Comparison of two major staging systems of esophageal cancer—toward more practical common scale for tumor staging

Harushi Udagawa, Masaki Ueno

Department of Gastroenterological Surgery, Toranomon Hospital, Okinaka Memorial Institute for Medical Research, Tokyo, Japan

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Correspondence to: Harushi Udagawa, MD, PhD, FACS; Masaki Ueno, MD, PhD. Department of Gastroenterological Surgery, Toranomon Hospital, Okinaka Memorial Institute for Medical Research, 2-2-2 Toranomon, Minato-ku, Tokyo 105-8470, Japan.
Email: udagawah@toranomon.gr.jp; ueno.m@nifty.com.

Abstract: The latest 8th edition of TNM Classification of Malignant Tumours by Union for International Cancer Control (UICC) and 11th edition of Japanese Classification of Esophageal Cancer by Japan Esophageal Society (JES) are the two major classifications widely accepted as tools for clinical staging of esophageal cancer. Both systems consist of three main categories, i.e., T, N, and M, but large difference exists between the two. JES system has more detailed sub-classification of T1 tumors reflecting meticulous work by Japanese investigators on superficial esophageal cancer. N-category shows the largest difference. UICC defines the N-category according to only the number of the metastatic regional lymph nodes. The definition of regional nodes in UICC system is static and uniform, and supraclavicular nodes are definitely excluded. In JES system, regional nodes are subgrouped into five different patterns according to the main tumor location, and the supraclavicular nodes are always regional nodes for thoracic esophageal cancer. Japanese surgeons have described the evidence that regional nodes should be dynamically defined according to tumor location and supraclavicular nodes should be included in regional nodes. Compared to the simplified N-category, the staging matrix of UICC system is somewhat complicated. The clinical stage and pathological stage of UICC system are not identical and difference exists also between squamous cell carcinoma (SCC) and adenocarcinoma. It has another system of pathological prognostic grouping. We can imagine several reasons for the difference occurred between the two systems. One is the difference of major pathology. Another reason is the difference of basic concept of cancer treatment. The relative "dependence" on radical surgery in Japan has required the detailed definition of each lymph node station and the evaluation of "efficacy index" of each station. The strict and detailed definition of lymph node stations has been regarded as an obstacle to those who are not familiar with it. Some simplification can be done but maintaining dynamic definition of regional lymph nodes linked to tumor location. If UICC system can accept this concept, I think the two systems can be unified to realize more practical and useful staging system as an international common language.

Keywords: Union for International Cancer Control (UICC); Japan Esophageal Society (JES); staging of esophageal cancer; supraclavicular lymph nodes

Introduction

Union for International Cancer Control (UICC) released the 8th edition of TNM Classification of Malignant Tumours (1) and it became effective since the beginning of 2017. On the other hand, Japan Esophageal Society (JES) released the 11th edition of Japanese Classification of Esophageal Cancer (2,3) in October, 2015. The former is almost identical to AJCC classification (4) and used as international common scale for the staging of esophageal cancer. The latter is widely accepted particularly in Asian countries (5,6) where squamous cell cancer is the major pathology and also in Europe (7) mainly because of its meticulous anatomical classification of lymph node stations. In this review, we would like to clarify the difference of basic concepts of the two classifications and discuss their advantage and disadvantage.

T-category

Both UICC and JES Classifications consist of three main categories, i.e., T, N, and M.

The definition and expression of T-category are almost identical except for two points. One is the fact that "T4" can be applied in JES classification not only to main tumor but also to metastatic lymph nodes with extranodal tumor involvement. Another difference is the much more detailed sub-classification of T1 tumors in JES system. T1a and T1b in UICC classification are both subclassified into three levels, i.e., T1a to T1a-EP, T1a-LPM, and T1a-MM, and T1b to T1b-SM1, T1b-SM2, and T1b-SM3. This meticulous subclassification in JES system is based on the large data of superficial cancer treatments in Japan (8,9), T1a-EP and T1a-LPM are usually handled in one group and regarded as good candidates of local treatment such as endoscopic submucosal dissection (ESD) because almost no lymph node metastases have been experienced in these patients (10). T1b-SM2 and T1b-SM3 are associated with 40% or more frequent nodal involvement, and radical surgery similar to T2 or more advanced tumors is recommended.

N-category

N-category shows the largest difference between the two systems. UICC defines the N-category according to only the number of the metastatic regional lymph nodes. In JES system, regional nodes are subgrouped into group 1 to 4 in 5 different patterns according to the main tumor location. The highest number of the lymph node group containing metastasis is defined as N-category of the patient. Although many Japanese surgeons admit that number of metastatic nodes is the strongest prognostic factor (11,12), it is also true that the Japanese N-category and number of metastatic nodes have close relation (13). Because clinical diagnosis of lymph node metastasis still remains far from ideal (14-16), UICC cN-category which is defined by counting number of metastatic nodes in imaging examinations seems unreliable. The concept of regional nodes in JES system is applied to group 1, 2, and 3 nodes and metastasis in group 4 nodes is almost regarded as distant metastasis, but it is still expressed as N4 instead of M1 and only Stage IVa is applied as long as neither hematogenous metastasis nor serosal dissemination is diagnosed. The regional nodes in JES system vary according to main tumor location, but they always contain supraclavicular nodes and cervical paraesophageal nodes when the main tumor locates in the thoracic esophagus. In the abdomen, nodes around the celiac axis (No. 9 in JES system) are not regional nodes for upper thoracic esophageal cancer, but not only No. 9 nodes but also nodes along the common hepatic artery (No. 8) and nodes along the proximal half of splenic artery (No. 11p) are all included in regional nodes when the tumor locates in the lower thoracic esophagus. Compared to this, the definition of regional nodes in UICC system is static and uniform. The cervical paraesophageal nodes and celiac axis nodes are clearly included in the 8th edition, but supraclavicular nodes are definitely excluded even when the tumor locates in the upper thoracic esophagus.

M-category

M-category is almost similar in the two systems except the difference of the definition of regional nodes and the handling of extra-regional node metastasis in JES system (described in the previous paragraph).

Staging

Both systems have different complicated staging matrix defined by the combination of T, N, and M categories. It is very natural that one patient is often classified in different stage groups in the two systems, because the stage matrix was determined so that it would stratify the prognoses clearly at every point of time and precisely in order of

stages (17-19) but using completely different databases. The databases for two classifications should be largely different in distribution of tumor location, extent of lymph node dissection in surgery, treatment patterns other than surgery and pathology. One system includes the information of tumor location as an important key and another does not. Japanese surgeons feel that for at least squamous cell cancer, which occurs at any level of the esophagus and generally has tendency of higher location, JES system can express more precise state of tumor spread.

Clinical stage and pathological stage

UICC defines two different staging systems for clinical stage and pathological stage. The clinical stage classifications for squamous cell carcinoma and adenocarcinoma are a little bit different, though the pathological stage matrix is identical. This very complicated definition might be the result of the intention to make the prognoses of patients with the same stage expression in different staging systems similar. However, as a consequence, some patients with accurate clinical staging can be up-staged after operation in spite that the preoperative clinical staging was very accurate. For example, a patient with squamous cell carcinoma diagnosed as cT1N1M0 is classified as cTNM Stage I, but after operation, if the diagnosis was accurate, then the one will be classified as pT1N1M0, pTNM Stage IIB. If the pathology is adenocarcinoma, the similar tumor will be classified as cTNM Stage IIA and will be up-staged as pTNM Stage IIB. This seems very strange.

Pathological prognostic group

UICC has another complicated classification of pathological prognostic grouping. Here, a factor other than TNM appears. It is histopathological grading, and is the concept first introduced in the 7th edition of TNM classification. The complicated modification of the pathological stage to pathological prognostic group is defined only in rather early stages or groups (Stage/Group IB to IIB). It is not defined either dominant histopathological grade or the highest grade should be adopted. Although I admit that histopathological grading surely has close relation to the probability of lymph node involvement in T1a-MM and T1b tumors, more detailed discussion is necessary on this issue (20-22). Though this grouping would have been defined so that the prognoses can be properly stratified, it should be database-restricted, and i.e., therapeutic measure-

restricted. Perhaps because of the complexity, pathological prognostic group does not affect NCCN guidelines directly.

Tumor location

JES system includes the information of tumor location at the first step of staging through the definition of N-grouping which is tumor location dependent. In UICC system, it is mentioned only in very small part of the definition of pathological prognostic group for squamous cell cancer. It seems to me that UICC does not suppose that adenocarcinoma can occur in upper thoracic esophagus and it suppose that upper and middle thoracic esophageal squamous cell cancer inevitably has worse prognosis. Distribution of lymph node metastasis and its impact on prognosis has been clearly shown to be related to tumor location by many investigators (13,23). Therefore, we have been claiming that N category should be defined in relation to main tumor location, or at least, the definition of regional lymph nodes should be. The ultimate difference of the two systems lies on this point. The typical conflict is the attitude toward the supraclavicular nodes.

Significance of supraclavicular node metastasis

As has been discussed, the implication of the metastasis in supraclavicular nodes in UICC and JES system is largely different. Many Japanese surgeons have tried to claim that the supraclavicular nodes should be regarded as regional nodes at least for upper and middle thoracic esophageal cancer (13,24,25). This argument has been supported by some Asian and western surgeons (26,27). In the latest JES classification, supraclavicular nodes are classified as group 3 nodes for lower thoracic esophageal cancer. Because group 3 nodes mean most distant regional nodes, many proposals of their selective dissection have been reported (28-30). On the other hand, supraclavicular nodes are classified as group 2 for upper and middle thoracic esophageal cancer (2) and the value of their dissection has been widely accepted.

Why the two systems differ so much?

As has been discussed, JES system seems more practical and widely adaptable to esophageal cancers in any location. It can be more detailed guide to determine actual treatment strategy. UICC system is based on too simplified definition of regional lymph nodes and too complicated staging matrix. We can imagine several reasons for the difference

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occurred between the two systems.

One is the difference of major pathology. Squamous cell carcinoma is the majority in Asian countries. It occurs widely at any location of the esophagus. On the other hand, adenocarcinoma, which usually arises in the Barrett mucosa, tends to be located in the lower esophagus. Therefore, it might be a rare occasion for western doctors to face the need for consideration of cervical lymph node metastases. However, we think that the staging system of esophageal cancer should include all the possible location of tumors irrespective of pathology.

Another reason is the difference of basic concept of cancer treatment. Although the concept of radical surgery had been emphasized in western countries (31), it has shifted to multimodality treatment, and the role of radical surgery became smaller. All the malignancies are regarded as potentially systemic diseases, and marginal spread of cancer such as supraclavicular lymph node metastasis from thoracic esophageal cancer seems to change its position from regional disease to an expression of systemic disease. The importance of multimodal treatment is recognized in Japan also. Japanese current nation-wide RCT of JCOG1109 is a three-armed comparative study of neoadjuvant treatments (32). However, the radical surgery represented by 3-field lymph node dissection still maintains the popularity, and included in the requirement of surgery in such studies. This "dependence" on radical surgery in Japan has been supported by our excellent short term results (33) and good long term survival (34,35). Because of the relatively larger role of surgery, the importance of detailed definition of each lymph node station and the evaluation of "efficacy index" of each station has been emphasized (13,36).

The other reason is the difference of handling of surgical specimen. In Japan, lymph nodes are meticulously detached from the operative specimen by surgeons and sorted out according to JES classification of lymph node stations. Pathologists, even when the total number of such lymph nodes exceeds 100, examine all the nodes histopathologically and send back surgeons a full report sorted out along JES classification. We believe that this collaboration is of great importance. Surgical anatomy is too complicated for pathologists to carry out this "another operation" on the specimen accurately. Based on the large database prepared this way, JES system has been created and revised to the current style. This complexity and requirement of elaboration is a large obstacle for new entrants. Compared to this, UICC classification is much easier to adopt except for complicated prognostic grouping.

Conclusions

As one of Japanese surgeons, I believe that JES system is superior to UICC system in describing the spread of a given esophageal cancer, and in discussing its treatment strategy. However, the strict and detailed definition of lymph node stations could be regarded as an obstacle to those who are not familiar with it. Some simplification can be done for at least clinical (non-surgical) staging. However, we strongly feel the need to maintain dynamic definition of regional lymph nodes linked to tumor location. To include supraclavicular nodes in regional lymph nodes of (upper and middle) thoracic esophageal cancer is one of the major points we would like to claim. If UICC system can accept this concept, I think the two systems can be unified, and we can obtain more practical and useful staging system as an international common language.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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