Clinical and Therapeutic Implications of the 8th Edition TNM Classification of Adenocarcinomas of the Esophagogastric Junction

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Rezumat

Implicațiile clinico-terapeutice ale celei de a 8-a ediții a clasificării TNM pentru adenocarcinomul de jonțiune esogastrică

Cea de-a 8-a ediție a stadializării TNM a cancerului se bazează pe analiza datelor unor cohorte largi de pacienți, date colectate prin grupul Worldwide Collaboration Cancer Esophageal (WECC) sau pe cele ale Asociației Internaționale pentru Cancer Gastric (IGCA), inclusiv pacienți tratați chirurgical per primam sau după tratamentul neo-adjuvant. Aceasta ediție redefineste tumorile de jonțiune eso-gastrică și recomandă stadializare TNM diferită pentru aceste tumori: tipul Siewert I și II trebuie clasificate conform recomandărilor TNM pentru adenocarcinomul esofagian, în timp ce pentru tipul Siewert III trebuie aplicată clasificarea TNM pentru cancerul gastric. Categoriile anatomice vizează tipul T (invazia tumorală), tipul N (invazia limfoganglionară regională) și tipul M (metastaze la distanță). Categoriile non-anatomice includ gradul de diferențiere celulară (G) și localizarea tumorii (L). Descriptorii de categorii sunt în prezent evaluați prin endoscopie cu biopsie, ecoendoscopie cu puncție aspirativă (EUS-FNA), tomografie computerizată toracică-abdominală-pelvină (CT) și tomografie cu emisie de pozitroni (CT-PET). Noua ediție de stadializare TNM prezintă clasificări separate aplicabile în funcție de strategia terapeutică: cTNM clinică (înainte de orice tratament), pTNM patologică (după intervenția chirurgicală per primam) și ypTNM patologică postneoadjuvantă (după tratamentul neoadjuvant urmat de intervenție chirurgicală). Rafinarea fiecărei categorii și subcategorii T, N, M face ca ediția a 8-a să fie mai exactă și mai

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adaptabilă la practica actuală, inclusiv la strategia terapeutică pentru pacienții cu adenocarcinoame de joncțiune esogastrică. Scopul acestui studiu este evaluarea implicațiilor clinico-terapeutice ale acestei ediții pentru pacienții cu adenocarcinom de joncțiune esogastrică.

Cuvinte cheie: adenocarcinom, joncțiune esogastrică, stadializare TNM

Abstract

The 8th edition of TNM cancer staging is based on data from large patient cohorts, data collected from the Worldwide Collaboration Cancer Esophageal (WECC) group, or the International Association for Gastric Cancer (IGCA), including treated patients surgically per primate or after neoadjuvant treatment. This edition redefines the esophago-gastric junction tumors and recommends different TNMs staging: Siewert type I and II should be classified according to TNM recommendations for esophageal adenocarcinoma, while for Siewert type III the TNM classification for gastric cancer should be considered. Anatomical characteristics feature type T (tumor invasion), type N (regional lymph node invasion) and type M (distant metastasis). Non-anatomic characteristics include tumor differentiation (G) and tumor localization (L). Category descriptors are currently evaluated by endoscopy with biopsy, fine needle aspiration (EUS-FNA), thoraco-abdomino-pelvic computer tomography (CT) and positron emission tomography (CT-PET). The new TNM staging edition presents separate classifications applicable for therapeutic strategy: clinical staging cTNM (prior to any treatment), pathological staging pTNM (after surgery first) and neoadjuvant pathologic staging ypTNM (after neoadjuvant treatment followed by surgery). The refinement of each category and subcategory of T, N, M makes the 8th edition more accurate and adaptable to current practice, including for therapeutic strategy. The purpose of this study is to evaluate the clinical and therapeutical implications of the 8th edition of the TNM staging for esophago gastric junction adenocarcinoma.

Key words: adenocarcinoma, esophagogastric junction, TNM stage

Introduction

Since 1998, Siewert and Stein have recommended a classification, widely accepted, for the esophago-gastric junction (EGJ) adenocarcinomas based on the anatomical location of the tumor that divided these tumors into three subgroups, depending on the distance from the tumor center to the EGJ: type I center located between 1-5 cm proximal to EGJ, type II center located between 1cm above and 2 cm below the EGJ and type III at 2-5 cm distal to EGJ (1). Most of the authors recognizing the undeniable value of this classification primarily for establishing the surgical approach and type of esophageal and gastric resection, but also for the type of

neoadjuvant treatment used or the application of TNM staging.

The 8th edition of TNM staging restrict the limits of these tumors, defining EGJ adenocarcinomas as tumors with their center located 2 cm above and below EGJ (2).

In the new edition, genuine Siewert type II is an authentic EGJ tumor, while genuine type III is no longer an EGJ adenocarcinoma.

The 8th edition of the TNM classification included numerous significant changes for the staging of EGJ adenocarcinomas: cancers invading junction with their center within 2 cm of the esophago gastric junction (Siewert type I/II) are to be classified as esophageal adenocarcinoma. Tumors with epicenter more than 2 cm below to the junction, even if the

junction is involved, should be staged as gastric cancers.

Thus, it can be noticed that Siewert II tumors are still assigned to the TNM classification for the esophagus. The last seven editions of the AJCC staging system assign the esophageal junction tumors to the TNM system for the esophagus (3); however, some research has shown that the staging of esophageal tumors should be classified according to the TNM classification for gastric tumors (4,5).

Other studies have shown that none of these two systems could actually predict the prognosis of patients with esophageal tumors and a new staging system should be introduced for this entity (6,7).

Although Siewert III tumors differ from distal gastric cancer, they are now classified as gastric cancers and must be staged as such. The study of the International Association for Gastric Cancer (IGCA) compared patients with Siewert II and III and demonstrated that the TNM classification for gastric cancer was more appropriate in determining the prognosis of these patients than the one for esophageal cancer as recommended.

However, the prognosis of patients with Siewert II and III tumors was more reserved than for other patients with gastric cancer, the authors explaining the dissimilarity by different tumor biology or surgical approach which is more difficult for these tumors.

TNM 8th for stomach appears to improve staging, provides better separation of patients with Siewert III tumors stage III. Subtraction of N3 category (≥ 7 metastatic lymph nodes) into N3a (7-15 metastatic nodes) and N3b (≥ 16 metastatic nodes) and their inclusion in final staging resulted in an improved prognostic relevance. The TNM for stomach is, therefore, the best staging tool available so far, provided that correct lymphadenectomy is performed with at least 16 excised nodes. (8)

Staging Schemes

Adenocarcinoma increased dramatically in North America and Europe, accounting for

more than 60% of all cases of esophageal cancer in the United States, as opposed to squamous cell carcinoma that reported an incidence in a slight decrease. In addition to these different current epidemiological trends, the two histological subtypes differ in a number of features, including risk factors, tumor localization, tumor biology and outcomes (9).

Recognizing these differences between the two main types of esophageal tumors, the 8th edition of the American Committee for Cancer (AJCC) TNM classification recommends different staging schemes for squamous cell carcinoma and adenocarcinoma. The anatomical and non-anatomic characteristics of the esophageal tumors have also been included (10).

Based on patient data collected through the Worldwide Esophageal Collaboration Cancer (WECC) group (7-10), the 8th edition allows the application of different types of staging taking into account many characteristics of patients with EGJ adenocarcinomas: Siewert type, therapeutic strategy, being more adaptable to current practice, as it includes neoadjuvant therapy for advanced loco-regional tumors.

Differentiated provisional staging was justified by the criticism of previous editions due to the fact that decision making and prognosis were based only on the histopathological examination of the excised specimens (11,12).

Clinical staging (cTNM) was the same staging scheme as that used for pathological staging (pTNM) generating inadvertencies regarding: the prognostic significance of cTNM; pathological staging was inadequate for initial therapeutic decisions, which were based on clinical findings; patients without surgery have not been considered; patients following neoadjuvant treatment were included in the same staging, and the response to neoadjuvant therapy was not considered.

For these reasons, the 8th edition refers to the distinct and provisional cancer classification based on the treatment strategy: clinical cTNM (prior to any treatment), pathological pTNM (after primary surgery), and neoadjuvant pathological ypTNM (after neoadjuvant treatment followed by surgery).

For the first time, correlations between the

characteristics of the tumors (anatomical and non-anatomical) and long term survival were considered to generate staging groups for which survival was: (I) monotonous (survival decreases with increasing of stage); (II) distinctive between groups and (III) homogeneous in groups with the same prognostic.

The main objective of this study is to evaluate the clinical and therapeutic implications of the 8th edition of the TNM Classification for patients with EGJ adenocarcinoma, a condition increasing in incidence in Romania.

Starting in 2012, WECC has invited several institutions to develop the 8th edition of the TNM staging for esophageal cancer to create a large database including patients who received neoadjuvant treatment (13-15). Until 30 September 2014, 22,654 patients with esophageal cancer were enrolled: 22,123 patients had clinical data available prior to treatment, 13,814 patients presented esophageal adenocarcinoma. These patients were evaluated to develop the staging for cTNM (13,16). Of these, 13,300 patients had pathological staging after esophagectomy or endoscopic resection and formed a cohort for the staging of pTNM (14,17). The 7,773 remaining patients presented data on pathological staging following neoadjuvant therapy and formed the cohort for the staging of ypTNM (15,18).

Anatomical Categories

Category pT

For category T, division of pT1 into pT1a and pT1b led to prognostic stratification depending on the presence of submucosal invasion. Also, division of pT4 into pT4a and pT4b provides a much more reliable description of an advanced localized tumor that invades adjacent structures with doubtful resectability. With this new classification, surgeons have the opportunity to distinguish between a resectable tumor (T4a) and a non-resectable tumor (T4b). Now, the T4a tumor includes the direct invasion of the peritoneum.

Category pN

For N categories, regional mapping of lymph

nodes has been improved. The new map is shown in *Table 1*. The regional nodes map consists of identifying the ganglions from the adventitial or perisophageal tissue from the superior esophageal sphincter to the celiac trunk. Regional lymph nodes are grouped in 18 stations, including the supraclavicular group (station 1L and 1R) and the celiac ganglions (station 20) regardless of the histopathologic subtype.

Category pM

For category M, there is no change. metastases are designated M0 (without distant metastases) and M1 (with distant metastasis). M1a, M1b and MX subclassifications are no longer used.

Non-Anatomical Categories: Tumor Grading and Tumor Localization

The degree of differentiation (G) remains an important parameter for the pathological staging of incipient tumors. Undifferentiated tumors require additional immunohistochemical analyzes to clearly indicate the origin of the tumor type: if a glandular origin is identified, the tumor will be classified as G3 adenocarcinoma (*Table 2*).

Finally, localization of the tumor (L) and its reporting to the esogastric junction with the Siewert type is important for choosing the type of TNM staging for the esophagus or for the stomach. Tumor localization involves measuring the endoscopic distance between incisor teeth to the cranial edge of the tumor. Localization of the primary site of cancer is defined by the tumor center. Tumors involving the junction and having their center in between 2 cm from cardia (Siewert I / II type) are to be staged as esophageal adenocarcinomas. Tumors with epicenter more than 2 cm below cardia, even if the junction is involved, will be staged using the TNM classification of gastric cancer.

Recommended Staging in the 8th Edition

The new 8th edition for esophageal cancer and

Table 1. Regional distribution of lymph nodes of the esophagus and EGJ [from the 8th AJCC Classification (Rice)].

Station	Definition
1R	Left 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

Table 2. Esophageal and Esophago-gastric Junction tumors: categories and subcategories

Category	Criteria
T	
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	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades the adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Tumor invades other adjacent structures, such as the aorta, vertebral body, or trachea
N	
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	
M0	No distant metastasis
M1	Distant metastasis
G	
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	Poorly differentiated, with tumors composed of nest and sheets of cells with <50% of the tumor demonstrating glandular formation

EGJ is databased and considers separate and provisional cancer classification considering the therapeutic strategy: before any treatment (clinical staging cTNM); after surgical resection first or after endoscopic resection (pTNM pathological staging); after multimodal treatment prior to surgery (ycTNM); after multimodal treatment and surgery (ypTNM); at the time of recurrence (staging of recurrent tumors rTNM); and death (aTNM post mortem staging). Furthermore, the 8th edition considers the histopathological subtype as a distinct entity for TNM staging of esophageal tumors, distinguishing between adenocarcinoma and squamous cell carcinoma.

cTNM

The cTNM classification is useful for establishing the therapeutic strategy. The new edition provides a staging of cTNM distinct from pTNM and is differentiated according to the histopathological type. It is based mainly on imaging assessment and it is influenced by the performance of each individual technique. Therefore, it would be necessary to standardize staging methods. Since lymph node invasion (cN1) is an important prognostic factor, histological evidence of cN + should be the rule, even if the clinical stage or therapeutic strategy needs to be reconsidered. Therefore, every effort must be made to prove the regional or distant lymph node invasion (*Table 3*).

Clinical Determination of Anatomical and Non-Anatomic TNM Features

Clinical evaluation of anatomical (T, N, M) and non-anatomical features (tumor grading

and localization) is obtained using endoscopic biopsy, EUS-FNA, thoracic-abdominal-pelvic tomography, providing the basis for therapeutic strategy. If necessary, it can be supplemented with cervical lymph node biopsy, mediastinoscopy, thoracoscopy, laparoscopy, bronchoscopy, or percutaneous biopsy conducted by CT.

Determination of cT is mainly based on ecoendoscopy. The muscularis mucosae invasion distinguishes between T1a and T1b. The muscular invasion on its own, but limited to this layer, indicates a cT2. The invasion beyond its own muscularis defines cT3. When adjacent structures are invaded, cT4 is considered. The precision of ecoendoscopy for cT determination is approximately 80%, with the best accuracy for T3-T4 tumors (19-21).

Unfortunately, the method has limitations in the evaluation of large tumors: an unpassable tumor or a tumor length > 5 cm is highly predictive for an advanced stage and should be considered at least as a T3 tumor (22).

cT assay could be supplemented with tomography for cT3 with stenosis or cT4 tumor to evaluate invasion of adjacent structures.

cN determination is mainly based on ecoendoscopically guided aspiration puncture. The ecoendoscopy efficiency for N + disease detection is only 20%, resulting in overestimation in 80% of patients with pN0 (23). Malignancy criteria ecoendoscopically determined are the ganglion size > 5 mm, round, with hypoechoic center. Diagnostic effectiveness in cN determination with ecoendoscopically guided aspiration puncture is: sensitivity - 92%, specificity - 93%, positive predictive value - 100% and negative predictive value - 86% (24).

The determination of cN may be supplemented by other investigations. An enlarged lymph node on CT suggests lymph node metastasis. Intrathoracic and abdominal lymph nodes with the short axis > 1 cm are considered enlarged and a short axis > 0.6 cm is considered pathological for the supraclavicular and cervical lymph nodes.

PET - CT precision for cN determination is very variable, ranging from 37% to 90% (25). In a large meta-analysis, FDG-PET has a

Table 3. Clinical staging of cTNM for esophageal adenocarcinoma

	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

sensitivity of 57% (range, 43-70%) and a specificity of 85% (range, 76-95%) (25).

Determination of cM is based on investigations able to evaluate metastasis according to the most frequent locations: 35% liver, 20% lung and 2% adrenal gland. Current investigations include routine thoraco-abdominal-pelvic CT. Cerebral CT is not routinely performed because of the low rate of brain metastases (less than 1%). PET-CT is currently recommended. The accuracy of PET-CT seems excellent to exclude metastasis (88%). Positive and negative predictive values are 68% and 99% respectively for cM classification (26).

Moreover, through PET-CT, synchronic cancer is detected in nearly 2%.

The cM assessment can be complemented by exploratory laparoscopy or thoracoscopy. Laparoscopy is known to modify the treatment strategy in 10% of patients, allowing resection in 2% of patients over-staged by imaging methods and avoiding 8% resection due to undetectable peritoneal or hepatic metastases (27).

Restaging after Multimodal Therapy (ycTNM)

Another area in which clinical evaluation of the disease stage may pose problems is restaging after neoadjuvant therapy, the increasingly therapeutic sequence used in patients with locally advanced disease. In this situation, the ycT and ycN determinations are problematic. CT-thoracic-abdominal-pelvic CT is performed systematically for the morphological assessment of the mediastinum, peritoneal cavity or pelvis. Biopsy endoscopy is critical to assess possible residual disease and to allow distinction between responders and non-responders to neoadjuvant therapy. Eco-endoscopy does not allow accurate determination of ycT and ycN following neoadjuvant radiochemistry because it does not distinguish between cancer, post-treatment necrosis, fibrosis or inflammation. The accuracy of the method is only 27% to 59% in this situation (28-31).

On the contrary, determination of ycM can be achieved by PET-CT, as this investigation is able to detect distant metastases in about 8% of patients after radiochemotherapy (32).

Some oncologists evaluate by PET-CT four weeks after completing neoadjuvant therapy to determine ycM. In addition, PET-CT post-neoadjuvant therapy provides information on the metabolic response to this therapy. Some series suggest that metabolic responses had a significantly better prognosis than those who did not respond (33-35). However, PET-CT-targeted therapy can not yet be considered a standard approach.

Pathological Staging (pTNM)

The 8th edition was extended from the seventh edition that relied solely on the pTNM staging. Pathological staging takes into account tumor classification after per primam surgical resection or mucosal endoscopic resection and establishes postoperative progression or post-endoscopic treatment. It can not guide pre-therapeutic decisions.

However, this staging remains important for per primam resected incipient cancers. pTNM staging has lost clinical relevance for advanced tumors since neoadjuvant therapy replaces per primam esophagectomy (*Tabel 4*).

Pathological Staging (pTNM) or after Neoadjuvant Therapy (ypTNM)

Pathological staging is obtained from the definitive analysis of the resected specimen: after surgery (pTNM) or after neoadjuvant

Table 4. pTNM pathological staging for esophageal adenocarcinoma

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

treatment (ypTNM). Although there are recommendations for the handling of resected specimens (36), there are no standardized criteria for their examination.

The piece is sampled starting with the margins of proximal and distal surgical resection, the esophagus being proximal and the stomach being distal. The analysis of 8 to 11 sections is widely accepted. The margins of soft subtumoral tissues are marked with ink and are sectioned at the deepest point. The upper and lower tumor limits must be sampled.

All lymph nodes should be dissected from the resected specimen and evaluated as lymphadenectomy specimens. When possible, surgeons send specimens of lymph nodes for separate analysis. The surgeon and pathologist must collaborate to avoid a gap between the number of resected lymph nodes and the number of those analyzed. The lymph nodes are usually analyzed using a single representative section of each individual lymph node.

Pathological evaluation requires the removal of a sufficient number of lymph nodes for a proper pN or ypN staging. Because the highest N (N3) classification is ≥ 7 metastatic ganglia, any lymphadenectomy for Siewert I or II esogastric junction adenocarcinoma should theoretically include at least 7 lymph nodes for correct interpretation. The recommendations adopted by AJCC are to resect at least 10 lymph nodes for T1, 20 for T2 tumors and 30 for T3 tumors (12).

Optimal lymphadenectomy for patients with Siewert III is still a current problem. Some authors (37) have shown that patients with type II or III Siewert adenocarcinoma with appropriate lymphadenectomy (≥ 15 ganglia examined) have benefited from a more correct staging of the N1 category compared to patients with suboptimal lymphadenectomy in whom N0 patients who have showed similar survival to patients with N1.

The total number of resected lymph nodes is a good marker of adequate lymphadenectomy: multiple ganglia harvested lead to a more correct staging, reduces patient migration from one stage to another and provides more accurate information about long term prognosis.

However, extended lymphadenectomy is justified only if correlated with improved survival. Many studies have investigated the subject, reporting a general survival advantage without associating an additional risk of mortality with an increased number of excised ganglia (38-40).

Similarly, in gastric cancer, two studies (41, 42) demonstrated improved survival in patients with more than 21 and 30 resected lymph nodes.

Considering only N0 gastric cancer, other studies (43-45) showed improved survival with an increasing number of resected lymph nodes: 18, 22, and 25 ganglia harvested. The possible explanation is the elimination of micrometastases.

These are defined as metastases detectable only by immunohistochemistry in ganglia considered negative by routine histological examination. (46)

This advantage was observed especially in the case of advanced cancers. The explanation for better survival would be the more correct removal of metastatic tumor tissue that may be missed in a sub optimal lymphadenectomy.

Although the impact of the proximal and distal resection margins is well known, the definition of the circumferential security limit (CRM) continues to be debated (47).

The College of American Pathologists (CAP) defines a positive margin when tumor cells are identified at the edge of the resected specimen.

Following neoadjuvant treatment, the degree of tumor regression (TRG) should be evaluated. The Mandard classification can be applied even if its application in ypTNM determination is not well established.

The Mandard classification can assess the degree of tumor regression according to the amount of fibrosis relative to residual tumor cells (48). The prognostic value of tumor regression may even exceed the currently used systems.

However, there are some limitations regarding the variability of the interobserver, especially in the limit cases, the results can be improved by standardizing the resection

specimens and better training in the histopathological evaluation of the regression changes (49).

Pathological Staging Following Neoadjuvant Treatment (ypTNM)

Neoadjuvant therapy is increasingly being applied globally to patients with esophageal cancer and those with esophageal junctional tumors. However, patients treated with neoadjuvant therapy (ypTNM) and those with per primam esophagectomy (pTNM) can not fit at the same stage due to the random response to neoadjuvant therapy.

The new staging proposes the staged grouping of patients with neoadjuvant therapy and the pathological grouping of the resection specimen (ypTNM) (Table 5).

Included are the absence of equivalent pathological categories (pTNM) for specific neoadjuvant pathological categories (ypT0N0-3M0 and ypTisN0-3M0), staged groups with divergent compositions and very different survival profiles.

Grading and localization play no role in pathological staging after neoadjuvant therapy. The stages are identical regardless of the histopathological type. Prognosis is possible, but survival is reduced compared to what was classically included for the early and intermediate pTNM stages.

The persistence of regional lymphatic metastases (ypN1) leads to reduced survival, and sterilization of metastatic regional lymph nodes (ypN0) is not equivalent to healing. Patients with ypN0 cancers limited to the

esophageal wall or those with complete response have intermediate survival regardless of ypT.

Recurrences Staging (rTNM) and Autopsy Staging (aTNM)

Endoscopic surveillance of the gastric tube and of the esogastric anastomosis should be performed regularly and guided by any new symptoms of dysphagia. Surveillance is based on thoracic-abdominal tomography during the first 5 years (every 6 months in the first 2 years and annually over the last 3 years). Determination of local cancer recurrence (rT) can be determined by endoscopic biopsy or ecoendoscopically guided aspiration puncture. Determination of regional recurrences (rN) or distance (rM) can be obtained by any morphological investigation and may include any available technique (mediastinoscopy, thoracoscopy, laparoscopy, CT-guided biopsy). Diagnosis of relapse by PET-CT is characterized by a 100% sensitivity, 85% specificity, and 100% positive predictive value.

The recurrence of the disease after treatment with a disease free interval is staged using the rTNM staging.(50) This can be observed after a period of months or years after surgery, following neoadjuvant treatment and surgery or definitive (exclusive) chemoradiotherapy. When surgery is proposed as the last therapeutic option, surgery is called "rescue esophagectomy". Autopsy staging (aTNM) is when a post-mortem examination determines the stage of the disease. The aTNM staging can be determined in known and treated patients or in untreated patients. Natural history of the disease and associated risk factors can provide useful information in epidemiological studies.

Conclusions and Perspectives

The eighth edition redefines the tumors of JEG, and still attributes the staging of TNM to the esophagus to Siewert II tumors, recommending that Siewert III tumors be staged as gastric cancers. This is based on data and

Table 5. Pathological staging after neoadjuvant therapy (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

extends from the seventh edition for pTNM only, including pathological staging following neoadjuvant therapy (ypTNM) and clinical staging (cTNM). This TNM edition is a prognostic staging adapted to the histopathological type and anatomical localisation reported at the esogastric junction, adapted to dramatic epidemiological and therapeutic changes for the EGJ adenocarcinoma. The refinement of each T, N, M category and subcategory makes this edition more reliable and adaptable to current practice, including the neoadjuvant regimen. Another benefit that this edition brings is the regional mapping of lymph nodes and the importance of optimal lymphadenectomy. The introduction of temporal staging in the three variants (c, p or ypTNM) including grading, histopathology and localization should be interpreted as a complex stratification of prognosis from diagnosis to the last therapeutic sequence. But at the same time a critical assessment of this edition, intensive data collection, in-depth analyzes, and additional consensus assessment is required to move to the next edition scheduled to be published in 2024.

Conflict of Interest

The authors declare no conflicts of interests.

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