, vertebral body, or trachea
N category	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in ≥ 7 regional lymph nodes
M category	
M0	No distant metastasis
M1	Distant metastasis
Adenocarcinoma G category	
GX	Differentiation cannot be assessed
G1	Well differentiated, with >95% of the tumor composed of well-formed glands
G2	Moderately differentiated, with 50%-95% of the tumor showing gland formation
G3 ^b	Poorly differentiated, with tumors composed of nest and sheets of cells with <50% of the tumor demonstrating glandular formation
Squamous cell carcinoma G category	
GX	Differentiation cannot be assessed
G1	Well-differentiated, with prominent keratinization with pearl formation and a minor component of nonkeratinizing basal-like cells, tumor cells arranged in sheets, and mitotic counts low
G2	Moderately differentiated, with variable histologic features ranging from parakeratotic to poorly keratinizing lesions and pearl formation generally absent
G3 ^c	Poorly differentiated, consisting predominantly of basal-like cells forming large and small nests with frequent central necrosis and with the nests consisting of sheets or pavement-like arrangements of tumor cells that are occasionally punctuated by small numbers of parakeratotic or keratinizing cells
Squamous cell carcinoma L category^d	
LX	Location unknown
Upper	Cervical esophagus to lower border of the azygos vein
Middle	Lower border of the azygos vein to lower border of the inferior pulmonary vein
Lower	Lower border of the inferior pulmonary vein to the stomach, including the esophagogastric junction

^aSubcategories.

^bIf further testing of "undifferentiated" cancers reveals a glandular component, categorize as adenocarcinoma G3.

^cIf further testing of "undifferentiated" cancers reveals a squamous cell component or if after further testing they remain undifferentiated, categorize as squamous cell carcinoma G3.

^dLocation is defined by epicenter of esophageal tumor.

analyses to expose a histopathologic cell type. If glandular origin can be determined, 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, it is staged as a grade 3 squamous cell carcinoma (see Table 1).

Cancer location is not important for adenocarcinoma staging, but in conjunction with grade it is necessary to subgroup pT3N0M0 squamous cell carcinoma. The

definition of the esophagogastric junction is revised such that cancers involving it with epicenters no more than 2 cm into the gastric cardia are staged as adenocarcinomas of the esophagus and those with more than 2-cm involvement of the gastric cardia are staged as stomach cancers (Fig. 3). This was considered by the AJCC Upper Gastrointestinal Expert Panel as a placeholder until comprehensive genomic analysis could identify cell of origin rather than arbitrary measurement locations.¹¹

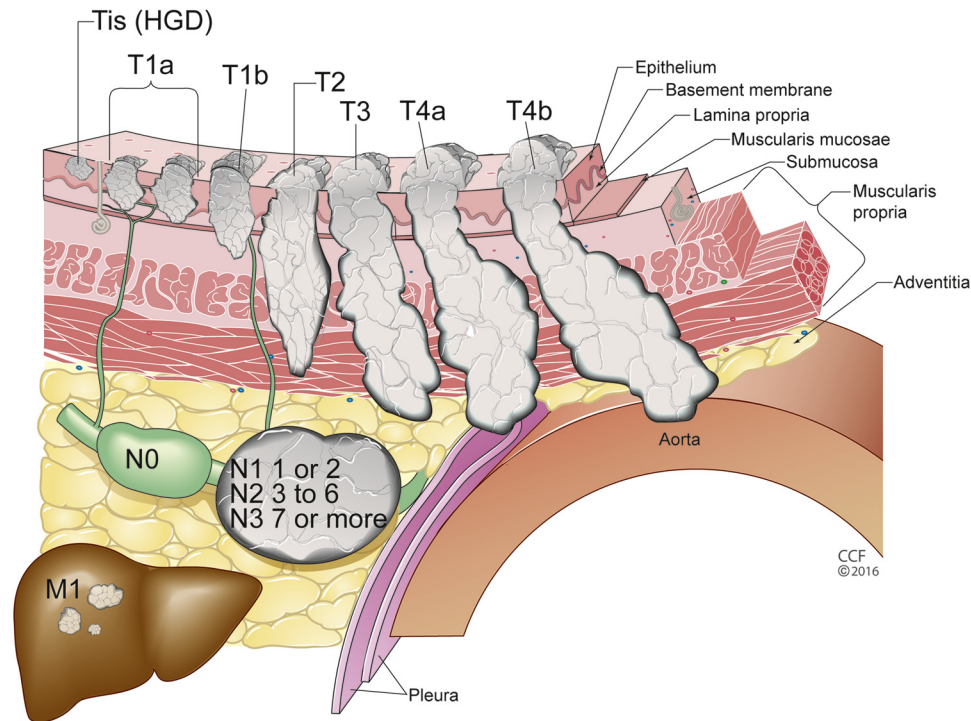


Figure 1. Eighth edition TNM categories. T is categorized as Tis: high-grade dysplasia (HGD). T1 is cancer that invades the lamina propria, muscularis mucosae, or submucosa and is subcategorized into T1a (cancer that invades the lamina propria or muscularis mucosae) and T1b (cancer that invades the submucosa); T2 is cancer that invades the muscularis propria; T3 is cancer that invades the adventitia; T4 is cancer that invades the local structures and is subcategorized as T4a (cancer that invades adjacent structures such as the pleura, pericardium, azygos vein, diaphragm, or peritoneum) and T4b (cancer that invades the major adjacent structures, such as the aorta, vertebral body, or trachea). N is categorized as N0 (no regional lymph node metastasis), N1 (regional lymph node metastases involving one to two nodes), N2 (regional lymph node metastases involving three to six nodes), and N3 (regional lymph node metastases involving seven or more nodes). M is categorized as M0 (no distant metastasis) and M1 (distant metastasis).

Stage Groups

Pathologic Stage Groups (pTNM)

Historically, pathologic stage grouping after esophagectomy alone has been the sole basis for all cancer staging. Today, pathologic staging is losing its clinical relevance for advanced-stage cancer as post-neoadjuvant therapy replaces esophagectomy alone. However, it remains relevant for early-stage cancers and as an important staging and survival reference point.

Adenocarcinoma. Stage subgroups increased from nine in the seventh edition to 10 in the eighth (Fig. 4A). pStage 0 is restricted to high-grade glandular dysplasia, pTis. Subcategorization of T1 combined with grade requires three pStage I subgroups: pStage IA (pT1aN0M0G1), pStage IB (pT1aN0M0G2 and pT1bN0M0G1-2), and pStage IC (pT1N0M0G3 and pT2N0M0G1-2). pT2N0M0G3 remains the sole cancer in pStage IIA. pStage IIB comprises T3N0M0 and pT1N1M0. pStage III is reserved for advanced cancers with relatively good survival. pT2N1M0 and pT1N2M0 form

pStage IIIA, whereas pT2N2M0, pT3N1-2M0, and pT4aN0-1M0 form pStage IIIB. pStage IV was subcategorized with the realization that the most locally advanced cancers have survival similar to that of cancers with metastasis to distant sites (M1). pT4aN2M0, pT4bN0-2M0, and pTanyN3M0 are pStage IVA. Cancers with metastasis to distant sites (M1) are restricted to pStage IVB.

Squamous cell carcinoma. In the eighth edition, there is no net change in the number of stage subgroups; there is, however, significant rearrangement and renaming (Fig. 4B). pStage 0 is restricted to high-grade glandular dysplasia, pTis. Subcategorization of T1 combined with grade requires two pStage I subgroups: pStage IA (pT1aN0M0G1) and pStage IB (pT1aN0M0G2-3, pT1bN0M0, and pT2N0M0G1). pStage IIA comprises pT2N0M0G2-3 cancers, pT3N0M0 cancers of the lower thoracic esophagus, and pT3N0M0G1 cancers of the upper middle thoracic esophagus. pStage IIB comprises T3N0M0G2-3 cancers of the upper middle thoracic esophagus and pT1N1M0 cancers. pStage III and pStage

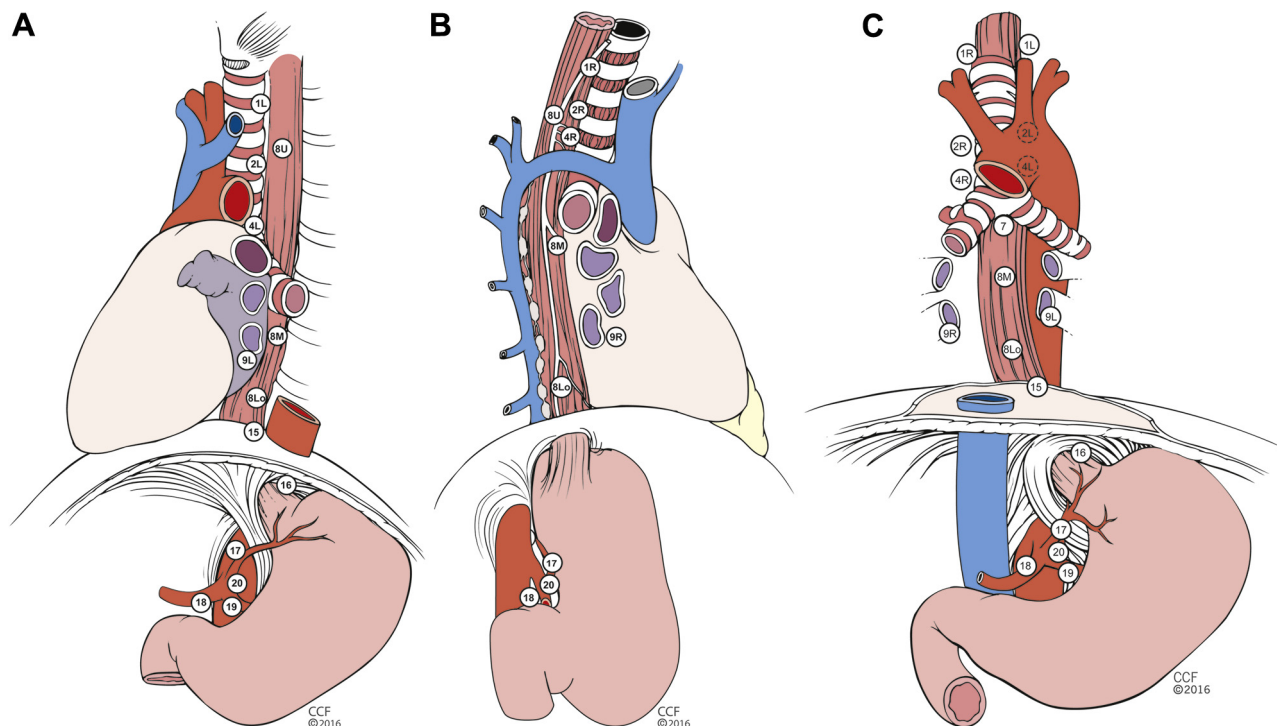


Figure 2. Lymph node maps for esophageal cancer. Regional lymph node stations for staging esophageal cancer from the left (A), right (B), and anterior (C). 1R, right lower cervical paratracheal nodes, between the supraclavicular paratracheal space and apex of the lung; 1L, left lower cervical paratracheal nodes, between the supraclavicular paratracheal space and apex of the lung; 2R, right upper paratracheal nodes, between the intersection of the caudal margin of the brachiocephalic artery with the trachea and apex of the lung; 2L, left upper paratracheal nodes, between the top of the aortic arch and apex of the lung; 4R, right lower paratracheal nodes, between the intersection of the caudal margin of the brachiocephalic artery with the trachea and cephalic border of the azygos vein; 4L, left lower paratracheal nodes, between the top of the aortic arch and the carina; 7, subcarinal nodes, caudal to the carina of the trachea; 8U, upper thoracic paraesophageal lymph nodes, from the apex of the lung to the tracheal bifurcation; 8M, middle thoracic paraesophageal lymph nodes, from the tracheal bifurcation to the caudal margin of the inferior pulmonary vein; 8Lo, lower thoracic paraesophageal lymph nodes, from the caudal margin of the inferior pulmonary vein to the esophagogastric junction; 9R, pulmonary ligament nodes, within the right inferior pulmonary ligament; 9L, pulmonary ligament nodes, within the left inferior pulmonary ligament; 15, diaphragmatic nodes, lying on the dome of the diaphragm and adjacent to or behind its crura; 16, paracardial nodes, immediately adjacent to the gastroesophageal junction; 17, left gastric nodes, along the course of the left gastric artery; 18, common hepatic nodes, immediately on the proximal common hepatic artery; 19, splenic nodes, immediately on the proximal splenic artery; 20, celiac nodes, at the base of the celiac artery. Cervical periesophageal level VI and level VII lymph nodes are named as per the head and neck map.

IV are identical for both adenocarcinoma and squamous cell carcinoma.

Postneoadjuvant Pathologic Stage Groups (ypTNM)

New to the eighth edition is stage grouping of patients with esophageal cancers who have undergone postneoadjuvant therapy and had pathologic review of the resection specimen (Fig. 5). Drivers of this addition include absence of equivalent pathologic (pTNM) categories for the peculiar postneoadjuvant pathologic categories (ypT0N0-3M0 and ypTisN0-3M0), dissimilar stage group compositions, and markedly different survival profiles.

The groups are identical for both histopathologic cell types. Grade is not included in postneoadjuvant pathologic staging. ypStage I comprises ypT0-2N0M0 cancers. ypStage II consists of the single entity ypT3N0M0. ypStage IIIA comprises cancers confined to the esophageal wall with ypN1 regional nodal category (ypT0-2N1M1). ypStage IIIB comprises ypT1-3N2M0, ypT3N1M0, and ypT4aN0M0 cancers. ypStage IVA includes ypT4aN1-2M0, ypT4bN0-2M0, and ypTanyN3M0. ypStage IVB comprises ypM1 cancers.

Clinical Stage Groups (cTNM)

Also new to the eighth edition is clinical stage grouping (cTNM) before treatment decision. Clinical

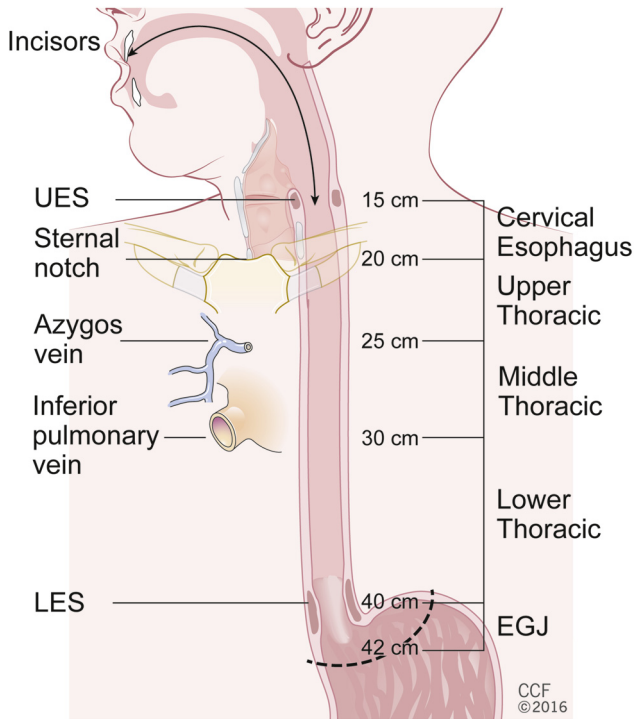


Figure 3. Location of esophageal cancer primary site, including typical endoscopic measurements of each region measured from the incisors. Exact measurements depend on body size and height. Location of cancer primary site is defined by cancer epicenter. Cancers involving the esophago-gastric junction (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, even if the EGJ is involved, will be staged using the stomach cancer TNM and stage groups. LES, lower esophageal sphincter; UES, upper esophageal sphincter.

staging is done largely in the absence of histologic cancer data in that the TNM categories are typically defined by imaging and not by microscopic examination of a resection specimen. Dissimilar stage group

ypTNM

	N0	N1	N2	N3	M1
T0	I	IIIA	IIIB	IVA	IVB
Tis	I	IIIA	IIIB	IVA	IVB
T1	I	IIIA	IIIB	IVA	IVB
T2	I	IIIA	IIIB	IVA	IVB
T3	II	IIIB	IIIB	IVA	IVB
T4a	IIIB	IVA	IVA	IVA	IVB
T4b	IVA	IVA	IVA	IVA	IVB

Figure 5. Postneoadjuvant pathologic stage groups (ypTNM): adenocarcinoma and squamous cell carcinoma.

composition and survival profiles necessitated clinical stage groups (cTNM) separate from pathologic stage groups (pTNM).

Adenocarcinoma. cStage0 comprises cTis (Fig. 6A). cStage I consists exclusively of cT1N0M0. cStage IIA is cT1N1M0 and cStage IIB is cT2N0M0. cStage III comprises cT2N1M0 and cT3-4aN0-1M0. cStage IVA consists of T4bN0-1M0 and all cN2-N3M0 cancers. cStage IVB comprises all cM1 cancers.

Squamous Cell Carcinoma. cStage 0 comprises cTis (Fig. 6B). cStage I consists exclusively of cT1N0-1M0. cStage II comprises cT2N0-1M0 and cT3N0M0 cancers. cStage III comprises cT3N1M0 and cT1-3N2M0 cancers. cT4N0-2M0 and all cN3M0 cancers are placed in cStage IVA. cStage IVB is reserved for cM1 cancers.

A pTNM Adenocarcinoma

		N0	N1	N2	N3	M1
Tis	0					
	G1	IA	IIIB	IIIA	IVA	IVB
T1a	G2	IB	IIIB	IIIA	IVA	IVB
	G3	IC	IIIB	IIIA	IVA	IVB
	G1	IB	IIIB	IIIA	IVA	IVB
T1b	G2	IB	IIIB	IIIA	IVA	IVB
	G3	IC	IIIB	IIIA	IVA	IVB
	G1	IC	IIIA	IIIB	IVA	IVB
T2	G2	IIA	IIIB	IIIB	IVA	IVB
	G3	IIA	IIIB	IIIB	IVA	IVB
T3	G1	IIIB	IIIB	IIIB	IVA	IVB
T4a	G1	IIIB	IIIB	IVA	IVA	IVB
T4b	G2	IVA	IVA	IVA	IVA	IVB

B pTNM Squamous Cell Carcinoma

		N0		N1	N2	N3	M1
		L	U/M	N1	N2	N3	M1
Tis	0						
	G1	IA	IA	IIIB	IIIA	IVA	IVB
T1a	G2-3	IB	IB	IIIB	IIIA	IVA	IVB
	G1	IB		IIIB	IIIA	IVA	IVB
	G2-3	IB	IB	IIIA	IIIB	IVA	IVB
T2	G1	IIA	IIA	IIIB	IIIB	IVA	IVB
	G2-3	IIA	IIA	IIIB	IIIB	IVA	IVB
T3	G1	IIA	IIA	IIIB	IIIB	IVA	IVB
T4a	G2-3	IIA	IIA	IIIB	IIIB	IVA	IVB
	G1	IIIB		IIIB	IVA	IVA	IVB
T4b	G2-3	IIIB		IIIB	IVA	IVA	IVB

Figure 4. (A) Pathologic stage groups (pTNM): adenocarcinoma. (B) Pathologic stage groups (pTNM): squamous cell carcinoma.

A cTNM Adenocarcinoma						B cTNM Squamous Cell Carcinoma					
	N0	N1	N2	N3	M1		N0	N1	N2	N3	M1
Tis	0					Tis	0				
T1	I	IIA	IVA	IVA	IVB	T1	I	I	III	IVA	IVB
T2	IIB	III	IVA	IVA	IVB	T2	II	II	III	IVA	IVB
T3	III	III	IVA	IVA	IVB	T3	II	III	III	IVA	IVB
T4a	III	III	IVA	IVA	IVB	T4a	IVA	IVA	IVA	IVA	IVB
T4b	IVA	IVA	IVA	IVA	IVB	T4b	IVA	IVA	IVA	IVA	IVB

Figure 6. (A) Clinical stage groups (cTNM): adenocarcinoma. (B) Clinical stage groups (cTNM): squamous cell carcinoma.

Conclusions

Eighth edition staging of cancer of the esophagus and esophagogastric junction is data driven and expanded from the seventh edition of pathologic stage groups (pTNM) only, to include pathologic stage groups after postneoadjuvant therapy (ypTNM) and clinical stage groups (cTNM) before treatment decision (Table 2).

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Table 2. Changes in Eighth Edition from Seventh Edition by Classification

Stage	Changes
pTNM	
Categories	
T	T1 subcategorized as T1a and T1b, producing stage subgroups IA and IB for squamous cell carcinoma and IA and IC for adenocarcinoma T2 squamous cell carcinoma: location removed as staging category T4a includes direct invasion of peritoneum
G	G4 was eliminated, and additional testing is required to uncover glandular (G3 adenocarcinoma) or squamous (G3 squamous) differentiation. If the cancer remains undifferentiated, it is categorized as G3 squamous cell carcinoma
L	Cancers of the esophagogastric junction that have their epicenters within the proximal 2 cm of the gastric cardia are staged as esophageal cancers. Those with epicenters >2 cm distal to the esophagogastric junction, staged in the seventh edition as esophageal cancers, even if the esophagus is involved, are staged as stomach cancers
Stage groups	
III	Subgroup IIIC in seventh edition removed
IV	Subgrouped as IVA and IVB
ypTNM	
Stage groups	
All	Not shared with pTNM. Identical grouping for adenocarcinoma and squamous cell carcinoma
cTNM	
Stage groups	
All	Not shared with pTNM. Separate groupings for adenocarcinoma and squamous cell carcinoma

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