Staging of Cancer of the Esophagus and Esophagogastric Junction

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Staging of cancer of the esophagus and esophagogastric junction for the eighth edition of the AJCC and UICC cancer staging manuals [1, 2] was constructed on a strong foundation of seventh edition data and analysis [3, 4]. A greatly expanded eighth edition Worldwide Esophageal Cancer Collaboration (WECC) database, with a substantial increase in both numbers of patients entered and variables collected [5–7], facilitated 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.

Key to eighth edition staging is stage groupings by classifications. There are three separate classifications each with separate recommendations for both adenocarcinoma and squamous cell carcinoma: the classic reference pathologic (pTNM) stage groupings, the newly introduced neoadjuvant pathologic (ypTNM) stage groupings, and clinical (cTNM) stage groupings [8–10].

Cancer Classifications

Published in 1977, the AJCC "first edition" Manual for Staging of Cancer introduced AJCC designated TNM definitions and, where possible, stage groupings for 18 disease sites, including the esophagus. Importantly, "general rules and the relationship between time and the staging of cancer" were introduced. These "Rules for Classification" included pretreatment information, which was designated clinical diagnostic staging (cTNM); information obtained at surgical exploration, designated surgical-evaluation staging (sTNM); information from gross and histologic examination of the resection specimen, designated posttreatment pathologic staging

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(pTNM); information obtained at treatment failure and before additional treatment, designated retreatment staging (rTNM); and information found at autopsy, designated autopsy staging (aTNM) [11]. These have evolved primarily into clinical (cTNM), pathological (pTNM), and postneoadjuvant (ypTNM) stage groups.

Inconsistent and ineffective clinical staging modalities and newness of neoadjuvant therapy, compared to the conclusiveness of pathologic assessment of resection specimens, have led to sharing of pathologic stage grouping (pTNM) with corresponding cTNM or ypTNM groups. However, this sharing implies more than a common TNM language. The dual purpose of staging as outlined in the "first edition" UICC Cancer Staging Manual states "(TNM) classification is a means of recording facts observed by the clinician [about the cancer] whereas staging implies interpretation of these facts regarding prognosis" [12]. Therefore both terminology and prognosis need to be shared. This sharing of stage groups among classifications was examined by the AJCC Upper GI Task Force in preparing the eighth edition cancer staging manual. The need for separate stage groups based on category (TNM) was identified, although the need to harmonize with prognosis was not. As a consequence, a given clinical stage group does not carry the same prognosis as the identical pathologic stage group or the identical postneoadjuvant stage group.

Cancer Categories

Another consequence of sharing among classifications was the sloppy use of the term "classification," to describe both the relationship of time to cancer staging (classification) and the cancer characteristics, now defined as categories [1]. Criteria define the elements of categories. Esophageal anatomic cancer categories include primary tumor (T), regional lymph node (N), and distant site (M) (Table 6.1; Fig. 6.1). Subcategorization of pT1 into pT1a and pT1b has refined and improved Stage I grouping. Regional lymph nodes (N), which are found in the periesophageal tissue from the upper esophageal sphincter to the celiac artery, are clarified in a new map (Fig. 6.2). The non-anatomic cancer category Grade (G) is important for pathologic stage grouping (pTNM) of early-stage cancers (Table 6.1). Undifferentiated cancers require additional 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 (Table 6.1). Cancer location is not important for adenocarcinoma stage grouping but in conjunction with Grade is necessary to subgroup pT3N0M0 squamous cell carcinoma. The definition of the esophagastric junction is revised such that cancers involving the esophagastric junction 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. 6.3). Location 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 [13].

Table 6.1 Cancer staging categories for cancer of the esophagus and esophagogastric junction

T Category	Criteria
Tx	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, malignant cells confined by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosa, or submucosa
T1a[a]	Tumor invades the lamina propria or muscularis mucosa
T1b[a]	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a[a]	Tumor invading pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b[a]	Tumor invading other adjacent structures, such as aorta, vertebral body, and airway.
N category	*Criteria*
NX	Regional lymph nodes cannot be accessed
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 or more regional lymph nodes

M category	*Criteria*
M0	No distant metastasis
M1	Distant metastasis
Adenocarcinoma G category	*Criteria*
G1	Well differentiated, > 95% of tumor is composed by well-formed glands
G2	Moderately differentiated, 50% to 95% of tumor shows gland formation
G3	Poorly differentiated, tumors composed of nest and sheets of cells with <50% of tumor demonstrating glandular formation. Undifferentiated, if glandular origin can be identified
Squamous cell carcinoma G category	*Criteria*
G1	Well-differentiated, prominent keratinization with pearl formation and a minor component of nonkeratinizing basal-like cells. Tumor cells are arranged in sheets, and mitotic counts are low
G2	Moderately differentiated, variable histologic features, ranging from parakeratotic to poorly keratinizing lesions. Generally, pearl formation is absent
G3	Poorly differentiated, consists predominantly of basal-like cells forming large and small nests with frequent central necrosis. The nests consist of sheets or pavement-like arrangements of tumor cells, and occasionally are punctuated by small numbers of parakeratotic or keratinizing cells

[a]Subcategories

Cancer Stage Groupings

Pathologic Stage Grouping (pTNM)

Historically, pathologic stage groupings after esophagectomy alone have been the sole basis for all cancer staging. Today pathologic staging is losing its clinical relevance for advanced stage cancer as neoadjuvant therapy replaces esophagectomy

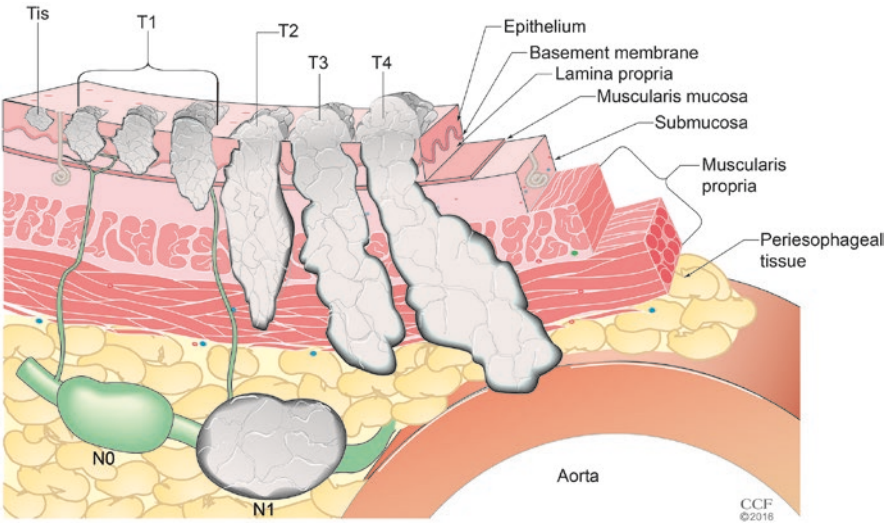

Fig. 6.1 Eighth edition TNM categories. T is categorized as Tis: high-grade dysplasia; T1: cancer invade lamina propria, muscularis mucosae, or submucosa and are subcategorized into T1a (cancer invades lamina propria or muscularis mucosae) and T1b (cancer invades submucosa); T2: cancer invades muscularis propria; T3: cancer invades periesophageal tissue; T4: cancer invades local structures and are subcategorized as T4a (cancer invades adjacent structures such as pleura, pericardium, azygos vein, diaphragm, or pericardium; and T4b (cancer invades major adjacent structures, such as aorta, vertebral body, or trachea). N is categorized as N0: no regional lymph node metastasis; N1: regional lymph node metastases involving 1–2 nodes; N2: regional lymph node metastases involving 3–6 nodes; and N3: regional lymph node metastases involving 7 or more nodes. M is categorized as M0: no distant metastasis; and M1: distant metastasis

alone. However, it remains relevant for early-stage cancers and as an important staging and survival reference point.

Squamous Cell Carcinoma

In the eighth edition, there is no net change in the number of staging subgroups; however, there is significant rearrangement and renaming (Table 6.2a). pStage 0 is restricted to high-grade glandular dysplasia, pTis. Subcategorization of T1 combined with Grade requires 2 pStage I subgroups: pStage IA (pT1aN0M0G1) and pStage IB (pT1aN0M0G2-3, pT1bN0M0, and pT2N0M0G1). pT2N0M0G2-3 cancers, pT3N0M0 cancers of the lower thoracic esophagus, and pT3N0M0G1 cancers of the upper thoracic esophagus comprise pStage IIA. pStage IIB is comprised of T3N0M0G2-3 cancers of the upper thoracic esophagus and pT1N1M0 cancers. pStage III and pStage IV are identical for both adenocarcinoma and squamous cell carcinoma.

Adenocarcinoma

Staging subgroups increased from 9 in the seventh edition to 10 in the eighth (Table 6.2b). pStage 0 is restricted to high-grade glandular dysplasia, pTis.

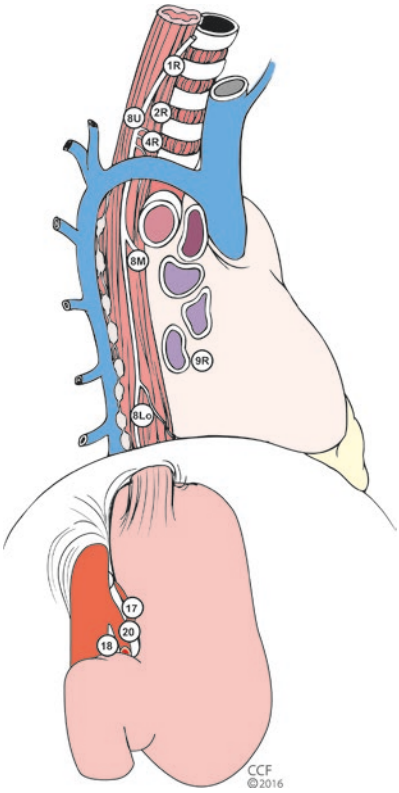

Fig. 6.2 (**a**–**c**): Lymph node maps for esophageal cancer regional lymph nodes, from left (**a**), right (**b**), and anterior (**c**). The regional lymph nodes are as follows: 1R: Right lower cervical paratracheal nodes: between the supraclavicular paratracheal space and apex of the lung, 1L: Left 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 innominate artery with the trachea and the apex of the lung, 2L: Left upper paratracheal nodes: between the top of the aortic arch and apex of the lung, R4: Right lower paratracheal nodes: between the intersection of the caudal margin of the innominate artery with the trachea and cephalic border of the azygos vein, L4: 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 EGJ, 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

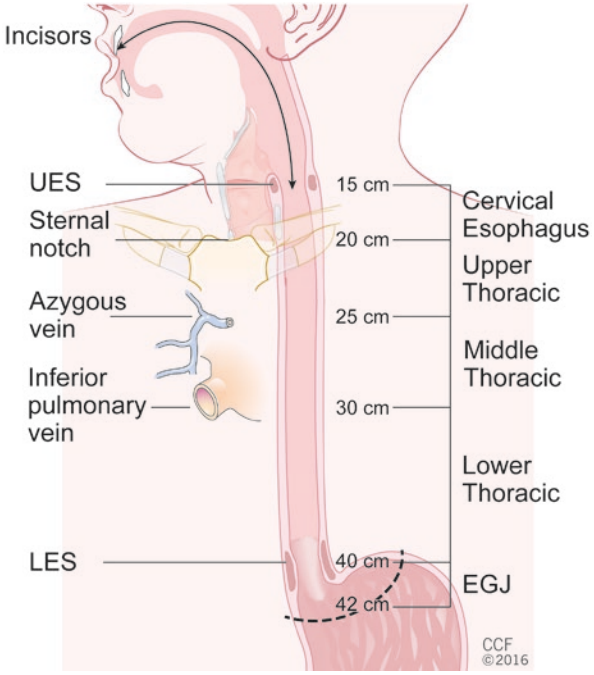

Fig. 6.3 Location of esophageal cancer primary site, including typical endoscopic measurements of each region measured from the incisors. Exact measurements depend on body size and height. Location of cancer primary site is defined by cancer epicenter. Cancers involving the EGJ that have their epicenter 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 groupings. EGJ esophagogastric junction, LES lower esophageal sphincter, UES upper esophageal sphincter

Subcategorization of T1 combined with Grade requires 3 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. T3N0M0 and pT1N1M0 comprise pStage IIB. pStage III is reserved for advanced cancers with relatively good survival. pT2N1M0 and pT1N2M0 form pStage IIIA, while 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 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.

Neoadjuvant Pathologic Stage Grouping (ypTNM)

New to the eighth edition is stage grouping of patients with esophageal cancers that have undergone neoadjuvant therapy and pathologic review of the resection specimen. Drivers of this addition include absence of equivalent pathologic (pTNM)

Table 6.2 (**a**) Pathologic Stage Groupings (pTNM)—squamous cell carcinoma. (**b**) Pathologic Stage Groupings (pTNM)—adenocarcinoma

a

		N0		N1	N2	N3	M1
		L	U/M				
Tis		0					
T1a	G1	IA	IA	IIB	IIIA	IVA	IVB
	G2-3	IB	IB				
T1b		IB		IIB	IIIA	IVA	IVB
T2	G1	IB	IB	IIIA	IIIB	IVA	IVB
	G2-3	IIA	IIA				
T3	G1	IIA	IIA	IIIB	IIIB	IVA	IVB
	G2-3	IIA	IIB				
T4a		IIIB		IIIB	IVA	IVA	IVB
T4b		IVA		IVA	IVA	IVA	IVB

b

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

categories for the peculiar neoadjuvant pathologic categories (ypT0N0-3M0 and ypTisN0-3M0), dissimilar stage group compositions, and markedly different survival profiles.

The groupings are identical for both histopathologic cell types (Table 6.3). Grade plays no role in neoadjuvant pathologic stage grouping. ypStage I is comprised of ypT0-2N0M0 cancers. ypStage II is the single entity ypT3N0M0. ypStage IIIA is comprised of cancers confined to the esophageal wall with ypN1 regional nodal

Table 6.3 Neoadjuvant pathologic stage groupings (ypTNM)—adenocarcinoma and squamous cell carcinoma

	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

category (ypT0-2N1M1). ypStage IIIB is comprised of ypT1-3N2M0, ypT3N1M0, and ypT4aN0M0 cancers. ypStage IVA includes ypT4aN1-2M0, ypT4bN0-2M0, and yp TanyN3M0. ypStage IVB is comprised of ypM1 cancers.

Clinical Stage Grouping (cTNM)

Also new to the eighth edition is clinical stage grouping (cTNM) prior to treatment decision (Table 6.4). Clinical 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 composition (Tables 6.2 and 6.4) and survival profiles necessitated clinical stage grouping (cTNM) separate from pathologic stage grouping (pTNM).

Squamous Cell Carcinoma

cStage 0 is comprised of cTis (Table 6.3a). cStage I is exclusivelycT1N0-1M0. cStage II is comprised of cT2N0-1M0 and cT3N0M0 cancers. cStage III is comprised of cT3N1M0 and cT1-3N2M0 cancers. cT4a-bN0-2M0 and all cN2-N3M0 cancers are placed in cStage IVA. cStage IVB is reserved for cM1 cancers.

Adenocarcinoma

cStage 0 is comprised of cTis (Table 6.3b). cStage I is exclusively cT1N0M0. cStage IIA is cT1N1M0 and cStage IIB is cT2N0M0. cStage III is cT2N1, cT3-4aN0-1M0. T4bN0-1M0, and all cN2-N3M0 comprise cStage IVA. cStage IVB is comprised of all cM1 cancers.

Table 6.4 (**a**) Clinical stage groupings (cTNM)—squamous cell carcinoma. (**b**) Clinical stage groupings (cTNM)—adenocarcinoma

a

	N0	N1	N2	N3	M1
Tis	0				
T1	I	I	III	IVA	IVB
T2	II	II	III	IVA	IVB
T3	II	III	III	IVA	IVB
T4a	IVA	IVA	IVA	IVA	IVB
T4b	IVA	IVA	IVA	IVA	IVB

b

	N0	N1	N2	N3	M1
Tis	0				
T1	I	IIA	IVA	IVA	IVB
T2	IIB	III	IVA	IVA	IVB
T3	III	III	IVA	IVA	IVB
T4a	III	III	IVA	IVA	IVB
T4b	IVA	IVA	IVA	IVA	IVB

Changes Between Seventh and Eighth Edition Cancer Staging

The changes in classifications and categories between the seventh and eighth edition are listed in Table 6.5.

Table 6.5 8th edition: changes from the seventh edition

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	pStage III	Subgroup IIIC in seventh edition removed
	pStage IV	Subgrouped as IVA and IVB
ypTNM		
Stage groups		No longer shared with pTNM, separate groupings identical for squamous cell carcinoma and adenocarcinoma
cTNM		
Stage groups		No longer shared with pTNM, separate groupings for squamous cell carcinoma and adenocarcinoma

Conclusions

Eighth edition staging for cancer of the esophagus and esophagogastric junction are data-driven and expanded from pathologic stage grouping (pTNM) to pathologic stage grouping after neoadjuvant therapy (ypTNM) and clinical staging (cTNM) before treatment decision.

References

1. Rice TW, Kelsen DP, Blackstone EH, et al. Esophagus and esophagogastric junction. In: Amin MB, Edge SB, Greene FL, et al., editors. AJCC cancer staging manual. 8th ed. New York, NY: Springer; 2017. p. 185–202.
2. International Union Against Cancer. Oesphagus including oesophagogastric junction. In: Brierley JD, Gospodarowicz MK, Wittekind C, editors. TNM classification of malignant Tumors. 8th ed. Oxford, England: Wiley; 2017. p. 57–62.
3. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. American Joint Committee on Cancer Staging Manual. 7th ed. New York: Springer-Verlag; 2010.
4. Sobin LH, Gospodarrowicz MK, Wittekind C, editors. TNM classifications of malignant tumors. International Union against Cancer. 7th ed. Oxford, England: Wiley-Blackwell; 2009.
5. Rice TW, Chen L-Q, Hofstetter WL, et al. Worldwide Esophageal cancer collaboration: pathologic staging data. Dis Esophagus. 2016;29:724–33.
6. Rice TW, Lerut TEMR, Orringer MB, et al. Worldwide Esophageal cancer collaboration: neoadjuvant pathologic staging data. Dis Esophagus. 2016;29:715–23.

7. Rice TW, Apperson-Hansen C, DiPaola LM, et al. Worldwide Esophageal Cancer Collaboration: clinical staging data. Dis Esophagus. 2016;29:707–14.
8. Rice TW, Ishwaran H, Hofstetter WL, Kelsen D, Blackstone EH. Recommendations for pathologic stage grouping (pTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. Dis Esophagus. 2016;29:897–905.
9. Rice TW, Ishwaran H, Kelsen D, Hofstetter WL, Blackstone EH. Recommendations for neoadjuvant pathologic stage grouping (ypTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. Dis Esophagus. 2016;29:906–12.
10. Rice TW, Ishwaran H, Blackstone EH, Hofstetter WL, Kelsen D. Recommendations for clinical stage grouping (cTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. Dis Esophagus. 2016;29:913–9.
11. Manual for Staging of Cancer 1977. American Joint Committee for Cancer Staging and End-Results Reporting. Chicago; 1977.
12. International Union Against Cancer (UICC). TNM Classification of Malignant Tumors. Geneva; 1968.
13. Hayakawa Y, Sethi N, Sepulveda AR, Bass AJ, Wang TC. Oesophageal adenocarcinoma and gastric cancer: should we mind the gap? Nat Rev Cancer. 2016;16:305–18.