

**Review  
Article**

# Review of the Japanese Classification of Esophageal Cancer 12th Edition, and Proposals for the 13th Edition

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**In this review, we summarize the modifications made in the Japanese Classification of Esophageal Cancer 12th edition, identify several issues, and discuss the prospects for the next 13th edition.**

**Keywords:** Japanese classification, esophageal cancer

## Introduction

In September 2022, the Japanese Classification of Esophageal Cancer, 12th edition, was published. It had taken about 7 years to revise the former 11th edition.<sup>1,2)</sup> During this period, the members of the committee of the Japanese Classification of Esophageal Cancer, together with working group members, worked earnestly to create a new Japanese Classification. As a result, we can publish a distinctly new Japanese Classification with major changes. In this regard, we are extremely appreciative of the efforts of every member of the committee of the Japanese Classification of Esophageal Cancer and the contribution of each working group.

On the other hand, certain major modifications may impact the clinical practice of esophageal cancer. It is, therefore, important to ensure that these changes are valid. Furthermore, we must prepare for the next 13th edition. In this review, we will summarize the

modifications made in the 12th edition, identify several issues, and discuss the prospects.

## Major Modifications

1. Introduction of cT3 subclassification (cT3 resectable: cT3r and cT3 borderline resectable: cT3br) and abolishment of cT4 subclassification (cT4a and cT4b).
2. The supraclavicular lymph node station (104) is classified as M1a.
3. N grading system changes from the location of nodal metastasis to the number of nodal metastases, as well as the TNM classification.
4. Regional lymph nodes and the extent of lymph node dissection are unified, irrespective of tumor location for thoracic esophageal cancer.
5. The stage is divided into a clinical stage and a pathological stage.
6. The naming of the abdominal esophagus (Ae) is abolished, and the zone of the esophagogastric junction (Jz) is adopted.
7. Response evaluation criteria in radiotherapy and chemotherapy for esophageal cancer have changed, especially concerning neoadjuvant treatment. Specifically, we have adopted new measuring methods for the size of the primary tumor using CT images, and the reduction rate of this measurement is incorporated into the response evaluation criteria. In addition, we have created a new subclassification of remarkable response (RR) in non-complete response (CR)/non-progressive disease (PD) using endoscopy.

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Received: April 2, 2024; Accepted: June 10, 2024

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## Details, Problems, and Prospects in Relation to Each Modification

### 1. cT3r, cT3br, and cT4

#### *Reasons for modifications*

We have often encountered patients with cT3 or cT4, whose primary tumor presents with diagnostic difficulties. At some meetings in Japan, these tumors were sometimes called tumors with cT3.5. Since 2016, the Japanese Pancreas Society has adopted a resectability classification including R (resectable), BR (borderline resectable), and UR (unresectable). Using this as a reference, we have divided cT3 into cT3r and cT3br; and “r” means resectable, and “br” means borderline resectable. The target organs of the “br” are limited to the aorta, major vessels, trachea, and bronchus. Thus, we do not use cT3br when the target organs are pleura, pericardium, diaphragm, lung, or nerves because these organs are resectable. In that case, we use either cT3r or cT4.

On the other hand, we subclassified cT4 (cT4a and cT4b) in the former 11th edition. T4a meant that the tumor invaded the adjacent organs, including the pleura, pericardium, diaphragm, lung, thoracic duct, azygos vein, and nerve. These T4a organs could be partially resected rather easily. T4b meant that the tumor had invaded the adjacent organs, including the aorta (major vessel), trachea, bronchus, pulmonary vein, pulmonary artery, and vertebral body. Those T4b organs are generally considered not to be resectable. This cT4 subclassification was abolished in the 12th edition because the distinction between cT4a and cT4b is ambiguous.

#### *Prospects in 13th edition*

In the 12th edition, we exhibited typical CT images of cT3r, cT3br, and cT4 cases. We have to validate this new classification regarding the agreement rate and clinical usefulness. Furthermore, we have to develop another diagnostic modality, including magnetic resonance imaging (MRI),<sup>3)</sup> for a more exact diagnosis of cT3r, cT3br, and cT4.

### 2. Supraclavicular lymph node (104)

#### *Reasons for modifications*

The Japan Esophageal Society (JES) had regarded this supraclavicular lymph node (104) as a regional node for a long time, and this station of 104 had been considered to have to be prophylactically resected for upper or

middle esophageal cancer. Meanwhile, there are debates regarding its clinical importance, especially concerning the pros and cons of prophylactic resection. This time, we retrospectively collected data and investigated the survival of patients with supraclavicular lymph node metastasis in JES. Even if metastasis occurred to the supraclavicular lymph node station (104), lymph node dissection was effective; therefore, it was given the same weight as N2-3 in the cStage classification and N3 in the pStage classification. However, in this 12th edition, this station of 104 has been defined as M1 according to the TNM classification. It was defined as M1a because certain survival benefits may be expected from resection of the station of 104 based on our data. JES suggested that esophagectomy with therapeutic supraclavicular lymph node dissection should be performed for esophageal cancer with metastasis 104, although little evidence exists to support this strategy.

#### *Prospects in the 13th edition*

This debate will be answered by the long-term results of the JCOG2206 study, a randomized controlled trial investigating the clinical importance of prophylactic lymphadenectomy of the supraclavicular lymph node for upper or middle thoracic esophageal squamous cell carcinoma. However, this outcome will not be clarified in the next edition.

### 3. N grading system

#### *Reasons for modifications*

JES had adopted the N grading system based on the location of the main tumor in the previous edition. On the other hand, TNM classification was based on the number of nodal metastases.<sup>4)</sup> It is well known that the number of nodal metastases is a strong prognostic factor in esophageal cancer. Hence, JES adopted the N grading system, which combined the location of the main tumor with corrections by the number of nodal metastases in the 10th edition. As this N grading system, with both the tumor location and number, was too complicated to use, it was returned to its original N grading system of the location of the main tumor in the 11th edition. This time, JES investigated whether the classification based on the tumor location or based on the number of nodal metastases was more predictable for survival. Based on our study, we found that the N grading system based on the number of nodal metastases was more accurate. Therefore, we changed this system.

*Prospects in the 13th edition*

We have to validate this new classification system from the newly collected database. Furthermore, our next edition will discuss the ypStaging system as in the American Joint Committee on Cancer 8th edition.

#### **4. Unifying regional lymph nodes and the extent of lymph node dissection in thoracic esophageal cancer**

*Reasons for modifications*

As described above, we have abolished the N grading system based on the tumor location. Besides, when most Japanese esophageal surgeons perform esophagectomy, the extent of the lymphadenectomy is almost the same, irrespective of the tumor location in the thorax. Therefore, for thoracic esophageal cancer, we have identified the following nodes (101R, 101L, 105, 106recR, 106recL, 106tbL, 107, 108, 109R, 109L, 110, 111, 112aoA, 112pulR, 112pulL, 1, 2, 3a, 7, 8a, 9, 11p, 19, and 20) as regional lymph nodes, regardless of tumor location. When we resect all these regional nodes, this is defined as a D2 extent of lymph node dissection. Therefore, for thoracic esophageal cancer, D2 lymph node dissection is unified, although there were D2 lymph node dissections for upper, middle, and lower esophageal cancers, respectively in the previous 11th edition. Furthermore, supraclavicular lymph node stations (104) were excluded from D2 extents, even if the tumor was in the upper or middle esophagus. Some lymph node stations, including 106tbL, 111, 8a, and 11p, can be omitted.

*Prospects in the 13th edition*

As this change in the definition of regional lymph nodes and the extent of lymph node dissection are large, we confirm how the extent of lymph node dissection will change in practice. In addition, we will have to know whether this modification has some impact on the survival of patients who undergo esophagectomies.

#### **5. Staging is divided into clinical and pathological one**

*Reasons for modification*

These days, most patients with cStage II or III esophageal cancer have received neoadjuvant treatment before esophagectomies. As a result, a discrepancy between clinical staging and pathological staging has been obvious. In addition, staging for esophageal cancers in TNM classification has been divided into clinical and pathological categories since the 8th edition.<sup>4)</sup> We, therefore,

decided to divide staging into clinical and pathological stages.

When clinical and pathological staging was stratified, we compared the previous N grading system based on its location with a new N system based on a number from the viewpoint of the splitting survival curves. In pathological staging, the new N system based on the number was superior to the stratification of the survival curves of the previous N system based on location. In clinical settings, the previous N system, based on its location, could stratify the survival curves well. However, the new N system, based on numbers, is better. Finally, we changed the N system from the previous one to the new one as described above.

*Prospects in 13th edition*

We have to use these staging systems and will have to modify them if necessary.

#### **6. Naming of the esophagogastric junction**

*Reasons for modification*

Based on an enthusiastic argument at the joint meeting of JES and Japanese Gastric Cancer Association (JGCA), this edition adopted the Nishi classification for the definition of esophagogastric junction (EGJ) and one of the reasons is that it could be applied to a wider range of esophagogastric junctional cancers than Siewert type II, allowing more data to be collected. Nishi classification defines an EGJ tumor as a tumor with an epicenter within 2 cm above or below the EGJ.<sup>5)</sup> The major difference from the Siewert type II classification is that this includes tumors that are squamous cell carcinomas and tumors without esophageal invasion. In addition, we abolished the term “abdominal esophagus” (Ae). Instead, “zone of the esophagogastric junction” (Jz) has been introduced. Jz signifies the exact site of Nishi classification or the area within 2 cm above or below the EGJ. Therefore, Jz is not equal to Ae. This new classification concerning EGJ was determined by a joint committee of the JES and the Japanese Gastric Cancer Association.

*Prospects in 13th edition*

The definition of EGJ has been standardized by both the JES and the JGCA. As the incidence of EGJ cancer is expected to increase, both societies will have to perform clinical studies using the same definition to improve the outcomes of treatment for EGJ cancer.

## 7. New primary tumor size evaluation methods using CT images, and a new subclassification of RR in non-CR/non-PD using endoscopy

### *Reasons for modification*

As described above, most patients with cStage II or III disease undergo neoadjuvant treatment before esophagectomy. Although a significant positive correlation between the response of primary tumors to neoadjuvant treatment and patient survival is well known,<sup>6–8)</sup> the primary tumor is not considered a target lesion in the response evaluation criteria for solid tumors (RECIST).<sup>9)</sup> In the 12th edition, we introduced two new methods for evaluating primary tumor size using CT images: one uses the short diameter of the primary tumor, and the other uses the esophageal cross-sectional area.<sup>10,11)</sup> Both evaluation methods yielded significant correlations with survival in patients who underwent esophagectomy after neoadjuvant treatment.

We also introduced a new classification of RR in non-CR/non-PD patients because several studies have shown that endoscopic evaluation of primary tumors after neoadjuvant treatment correlated significantly with patient survival.<sup>12–14)</sup> This new subclassification should be useful for evaluation after neoadjuvant chemotherapy, chemoradiotherapy, or definitive chemoradiotherapy.

### *Prospects in 13th edition*

These new methods or subclassifications for evaluating the primary tumor will have to be validated.

## Other Issues in the Next Edition

### 1. Clinical diagnosis of nodal metastasis

The number of nodal metastases in esophageal cancer is one of the strongest prognostic factors. So, a clinical diagnosis for nodal metastases is as important as a pathological diagnosis. However, clinical diagnoses for nodal metastases depend on each institution and each doctor, and there might be a difference in the exact criteria for diagnosis. Therefore, we attempted to determine a cutoff value for positive or negative nodal metastasis in this edition. We proposed 6 mm in the short diameter of the lymph node using CT images, but the sensitivity is low. As the values relating to PET-CT (e.g., SUV max) are not absolute and are affected by many factors, we were not able to adopt the criteria using PET-CT. In the future, we will have to increase the accuracy of clinical diagnosis for nodal metastases.

### 2. The exact definition of each nodal station

By publishing the 13th edition of the Japanese Classification of Esophageal Cancer, we redefine nodal stations whose boundaries are obscure (e.g., 106tbL, 110, 112aoA).

### 3. Circumferential resection margin

The Japanese Classification of Esophageal Cancer has defined the radial margin as RM0 or RM1. RM0 means that the tumor is not exposed on the radial resection margin, RM1 means that the tumor is exposed on the radial resection margin, and the cutoff value for the distance of the circumferential resection margin (CRM) is not determined. However, several studies have shown that CRM is an independent prognostic factor for esophageal cancer.<sup>15,16)</sup> These studies indicate that CRM distance is significant. We thus aim to investigate the clinical significance of CRM in the future and determine the cutoff value, if necessary.

### 4. Definition of T4

According to the TNM classification, T status means only the extent of the primary tumor. So, if a lymph node invades the adjacent organ, it does not mean T4. However, according to the Japanese Classification of Esophageal Cancer, T4 cancer is defined as having invaded adjacent organs, including the recurrent laryngeal nerve, trachea, or main bronchus, by a metastatic node, without primary tumor invasion. As there is a big discrepancy between these two classifications, we would like to discuss this issue in the next edition.

The continuing improvement of the Japanese Classification of Esophageal Cancer is important so that it becomes easily comprehensible and useful in clinical practice and studies, to enhance treatment outcomes and the quality of life of patients.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Funding

Not applicable.

**Data availability**

Not applicable.

**Author contribution**

Only the corresponding author.

**Disclosure statement**

The author declares no conflict of interest for this study.

**References**

- 1) Japan Esophageal S. Japanese Classification of Esophageal Cancer, 11th Edition: part I. *Esophagus*. 2017; **14**: 1–36.
- 2) Japan Esophageal S. Japanese Classification of Esophageal Cancer, 11th Edition: part II and III. *Esophagus*. 2017; **14**: 37–65.
- 3) Harino T, Yamasaki M, Murai S, et al. Impact of MRI on the post-therapeutic diagnosis of T4 esophageal cancer. *Esophagus* 2023; **20**: 740–8.
- 4) Brierley JD, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours Eighth Edition. New York: Wiley-Blackwell; 2016.
- 5) Nishi M, Kajisa T, Akune T, et al. Cardia cancer—proposal of cancer in the esophagogastric junction. *Geka Shinryo*. 1973; **15**: 1328–38. (in Japanese)
- 6) Bremm J, Brunner S, Celik E, et al. Correlation of primary tumor volume and histopathologic response following neoadjuvant treatment of esophageal adenocarcinoma. *Eur J Surg Oncol* 2024; **50**: 108003.
- 7) Hagi T, Shiraishi O, Nakanishi T, et al. Utility of initial tumor reduction as a prognostic factor in esophageal squamous cell cancer patients undergoing neoadjuvant chemotherapy followed by surgery. *Ann Surg Oncol* 2024.
- 8) Matsumoto S, Wakatsuki K, Nakade H, et al. Impact of CT-assessed changes in tumor size after neoadjuvant chemotherapy on pathological response and survival of patients with esophageal squamous cell carcinoma. *Langenbecks Arch Surg* 2022; **407**: 965–74.
- 9) Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–47.
- 10) Taniyama Y, Murakami K, Yoshida N, et al. Evaluating the effect of Neoadjuvant chemotherapy for esophageal Cancer using the RECIST system with shorter-axis measurements: a retrospective multi-center study. *BMC Cancer* 2021; **21**: 1008.
- 11) Yoshida N, Taniyama Y, Murakami K, et al. Novel criterion using esophageal major and minor axes is useful to evaluate the therapeutic effect and prognosis after neoadjuvant chemotherapy followed by surgery in locally advanced esophageal cancer. *Ann Surg Oncol* 2021; **28**: 8474–82.
- 12) Yano T, Hayashi Y, Ishihara R, et al. Remarkable response as a new indicator for endoscopic evaluation of local efficacy of non-surgical treatments for esophageal cancer. *Esophagus* 2024; **21**: 85–94.
- 13) Kadota T, Abe S, Yoda Y, et al. Clinical outcomes according to the modified endoscopic criteria for neoadjuvant chemotherapy in resectable esophageal squamous cell carcinoma. *Dig Endosc* 2020; **32**: 337–45.
- 14) Nagai Y, Yoshida N, Baba Y, et al. Clinical significance of evaluating endoscopic response to neoadjuvant chemotherapy in esophageal squamous cell carcinoma. *Dig Endosc* 2020; **32**: 39–48.
- 15) Salih T, Jose P, Mehta SP, et al. Prognostic significance of cancer within 1 mm of the circumferential resection margin in oesophageal cancer patients following neo-adjuvant chemotherapy. *Eur J Cardiothorac Surg* 2013; **43**: 562–7.
- 16) Haneda R, Kikuchi H, Nagakura Y, et al. Development and validation of the optimal circumferential resection margin in pathological T3 esophageal cancer: a multicenter, retrospective study. *Ann Surg Oncol* 2022.