A cancer staging primer: Esophagus and esophagogastric junction

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Staging cancer of the esophagus and esophagogastric junction has been extensively changed and improved in the 7th edition of the American Joint Committee on Cancer (AJCC), *Cancer Staging Manual*.¹ Changes address problems of empiric stage grouping and lack of harmonization with stomach cancer. This was accomplished by assembling worldwide data and using modern machine learning techniques for data-driven staging.²⁻⁴ Improvements include new definitions of Tis, T4, regional lymph node, N classification, and M classification, and addition of the nonanatomic cancer characteristics: histopathologic cell type, histologic grade, and cancer location. Stage groupings were constructed by adherence to principles of staging, including monotonic decreasing survival with increasing stage group, distinct survival between groups, and homogeneous survival within groups.

CLASSIFICATIONS: CHANGES AND ADDITIONS

Primary tumor (T) classification has been changed for Tis and T4 cancers (Figure 1, Table 1). Tis is now defined as high-grade dysplasia and includes all noninvasive neoplastic epithelium that was previously called carcinoma in situ. T4, tumors invading local structures, has been subclassified as T4a and T4b; T4a tumors are resectable cancers invading adjacent structures, such as pleura, pericardium, or diaphragm. T4b are unresectable cancers invading other adjacent structures, such as aorta, vertebral body, or trachea. Otherwise, T classifications are unchanged.

A regional lymph node has been redefined to include any paraesophageal lymph node extending from cervical nodes to celiac nodes (Table 1). Data analyses support convenient coarse groupings of the number of cancer-positive nodes.²⁻⁴ Regional lymph node (N) classification comprises N0 (no cancer-positive nodes), N1 (1 or 2), N2 (3–6), and N3 (≥7). N classifications for cancers of the esophagus and esophagogastric junction are identical to stomach cancer N classifications.

The subclassifications M1a and M1b have been eliminated, as has MX (Table 1). Distant metastases are simply designated M0, no distant metastasis, and M1, distant metastasis.

Nonanatomic cancer characteristics identified as important for stage grouping were histopathologic cell type, histologic grade (Table 1), and tumor location (Table 1; Figure 2). Increasing histologic grade was associated with incrementally decreasing survival for early-stage cancers. For adenocarcinoma, the distinction of G1 and G2 (well and moderately differentiated) cancers from G3 (poorly differentiated) cancers was important for grouping stage I and IIA cancers. For squamous cell carcinoma, the distinction of G1 cancers from G2 and G3 cancers was important for grouping stage I and II cancers. Uncommon G4 (undifferentiated) cancers are staged as squamous cell carcinoma. Tumor location (upper and middle thoracic esophagus vs lower thoracic esophagus) was important for grouping T2-3N0M0 squamous cell cancers.

STAGE GROUPINGS

Stages 0 and IV are by definition (not data driven) TisN0M0 and T any N any M1, respectively. Stage groupings for M0 adenocarcinoma are shown in Figure 3. For T1N0M0 and T2N0M0 adenocarcinoma, subgrouping is by histologic grade, G1, and G2 (not G3) versus G3. The difference in survival between adenocarcinoma and squamous cell carcinoma was best managed by separate stage groupings for stages I and II.

Stage groupings for M0 squamous cell carcinoma are shown in Figure 4. For T1N0M0 squamous cell carcinoma, subgrouping is by histologic grade: G1 versus all other G (Figure 4, A). For T2N0M0 and T3N0M0 squamous cell carcinoma, stage grouping is by histologic grade and location (Figure 4, B). The 4 combinations range from G1 lower thoracic squamous cell carcinoma (stage IB), which has the best survival, to G2 to G4 upper and middle thoracic squamous cell carcinomas (stage IIB), which have the worst. G2 to G4 lower thoracic squamous cell carcinomas and G1 upper and middle thoracic squamous cell carcinomas are grouped together (stage IIA) with intermediate survival.

Stage 0, III, and IV adenocarcinoma and squamous cell carcinoma are identically stage grouped. Adenosquamous carcinomas are staged as squamous cell carcinoma.

ESOPHAGOGASTRIC JUNCTION CANCERS

In addition to being data driven, the 7th edition of the *AJCC Cancer Staging Manual* harmonizes staging of cancer across the esophagogastric junction. Previous staging editions

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FIGURE 1. Seventh edition TNM classifications. T is classified as Tis: high-grade dysplasia; T1: cancer invades lamina propria, muscularis mucosae, or submucosa; T2: cancer invades muscularis propria; T3: cancer invades adventitia; T4a: resectable cancer invades adjacent structures such as pleura, pericardium, or diaphragm; and T4b: unresectable cancer invades other adjacent structures, such as aorta, vertebral body, or trachea. N is classified as N0: no regional lymph node metastasis; N1: regional lymph node metastases involving 1 to 2 nodes; N2: regional lymph node metastases involving 3 to 6 nodes; and N3: regional lymph node metastases involving 7 or more nodes. M is classified as M0: no distant metastasis; and M1: distant metastasis.

produced different stages for these cancers depending on use of either esophageal or gastric stage groupings. The 7th edition staging is for cancers of the esophagus and esophagogastric junction and includes cancer within the first 5 cm of the stomach that invade the esophagogastric junction (Siewert III). All other stomach cancers are staged groupings.

TABLE 1. Summary of changes in anatomic classifications and additions of nonanatomic cancer characteristics

Changes in anatomic classifications

T classification

Tis is redefined and T4 is subclassified

Tis high-grade dysplasia

T4a resectable cancer invades adjacent structures, eg, pleura, pericardium, diaphragm

T4b unresectable cancer invades adjacent structures, eg, aorta, vertebral body, trachea

N classification

Regional lymph node is redefined

Any periesophageal lymph node from cervical lymph nodes to celiac node

N is classified

N0 no regional lymph node metastases

N1 1–2 positive regional lymph nodes

N2 3–6 positive regional lymph nodes

N3 ≥7 positive regional lymph nodes

M classification

M is redefined

M0 no distant metastases

M1 distant metastases

CONCLUSIONS

The new staging recommendations for cancer of the esophagus and esophagogastric junction are data driven and harmonized with stomach cancer. This required changes in TNM definitions and addition of nonanatomic cancer characteristics. For cancers of the esophagus and esophagogastric junction,

TABLE 1. Continued

Additions of nonanatomic cancer characteristics

Histopathologic cell-type

Adenocarcinoma

Squamous cell carcinoma

Histologic grade

G1 well differentiated

G2 moderately differentiated

G3 poorly differentiated

G4 undifferentiated

Cancer location

Upper thoracic 20–25 cm from incisors

Middle thoracic >25–30 cm from incisors

Lower thoracic >30–40 cm from incisors

Esophagogastric junction includes cancers whose epicenter is (1) in the lower thoracic esophagus, (2) in the esophagogastric junction, or (3) within proximal 5 cm of the stomach (cardia) that extend into the esophagogastric junction or lower thoracic esophagus

FIGURE 2. Cancer location. Cervical esophagus, bounded superiorly by the cricopharyngeus and inferiorly by the sternal notch, is typically 15 to 20 cm from the incisors at esophagoscopy. Upper thoracic esophagus, bounded superiorly by the sternal notch and inferiorly by the azygos arch, is typically more than 20 to 25 cm from the incisors at esophagoscopy. Middle thoracic esophagus, bounded superiorly by the azygos arch and inferiorly by the inferior pulmonary vein, is typically more than 25 to 30 cm from the incisors at esophagoscopy. Lower thoracic esophagus, bounded superiorly by the inferior pulmonary vein and inferiorly by the lower esophageal sphincter, is typically more than 30 to 40 cm from the incisors at esophagoscopy; it includes cancers whose epicenter is within the proximal 5 cm of the stomach that extend into the esophagogastric junction or lower thoracic esophagus. UES, Upper esophageal sphincter; EGJ, esophagogastric junction.

Squamous Cell Carcinoma

		T1	T2 – T3	Grade/Location ■ Lower ■ Upper Middle
G1	A	IA	IB IIA	
		IB	IIA IIB	

Squamous Cell Carcinoma

		T1	T2	T3	T4	
					a	b
N0					IIIA	IIIC
N1		IIB	IIB	IIIA	IIIC	IIIC
N2		IIIA	IIIA	IIIB	IIIC	IIIC
N3		IIIC	IIIC	IIIC	IIIC	IIIC

FIGURE 4. Stage groupings for M0 squamous cell carcinoma. A, Stage groupings for T1N0M0 and T2-3N0M0 squamous cell carcinomas by histologic grade (G) and cancer location. B, Stage groupings for all other M0 squamous cell carcinomas.

Adenocarcinoma

		T1	T2	T3	T4	
					a	b
G1-2	N0	IA	IB	IIB	IIIA	IIIC
		IB	IIA			
G3	N1	IIB	IIB	IIIA	IIIC	IIIC
	N2	IIIA	IIIA	IIIB	IIIC	IIIC
	N3	IIIC	IIIC	IIIC	IIIC	IIIC

FIGURE 3. Stage groupings for M0 adenocarcinoma by T and N classification and histologic grade (G).

stages 0, III, and IV are identical for both adenocarcinoma and squamous cell carcinoma. However, stage groupings differ for stage I and II cancers on the basis of histopathologic cell type, histologic grade, and cancer location.

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