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METHODS

TNM system for staging esophageal cancer: A narrative review

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Cancer is a critical health concern worldwide, and this chronic disease is gradually growing. In 2020 alone, 19,292,789 new cases were reported globally; by 2025, this figure is expected to rise to 21,618,445. Among the various cancers, esophageal cancer is considered one of the most aggressive, with a poor survival rate. It currently ranks eighth in incidence and sixth in mortality among all cancers, and its frequency and mortality are progressively increasing, with 604,100 new cases and 5,44,000 deaths by 2020. Several staging systems have been proposed for esophageal cancer, including the Ellis, Japan Esophageal Society, and AJCC/UICC systems. However, since the AJCC/UICC established their staging criteria, these have been the most widely used and accepted by the medical community.

The different AJCC Cancer Staging Manual editions have progressively incorporated changes in the esophageal cancer staging as our understanding, which has been exponentially influenced by various conventional diagnostic means. The TNM staging system's editions are updated periodically, but how much have they changed since the first edition? What have been the main changes introduced in each edition concerning esophageal cancer? This narrative review aims to answer these questions through a thorough and comparative analysis of each TNM addition.

The esophageal cancer staging has changed with each TNM edition, allowing a better understanding of it and applying better therapeutic methods. The last two editions have introduced significant changes with the incorporation of non-anatomical categories into the staging grouping and the addition of a classification for patients undergoing neoadjuvant therapy.

Keywords: esophageal adenocarcinoma, esophageal cancer, esophageal squamous cell carcinoma, staging, TNM.

Introduction

Cancer a critical health issue worldwide, a pandemic with significant repercussions on individuals, families, and society (1). The World Health Organization (WHO) states it is the most crucial obstacle to globally increasing life expectancy (2). This chronic disease is gradually growing. In 2018, 18.1 million new cases were reported around the world. In 2020, 19.3 million; by 2025, this figure is expected to rise to 21 618 445. Annual global cancer mortality reported in 2020 was 9,958,137 deaths, with Asia having the highest mortality (5,809,789 deaths), followed by Europe (1,955,231 deaths) (3, 4).

Unsurprisingly, with such overwhelming figures, the scientific community considers it vital to develop measures to control, treat, and reduce cancer incidence and its effects on the world's population. One of the steps in this direction was creating a staging system (SS) that would allow a better understanding of cancer while adjusting to the specific characteristics of each patient's neoplasm. Staging

Abbreviations: OAC, Oesophageal adenocarcinoma; OC, Oesophagus cancer, OSCC, Oesophageal squamous cell carcinoma; OGJ, Oesophagogastric junction; SS, Staging system.

has guaranteed an optimal and scientific way of assessing the neoplasm's magnitude severity, the survival probabilities, the most appropriate therapeutic options for each case, and identifying clinical studies that could serve as treatment options (5). The International Union for Cancer Control (UICC) has defined six objectives for staging: To help plan treatment, provide a prognosis, evaluate treatment results, facilitate information exchange between centers, contribute to research into human malignant neoplasms, and support cancer control actions (6).

Today's SS has only sometimes been available to us; they have been gradually developed and perfected as medicine, particularly oncology, has reached higher standards. Technological developments within the biomedical sciences, surgical sciences advances, and cancer molecular biology understanding have provided essential tools, as have the countless studies focused on cancer. The credit for developing the first SS goes to the French surgeon Pierre Denoix of the Gustave Roussy Institute, who, between 1942 and 1953, created an anatomical SS for breast cancer based on tumor size, lymph node status, and metastases. This attempt to provide the scientific community with a unified system for staging cancer was reinforced by the International Union against Cancer, now known as the International Union for Cancer Control, the WHO, and the American Joint Committee on Cancer (AJCC) subsequent actions (7, 8).

The TNM is the most widely accepted SS globally. It is updated periodically, with a revision cycle of 6–8 years, in response to new clinical data and advances in the knowledge of cancer biology and prognostic factors (9). Since 1977, continuous revisions have been made to generate new editions of the AJCC Cancer Staging Manual, introducing significant changes in several of them. The most recent, although not widely used in the western hemisphere, is the TNM8, which has incorporated new elements, especially concerning oesophageal cancer (OC) (10, 11).

OC is an overly aggressive neoplasm with a meager survival rate. It currently ranks eighth in frequency and sixth in mortality among all cancers globally, (12) although these statistics may vary between geographic areas and even within countries (1, 13, 14). This sickness magnitude is alarming, with 604,100 new cases and 544,000 deaths reported in 2020 alone, responsible for one in every 18 cancer deaths that year (15). Several SS have been proposed for OC, including the Ellis, Japan Esophageal Society, and AJCC/UICC systems. However, since the AJCC/UICC established their staging criteria, these have been the most widely used and accepted by the medical community. Nevertheless, in 1997, Ellis proposed his SS based on the flaws observed in the TNM, and, assuming Skinner's criteria, his classification uses the WNM system (wall penetration, lymph nodes, and metastases). For all SS, the depth of invasion and the local and regional lymph node lesions extent influence the prognosis. However, the Ellis sort emphasizes the importance of invasion depth and the number of involved nodes' influence on survival (16, 17).

The different AJCC Cancer Staging Manual editions have progressively incorporated changes in the OC staging as our understanding of it has advanced, which has been exponentially influenced by various conventional diagnostic means such as radiography, upper endoscopy, and computed tomography (CT), (18–20) and more advanced ones such as endoscopic ultrasound (EUS), positron emission tomography (PET), (21, 22) and magnetic resonance imaging (MRI), (17, 23) as well as anatomopathological and molecular studies.

The TNM staging system's editions are updated periodically, but how much have they changed since the first edition? What have been the main changes introduced in each edition concerning esophageal cancer? This narrative review aims to answer these questions through a thorough and comparative analysis of each TNM addition. Since there is no manuscript in the literature available in databases that analyses all TNM staging system's editions as a whole and the importance of this staging system, it has been decided to conduct this narrative review, which offers a detailed exploration of distinct categories' esophageal cancer TNM and its evolution and changes over time. Undoubtedly, cancer SS is a crucial tool in oncology.

Methodology

Relevant statistics on cancer and esophageal cancer available in the WHO and International Agency for Research on Cancer (IARC) databases were consulted for background information. The AJCC Cancer Staging Manual was taken as the primary source of information for the review. The categories were compared according to the information obtained from PubMed, ClinicalKey, ClinicalTrials.gov, the Cochrane and SciELO databases, and browsers such as Google Scholar.

The strategy was based on a keyword combination: esophageal cancer, esophagus adenocarcinoma, esophagus cancer, esophagus cancer staging, esophagus squamous cell carcinoma, and their equivalents in US English, Spanish, and Portuguese, without language limit and with free abstract or full text. We also reviewed books and chapters dealing with OC and its staging.

Oesophagus anatomical division

In the first edition, as in subsequent editions, the esophagus was divided from an anatomic standpoint for cancer classification, staging, and reporting in diverse regions. In the TNM1 case, (24) the esophagus was divided into three principal regions, namely, the cervical, upper-midthoracic, and lower esophagus. No boundaries were

declared between the upper and midthoracic regions, but they were analyzed together.

In TNM2, (25) these regions remained unchanged. However, in TNM3, (26) unlike the previous ones, the esophagus was divided into two principal regions: cervical and intrathoracic. The latter was subdivided into upper, midthoracic, and lower thoracic and abdominal portions. The lower thoracic and abdominal regions were not considered separately but as a single region. In this edition, not only the regions' designations but also their boundaries and extent. The TNM3 also included the corresponding topographical code for each region according to the International Classification of Diseases for Oncology (ICD-O).

TNM4 did not establish changes concerning the anatomical division. However, in TNM5, it was stated that the oesophagogastric junction (OGJ), which until then had not been considered within the esophagus divisions, formed part of the lower intrathoracic portion together with the intra-abdominal esophagus portion (27, 28). This division has been maintained until TNM8 (29). However, in TNM6, (30) despite did not establish substantive changes concerning the anatomical division from a conceptual standpoint, the region previously known as the lower thoracic esophagus was denominated the lower thoracic and abdominal portion, and when defining the characteristics, the lower intrathoracic region changed its length from 8–3 cm.

The esophagus division into four regions has been maintained in the most recent TNM system editions (9, 29). However, it emphasizes that these divisions are purely arbitrary and that the esophagus is divided into three principal regions (cervical, thoracic, and abdominal) in the same way as the Japan Esophageal Society (JES) does (31). The abdominal esophagus is also described as part of the lower thoracic portion, and particular attention is paid to the OGJ (32, 33).

Oesophagogastric junction

While the first four AJCC/UICC Cancer Staging Manual editions (24–27) were silent on the OGJ, from TNM5 (28) onward, the OGJ was considered part of the lower intrathoracic portion. Therefore, tumors in this region were considered esophageal tumors. However, TNM6 (30) mentioned the controversies regarding distinguishing distal esophageal and OGJ tumors extending distally toward the cardia from proximal stomach tumors, which led to a different approach to the OGJ tumors. Determining exact boundaries was challenging. Therefore, TNM6 agreed that all tumors originating between the OGJ and the cardia with a minimum involvement of 2 cm or less of the esophagus should be considered primary gastric tumors (30). Although this edition recognized the Siewert-Stein classification (34) based on a prospective analysis of 107 cases with OGJ cancer, it suggested that this required further validation to determine whether it was feasible for staging or prognostication.

TNM7 further elaborated on the OGJ neoplasms without attempting to subclassify tumors according to their topographical origin, as did the Siewert-Stein classification (35) and stipulated that tumors with an epicenter in the lower thoracic esophagus or within 5 cm proximal to the stomach (cardia) with an esophageal extension would be staged similarly to oesophageal adenocarcinomas (OAC). While other neoplasms with an epicenter in the stomach more than 5 cm distal to the OGJ or within 5 cm but without extension into the OGJ or esophagus are staged with gastric cancer (non-OGJ) TNM (9, 31).

A notable change regarding OGJ tumors is evident in the TNM8, (30) where tumors whose epicenter is encountered 2 cm proximal or distal to the anatomical OGJ are deemed OAC, correlating them with the Siewert-Stein classification, these corresponding to some type I and all type II. If the epicenter is located more distally than 2 cm, they are considered gastric tumors (Siewert III), which may or may not invade the esophagus (32, 36). These changes have critical surgical implications since, at least theoretically, it is assumed that Siewert-Stein type I and II tumors should be treated by oesophagectomy and type III by total gastrectomy extended to the distal esophagus (32).

Given the lymph node metastasis pattern, the OGJ cancers differ from those of the lower esophagus or upper stomach. Therefore, the JES also proposes their treatment independently. They use the Nishi classification to classify these tumors, which considers all OGJ cancers with an epicenter between 2 cm proximal and distal to the OGJ, regardless of histology (37).

Primary tumor (T-Category)

Primary tumor characteristics assessment is essential to define the extent of the esophagus and adjacent organs' involvement. The T-category and its definitions in each TNM edition have varied over time (**Table 1**).

TMN1 divided T-category for the three segments defined in this edition into T0, Tis, T1, T2, and T3. The tumor had to be T1, $\leq$ 5 cm in length, and not cause obstruction or circumferentially affect the esophagus. A T2 had to be $\geq$ 5cm with no obstruction or involvement of the esophageal circumference, or any size tumor causing obstruction or involving the entire esophageal circumference. In both cases, however, there was no extra-esophageal spread evidence; if present, it was considered T3. (24)

TNM2 (25) established two classifications, one from the clinical perspective (cTNM) and the other from a pathological standpoint (pTNM). The first introduced TX, while the second appeared for the first time, and its types pT0, pT1, pT2, and pT3 differed from their clinical homologues. The pTNM subdivided pT3 into pT3a and

TABLE 1 | T-category comparison based on each AJCC Cancer Staging Manual edition.

Primary tumor	TNM staging system				
	TNM1	**TNM2**	**TNM3–TNM6**	**TNM7 and TNM8**	
TX	–	Minimal requirements to assess primary tumor cannot be met	Primary tumors cannot be met	Primary tumors cannot be assessed	
T0	No demonstrable esophageal tumor	No evidence of a primary tumor	No evidence of a primary tumor	No evidence of a primary tumor	
Tis	Carcinoma *in situ*	Carcinoma *in situ*	Carcinoma *in situ*	High-grade dysplasia	
T1	T involving ≤5 cm length without obstruction, circumferential involvement, or extra-esophageal spread.	T involving ≤5 cm in length does not cause obstruction or circumferential involvement and without extra-esophageal spread.	Tumor invades the muscularis propria and submucosa.	Tumor invades the muscularis propria and submucosa.	
				T1a invades lamina propria.	T1b invades lamina submucosa.
T2	T involves ≥5 cm in length and does not cause obstruction, circumferential involvement, or extra-esophageal spread. Any size T with an obstruction or involving the entire circumference without extra-esophageal spread.	T involves ≥5 cm in length and does not cause obstruction, circumferential involvement, or extra-esophageal spread. Any size T with an obstruction or involving the entire circumference without extra-esophageal spread.	Tumor invades the muscularis propria.	Tumor invades the muscularis propria.	
T3	Any size T with extra-esophageal spread	Any size T with extra-esophageal spread	Tumor invades adventitia.	Tumor invades adventitia.	
T4	–	–	Tumor invades adjacent structures.	Tumor invades adjacent structures.	
				T4a Tumor resectable	T4b Tumor unresectable

pT3b. This division disappeared in TNM3, establishing a single classification applicable to the cervical and thoracic esophagus and redefined T-category according to the esophagus' histological architecture involvement. (26) Thus, T1 corresponded to lamina propria or submucosa invasion, T2 to muscularis propria invasion, T3 to adventitia invasion, and T4 to adjacent structures invasion.

The T-category remained unchanged in subsequent editions until the advent of TNM7, which redefined Tis and no longer considered it as carcinoma *in situ* as this term was no longer applicable to gastrointestinal tract columnar mucosa tumors and termed it "high-grade dysplasia", a term that includes all non-invasive neoplastic epithelium previously known as carcinoma *in situ*. Additionally, T1 was divided into T1a (lamina propria and muscularis mucosae invasion) and T1b (submucosa invasion), and T4 was divided into T4a (resectable tumors invading the pleura-peritoneum, diaphragm, or pericardium) and T4b (unresectable tumors invading the aorta, carotid arteries, azygos vein, left main bronchus, and vertebral bodies). (9)

TNM8 made no profound changes concerning the previous edition. However, regarding T4a, the azygos vein, which in TNM7 was considered part of T4b, was added to the adjacent organs, and tumors involving the airways and vascular arch were involved and also defined as unresectable tumors (T4b). (9, 29)

Regional lymph nodes (N-category)

The regional lymph nodes corresponding to each esophagus anatomical portion have been stated in each TNM edition. However, the last three editions give the most detailed and complete descriptions. In TNM1, cervical or supraclavicular nodes belonged to the cervical esophagus, while adjacent mediastinal nodes were stated for the thoracic esophagus. More distant lymph nodes were considered metastases. The lymph node description stayed the same in TNM2 (24, 25). In contrast, in TNM3, a more detailed regional lymph node description of each esophageal subdivision was included. The following regional lymph nodes were recorded for the cervical esophagus: superior mediastinal, internal jugular, upper cervical, peri-oesophageal, supraclavicular, and cervical NOS. However, from TNM4 onward, the upper mediastinal nodes were not considered regional for the cervical esophagus. At the same time, the scalenes and

the lower cervical were added, and the cervical NOS were removed from TNM6 (26, 27, 30).

On the contrary, TNM7 and TNM8 specify that the cervical esophagus corresponds to the anterior compartment lymph nodes, level VI (paratracheal, pretracheal, and groove's esophageal lymph nodes), and the superior mediastinal nodes, level VII (paratracheal, pretracheal, precricoid, parathyroid, and nodes along the recurrent nerve) (9, 29).

Regarding the intrathoracic portion, lymph nodes in TNM3 were defined for each anatomical region for the upper-mid thoracic (internal jugular, tracheobronchial, peritracheal, peri-bronchial, carinal, hilar, posterior mediastinal, and peri-esophageal) and for the lower intrathoracic portion (left gastric, cardial, peri-gastric NOS, posterior mediastinal, and the minor curvature of the stomach lymph nodes). It was specified that any cervical, supraclavicular, scalene, or abdominal lymph nodes should be considered distant metastases for the upper and middle portions. In contrast, for the lower esophagus, any lymph node involvement not among those described for this region would be considered distant metastases (26).

Advances in the study and esophageal neoplasms understanding, particularly the excellent esophageal lymphatic drainage knowledge, led to a broader and more profound regional lymph nodes interpretation in the seventh edition. In the TNM7, esophageal lymphatic drainage characteristics were briefly presented. It was explained that this is intramural and longitudinal and that a submucosal lymphatic network favors early metastases in superficial cancers. The fact that the submucosal plexus is longitudinal leads to orthogonal lymphatic metastases, with the implication that the primary tumor location may not coincide with the lymph node involvement to which the tumor-affected region drains (9).

Both TNM7 and TNM8 give the thoracic esophagus regional lymph nodes a detailed description (**Figure 2**). TNM7 removed lymph nodes 18 and 19 (common hepatic and splenic artery lymph nodes, respectively) as regional lymph nodes; therefore, their involvement was regarded as distant metastases (9). Nevertheless, in TNM8, these lymph nodes were not eliminated, and it was specified that only those should be considered regional lymph nodes, those that were immediately on the common proximal hepatic and proximal splenic arteries (29).

The N-category description in TNM1 was made separately for the cervical and thoracic esophagus (**Table 2**), specifying the impossibility of accessing the lymph nodes corresponding to the thoracic esophagus by routine examination, making it imperative that they are determined during surgery. The N-category definition was based on mobility, whether they were palpable or not, and their bilaterality. TNM2 added the NX sort to define cervical tumors in which the minimum requirements for assessing regional nodes, previously used for thoracic esophagus tumors, could not be met.(24, 25) From TNM3 (26) onward, the N2 and N3 sort were eliminated, an element that would be kept in the two subsequent editions. What was known until TNM6 concerning lymph nodes experienced an exponential leap with the TNM7 publication, (9) where, in addition to the N2 and N3 sorts, they were redefined from N1–N3. The new definition was based on the number of nodes involved, and the criteria used previously were not kept. In TNM8, (29) no changes were made to the N definitions, but there were variations in the extension of nodes to be considered regional or distant metastases.

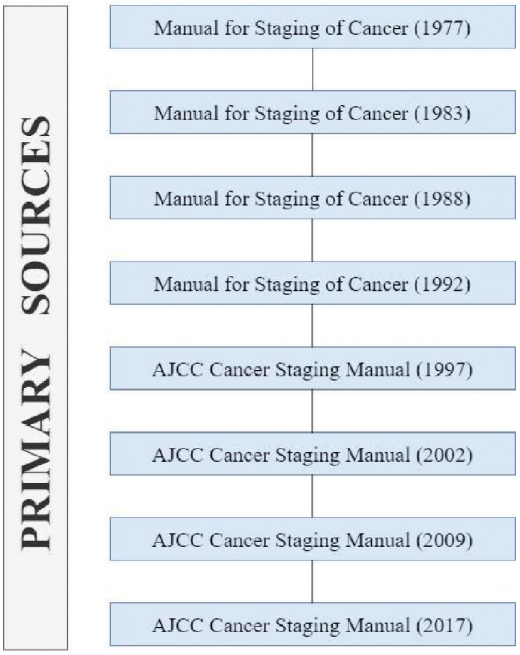

FIGURE 1 | Primary sources of information for comparison of the AJCC Cancer Staging Manual.

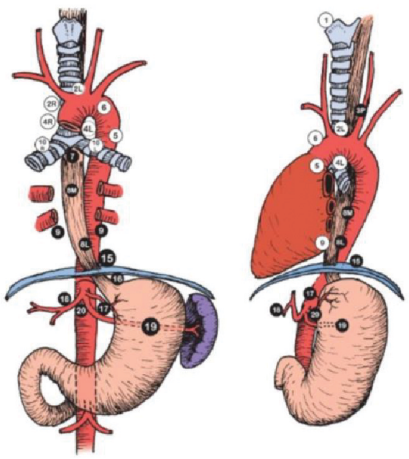

FIGURE 2 | Oesophagus lymph nodes according to the AJCC Cancer Staging Manual, seventh edition.

TABLE 2 | N-category comparison based on each AJCC Cancer Staging Manual edition.

Regional lymph node metastases	TNM staging system			
	TNM1	**TNM2**	**TNM3–TNM6**	**TNM7 and TNM8**
NX	–	Minimum requirements to assess regional nodes cannot be met	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No clinically palpable nodes	No clinically palpable nodes	No regional lymph node metastases	No regional lymph node metastases
	Surgical evaluation: non-positive nodes (thoracic esophagus)	Surgical evaluation: non-positive nodes (thoracic esophagus)		
N1	Palpable, mobile, unilateral nodes	Palpable, mobile, unilateral nodes	Regional lymph node metastases	Metastases in 1–2 regional lymph nodes
	Surgical evaluation: positive nodes (thoracic esophagus)	Surgical evaluation: positive nodes (thoracic esophagus)		
N2	Palpable, mobile, bilateral nodes	Palpable, mobile, bilateral nodes	–	Metastases in 3–6 regional lymph nodes
N3	Fixed nodes	Fixed nodes	–	Metastases in ≥7 regional lymph nodes

Distant metastases (M-category)

According to TNM7 and TNM8, the esophageal cancer metastases sites are all those that are not in direct continuity with the esophagus (9, 29). The M-category has varied with each edition. TNM1 defines three M-types: MX (not assessed), M0 (no known metastases), and M1 (distant metastases present). Until TNM4, these three M-types remained unchanged except for minor details in their definition that did not change the essence of what was argued in TNM1 (24–27).

However, TNM5 introduced a subdivision of M1 based on the esophagus's anatomical portions. M1a and M1b were defined for the three regions, with M1a and M1b being for the lower thoracic esophagus, celiac lymph node metastases, and other distant metastases, respectively. M1a was defined as cervical lymph node metastases for the upper thoracic esophagus, and M1b as other distant metastases. M1a was not applicable for the mid-thoracic esophagus, and M1b was like what was described for the previous regions (28). New changes were introduced in TNM7, (9) where only two M-types were defined, namely, M0 (no metastases evidence) and M1 (metastases evidence).

Tumor grade (G-category)

The term differentiation is applied in the case of neoplasms to parenchymal cells. It describes the grade to which parenchymal cells mimic comparable normal cells morphologically and functionally. It is assumed that well-differentiated tumors include cells that resemble the tissue's mature cells, from which they derive (38). For every TNM edition mentioned in the G-category. However, it was considered only from the TNM7 onward that its inclusion as a non-anatomical element in the OC staging (9).

Both TNM1 and TNM2 established the G-category for OC by designating it as G1 (well differentiated), G2 (moderately well differentiated), and G3–G4 (poorly to very poorly differentiated) (24, 25). The TNM3 introduced the GX sort (differentiation grade cannot be assessed) and further separated G3 and G4, defining them as poorly differentiated and undifferentiated. Unchanged along the next TNM, the most major change occurred when TNM7 was added to OC staging, and TNM7 specified that GX should be considered in the staging grouping like G1 for OAC and oesophageal squamous cell carcinoma (OSCC) and G4 as G3 in the OSCC case. Currently, the TNM8 group is G3, both poorly differentiated and undifferentiated tumors (9, 26, 29).

Tumor location (L-category)

L-category corresponds to the esophagus's anatomical divisions, so here we will stick only to how this has been conceived as a category for staging. In the AJCC Cancer Staging Manual's first six editions, cancer location was not considered a staging category; however, TNM7 incorporated it. It remains in the TNM8 as it plays a role in the OSCC staging. TNM7 stated that tumor location was defined by the tumor's upper (proximal) edge position in the esophagus (9). However, TNM8 noted that the tumor epicenter in the esophagus defined its location. The L-types were defined as follows: L (location unknown), upper (upper cervical esophagus to the azygos vein's lower edge), middle (azygos vein's lower edge to the inferior pulmonary vein's lower edge), and lower (inferior pulmonary vein's lower edge to the stomach and includes the OGJ) (29).

TABLE 3 | Host functional status (H) based on TNM1 and TNM2.

AJCC		ECOG Scale	Karnofsky Scale (%)
H0	Normal activity	0	90–100
H1	Symptomatic but ambulatory, self-care	1	70–80
H2	Ambulatory more than 50% of the time, occasionally needs assistance	2	60–50
H3	Ambulatory less than 50% of the time, needs nursing care	3	30–40
H4	Bedridden, may need hospitalization	4	20–10

Surgical margin (R-category)

Although not included in the categories used to group OC by stage, the R-category is vital as a prognostic factor in patients undergoing oesophagectomy. In both TNM1 and TNM2, the R-category was included along with its description but was not referred to in the subsequent ones (24, 25). Finally, TNM8 pointed out that the surgical margin is based on an intraoperative assessment combination by the surgeon and a pathological resected specimen evaluation. It also specifies that the assessment of the most profound margin should be made for tumors resected by endoscopic resection and that lateral margins are usually not applicable in fragmentary mucosal resection cases and should not be considered in the R designation (29). Host Functional Status (H).

Functional status measures how well a person can perform daily activities while living with cancer. There are two performance scales: one is the Eastern Cooperative Oncology Group (ECOG), and the other is the Karnofsky Performance Status (KPS). (39) While host functional status was never included as a category within the staging grouping for OC, the AJCC Cancer Staging Manual's first two editions (24, 26) had a host functional status that corresponded with the KPS and ECOG (**Table 3**). However, subsequent editions dispensed with this.

Histopathological type

Two histological varieties predominate in esophageal cancer, OAC and OSCC, which account for approximately 90% of all OC cases, and each has its characteristics; the remaining neoplasms are rare (10, 40, 41). OSCC was long assumed to be the predominant histological form. However, it has been observed in recent years that the OAC trend has increased significantly, mainly in Western countries (42–44). Although OSCC remains more frequent worldwide, the high incidence of OAC, coupled with recent findings showing genomic differences between OAC, OSCC, and OGJ adenocarcinoma cells, as well as significant differences for the survival by the stage of OAC and OSCC, were taken into account to develop a separate SS for both histopathological types (9, 29).

This new way of staging OC separately was adopted in TNM7 to establish one and is maintained in TNM8. Previous editions mentioned only the commonality of these two OC types or, as in TNM6, explained these histopathological types. However, they did not consider them a category within the staging grouping (9, 29, 30).

Staging

Grouping patients in the correct stage to provide adequate treatment is the fundamental aim of the TNM staging system. The T, N, and M categories have been used for staging, and the other categories mentioned in the manuals were not used as part of the grouping. This would change with TNM7, which presented significant changes concerning the previous editions. This edition was based on the Worldwide Esophageal Cancer Collaboration (WECC) results, created at the AJCC's behest and led by Dr. Thomas Rice and the Cleveland Clinic working group, which collected data from 4,627 patients who underwent oesophagectomy as their only treatment (9, 32).

Staging in TNM1 grouped patients into three stages. Stage I was applied to cervical and thoracic esophageal tumors, including Tis N0 M0 (carcinoma *in situ*), T1 N0 M0, and T1 NX M0. Stage II was applied to the cervical and thoracic esophagus separately. For the cervical esophagus, it included any tumor with mobile and palpable regional nodes. For the thoracic esophagus, it included T2 NX M0 and T2 N0 M0. Stage III, which was also developed independently for each region, stated that stage III for the cervical esophagus should be considered the presence of any T3, any N3, and distant metastases (24).

In TNM2, (25) two staging groupings were established, each with five stages (**Table 4**), a clinical-diagnostic group that did not apply to thoracic segment tumors as it was suggested that regional node determination belonging to this segment was not routinely possible, so this grouping was only appropriate for cervical segment tumors, and a post-surgical or pathological group applicable to all regions.

These staging groupings were changed in TNM3, (26) which, by merging the two, set up a five-stage TNM and divided stage II into A and B based on the lymph nodes involved. In addition, it should be noted that the changes mentioned earlier, when the T, N, and M categories were discussed for this edition, were introduced in the new stage grouping, such as reducing the numbers of N from five to three and the addition of T4. The new TNM classification did not change stages 0, I, and IV previously published in TNM2, but the rest did change. Stage II, now subdivided into IIA and IIB, includes in the case of IIA only T2 or T3 with no lymph node involvement or metastases (T2 N0 M0 and

TABLE 4 | Staging according to TNM2.

Stages	Clinical-Diagnostic			Post-Surgical–Pathological		
	T	N	M	T	N	M
0	Tis	0	0	–	–	–
I	1	0	0	1	0	0
II	1	1,2	0	2	0	0
	2	0–2	0			
III	3	3	0	3	0	0
	Any	3	0	Any	1–3	0
IV	Any	Any	1	Any	Any	1

TABLE 5A | Squamous cell carcinoma staging according to TNM7.

Stages	T	N	M	G	L
0	HGD	N0	M0	1, X	Any
IA	T1	N0	M0	1, X	Any
IB	T1	N0	M0	2–3	Any
	T2–3	N0	M0	1, X	Lower, X
IIA	T2–3	N0	M0	1, X	Upper, Middle
	T2–3	N0	M0	2–3	Lower, X
IIB	T2–3	N0	M0	2–3	Upper, Middle
	T1–2	N1	M0	Any	Any
IIIA	T1–2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1–2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

T3 N0 M0), and IIB includes T1 and T2 with lymph node metastases but no distant metastases (T1 N1 M0 and T2 N1 M0). Stage III was redefined as T3 N1 M0 and T4, any N, M0. In line with the changes made to the M-category in TNM5, this new edition subdivides stage IV, which had remained unchanged in TNM4, into IVA (any T, any N, M1a) and IVB (any T, any N, M1b).

Certainly, TNM7 (9) made a significant leap in staging esophageal cancer. It introduced non-anatomical elements, such as the tumor differentiation grade and histological type, into the staging grouping, setting up a grouping by stage according to the main histological OC types. It should also be noted that the L-category was also recognized in this edition as part of the staging grouping in OSCC. In TNM7, stages I, II, and III were subdivided into IA, IB, IIA, IIB, IIIA, IIIB, and IIIC, with each stage introducing the changes discussed when analyzing each category. **Tables 5A**, **5B** show this edition's stages.

TABLE 5B | Oesophageal adenocarcinoma staging according to TNM7.

Stages	T	N	M	G
0	HGD	N0	M0	1, X
IA	T1	N0	M0	1–2, X
IB	T1	N0	M0	3
	T2	N0	M0	1–2, X
IIA	T2	N0	M0	3
IIB	T3	N0	M0	Any
	T1–2	N1	M0	Any
IIIA	T1–2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1–2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
IV	Any	Any	M1	Any

TNM8

TNM8 was based on WECC-analyzed results from 22,654 patients (22,123 with complete data) from 33 hospitals with a high volume of esophageal cancer surgeries from all continents. Of these patients, 8,156 and 13,814 had OSCC and OAC, respectively, and both oesophagectomy and neoadjuvant therapies were considered, differentiating TNM8 from TNM7 (40).

This edition's novelty is that three classifications were formed depending on the evaluation time. One is the traditional, based on the pathological anatomical findings of previously untreated specimens, identified as pTNM; another, cTNM, is based on clinical diagnostic studies and will be used for therapeutic decision-making; and finally, given the significant number of patients operated on after neoadjuvant treatments, a new classification based on the post-neoadjuvant oesophagectomy specimen analysis is included, identified as ypTNM (11, 41).

In contrast to the TNM7, neither the location nor the degree of tumor differentiation was considered to form the OSCC cTNM. However, for the pTNM, the same happens with the AOC cTNM, where the G category is not included (9, 29).

Conclusion

The esophageal cancer staging has changed with each TNM edition, allowing a better understanding of it and applying better therapeutic methods. The last two editions have introduced significant changes with the incorporation of non-anatomical categories into the staging grouping and

the addition of a classification for patients undergoing neoadjuvant therapy.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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