Fluorodeoxyglucose-positron emission tomography (FDG-PET) and computed tomography (CT) have become the gold standard for staging of esophageal cancer by detecting distant metastases, but metastatic lymph nodes are often difficult to diagnose from the size and standardized uptake value (SUV). If we compare the diagnostic performance of endoscopic ultrasonography (EUS), CT, and FDG-PET in staging of esophageal cancer, EUS is the most sensitive method to identify the detection of regional lymph node metastases, whereas CT and FDG-PET are more specific tests. Combination study with CT, EUS and PETCT cannot make a precise diagnosis after neoadjuvant therapy (NAT). A precise staging might be determined by the fine needle aspiration biopsy (FNAB) under EUS and US screening in the neck and the abdomen even after NAT. Indication of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) for superficial cancer is sensitive because of difficulty in T1b cancer diagnosis. Detailed examination about vessel invasion and the possibility of residual tumor with dissected specimen will offer an appropriate additional therapy. New strategy like sentinel lymph node (SLN) navigation could supply more information about lymphatic routes and metastatic nodes. SLN navigation with ESD might become a new less invasive strategy for superficial esophageal cancer.

Keywords: esophageal cancer, staging, TNM, sentinel lymph node biopsy
TNM Staging

Based on the tumor staging, malignant potential, and patient’s physical status, the choice of strategies are informed to patients with the basis and the process of decision making. Then the appropriate treatment is selected (Fig. 1). Stages of esophageal cancer are represented by T (primary tumor), N (regional lymph nodes), and M (distant metastases). TNM staging were first introduced by the UICC (International Union Against Cancer) in 1968. In 1977, the first edition of the AJCC (American Joint Committee on Cancer) Manual for Staging Cancer introduced its TNM classifications and stage groupings for esophageal cancer. In 1992, the fourth edition did not change in esophageal cancer staging. In 1997, the fifth edition introduced a sub classification of staging: M1 became M1a (cervical lymph node metastasis for cancers of the upper thoracic esophagus and celiac lymph node metastasis for cancer of the lower thoracic esophagus) and M1b (all other distant metastasis), and the subclassification of stage IV into IVA and IVB. The sixth edition, published in 2002, was unchanged from the fifth edition.

In the seventh edition, released in 2010, T is classified as Tis for high-grade dysplasia, T1 for cancer that invades the lamina propria, muscularis mucosae, or submucosa; T2 for cancer that invades the muscularis propria; T3 for cancer that invades the adventitia, T4a for resectable cancer that invades adjacent structures such as pleura, pericardium, or diaphragm, and T4b for unresectable cancer that invades other adjacent structures, such as aorta, vertebral body, or trachea. N is classified as N0, no regional LN metastasis; N1, regional LN metastases involving 1 to 2 nodes; N2, regional LN metastases involving 3 to 6 nodes; and N3, regional LN metastases involving 7 or more nodes. M is classified as M0, no distant metastasis; and M1, distant metastasis.

The AJCC addressed the importance of identifying non-anatomic classifications that depend on histopathologic type, grade, and tumor location, concerning recent clinical data and cancer biology. Difference in survival between adenocarcinoma and squamous cell carcinoma is managed by separate stage groupings for stages I and II. Histologic grade is associated with survival for early-stage cancers. For adenocarcinoma, G1 and G2 (well and moderately differentiated) distinguished from G3 (poorly differentiated) for stage I and stage IIA cancers. For squamous cell carcinoma, G1 is distinguished from G2 and G3 for stage I and II cancers. Tumor location (upper and middle thoracic versus lower thoracic) is an important factor for grouping T2-3N0M0 squamous cell cancers. For T1N0M0 and T2N0M0 adenocarcinoma, subgrouping is made by histologic grade: G1 and G2 versus G3. Stage groupings for T1N0M0 squamous cell carcinoma, subgrouping is made by histologic grade: G1 versus G2 and G3. For T2N0M0 and T3N0M0 squamous cell carcinoma, stage grouping is made by histologic grade and location. The four combinations range from G1 lower thoracic squamous cell carcinoma (stage IB), to G2–G4 upper and middle thoracic squamous cell carcinomas (Stage IIB), which have the worst grades. G2–G4 lower thoracic squamous cell carcinomas and G1 upper and middle thoracic squamous cell carcinomas are grouped together (stage II A), with intermediate survival. Stage 0, III, and IV adenocarcinoma and squamous cell carcinoma are identical stage grouped. However, these new stage classifications are not included in UICC TNM 7th edition yet.

The current TNM staging system of the Japan Esophageal Society TNM classification (The 10th Edition) defines tumor extent classified as follows: TX (primary tumor cannot be evaluated), T0 (no evidence of primary tumor), Tis (carcinoma in situ, epithelial cancer), T1 (infiltration of lamina propria or tunica submucosa), T2 (infiltration of tunica muscularis propria), T3 (infiltration to adventitia), and T4 (infiltration to mediastinal structures). Regional lymph nodes are classified as follows: N0, no regional LN; N1, regional (group 1) LN metastases; N2, metastases to group 2 LN; N3, metastases to group 3 LN; N4, metastases to distant LN far from group.
The group of LN is defined by location of the primary tumor. Distant metastases are classified as follows: Mx, distant metastasis cannot be evaluated; M0, no distant metastases; M1, distant metastasis is present. TNM combinations correspond to one of the following stages: stage 0, T0, N0, M0; stage I, T1, N0, M0; stage II, T2, N0, M0, T1, N1, M0; stage III, T3, N0, M0, T2, N1, M0, T0-3 N2 M0; stage IVa, T4, N0-4 M0; stage IVb, T4, N1-4 M0; stage IVc, T4, N5-6 M0; stage IVd, T4, N0-4 M1. Stage IVc and IVd are further classified as IVc1, T4, N0-4 M0, and IVc2, T4, N0-4 M1. Stage IVd is further classified as IVd1, T4, N0-4 M1, and IVd2, T4, N0-4 M2.

Regional Lymph Nodes (N)**

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastases involving 1 to 2 nodes
N2 Regional lymph node metastases involving 3 to 6 nodes
N3 Regional lymph node metastases involving 7 or more nodes

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

SM1, cancer with invasion into one third of the submucosa; SM2, cancer with invasion into the middle third of the submucosa; SM3, cancer with invasion into the lower third of submucosa. As the result of analyses of superficial ESCC in Japan, the incidence of lymph node metastasis in M1, M2, and M3 was 0%, 3.3%, and 12.2%. In submucosal cancer, nodal metastasis was found in 26.5% of SM1, 35.8% of SM2, and 45.9% of SM3.

Endoscopic treatments, such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), have recently become possible choices for intraepithelial neoplasia. Based on the incidence of LN metastasis, the guideline recommends an absolute indication of EMR or ESD for an M1 or M2 tumor and a relative indication for an M3 or SM1 tumor. Almost half of Japanese patients with superficial ESCC underwent EMR or ESD, and the remaining half underwent surgical treatment. However, these techniques are appropriate for patients with no lymph nodes metastasis, who are expected to be poor candidates for invasive esophageal surgery.

A critical component for choosing an appropriate
management strategy for a superficial cancer is an accurate assessment of the tumor extent, using narrow band imaging (NBI) endoscopy and high frequency endoscopic ultrasoundography (EUS). The NBI endoscope became the standard examination for the early detection of superficial esophageal cancer for identifying the intrapapillary capillary loop pattern. However, the views of Japanese and Western pathologists have differed significantly. Before the term "intraepithelial neoplasia" was introduced, severe dysplasia as diagnosed by Western pathologists was the same as carcinoma in situ or noninvasive carcinoma as diagnosed by Japanese pathologists. This problem has been solved by the introduction of the Vienna classification; however, there are still some issues that need to be resolved. One of them is the presence of basal layer type carcinoma in situ, which is often underdiagnosed as low grade intraepithelial neoplasia by Western pathologists.14)

Modality for Tumor Staging

Tumor staging is decided with several imaging modalities. After diagnosis with endoscopic biopsy and pathology, tumor extent is examined with EUS, upper gastrointestinal series (fluorography), CT scan, MRI, FDG-PET, bone scintigraphy, and US. The guideline shows that the diagnosis should be made by the use of endoscopy and fluorography in patients with symptoms. Endoscopic examination is recommended for patients without symptoms.

Endoscopy that includes iodine staining, and fluorography, EUS, CT scan, and MRI are recommended for explanation of tumor extent. Metastases to other organs, including LNs, are diagnosed using a CT scan, MRI, EUS, bone scintigraphy, and FDG-PET/CT. Cervical and abdominal US also provide important information for staging diagnosis. Generally, Tumor length and width is measured by the use of fluorography and CT scan and invasion to neighboring organs and metastasis are diagnosed with CT scan and MRI. Distant organ metastases can be well figured out by FDG-PET/CT.8,11) EUS is a useful procedure for distinguishing T1 lesion from deeper infiltration. Meta-analysis of 19 international studies showed the sensitivity and specificity of the EUS for T1a staging were 0.85 and 0.87, 0.86 and 0.86 for T1b. Especially in T staging, EUS could play an important role in the choice of candidates for endoscopic and surgical treatment. Locoregional invasion in esophageal cancer can be predicted by PET/CT. The SUVmax of the primary tumor helps to identify patients with T1 tumors. Positive regional node SUVmax can help evaluate the severity of nodal involvement. However, the sensitivity, specificity, and accuracy of PET/CT were only 57.1%, 83.3%, and 71.1%, and even lower for detecting nonregional lymph node metastasis. It is not recommended to use FDG-PET or PET/CT alone as a diagnostic tool to determine clinical target volume (CTV) if pathologically involved lymphatic regions are to be included in the CTV in the treatment protocol. The accuracy of FDG-PET/CT must be further improved in order to better detect positive nodes and improve the definition of the CTV.17)

Modality for Lymph Node Metastases

Mediastinal LNs, especially those neighboring the trachea and main bronchus, are often large and round. Those are difficult to distinguish from metastasis, in size and shape. Okada et al. retrospectively reviewed regional LNs of esophageal cancer on contrast enhanced CT (CECT) images by two blinded evaluators on the basis of the following cutoff sizes: 7 mm for all regional LNs (Protocol A), 10 mm for paratracheal LNs (Protocol B), and 7 mm for others. In addition, the maximum standardized uptake value (SUVmax) on PET/CT was evaluated for positive uptake by LNs. The sensitivity, specificity, accuracy, positive, and negative predictive values of PET/CT were 60.0%, 99.5%, 94.8%, 93.8%, and 94.8%, whereas those of CECT were 60.0%, 95.1%, 91.0%, 62.5%, and 94.6% (Protocol A) and 56.0%, 97.3%, 92.4%, 73.7%, and 94.2% (Protocol B). Integrated PET/CT improves
the PPV of regional LNs when compared with CECT. The smallest LN metastasis detectable by PET/CT was 6 mm.18) Meta-analysis for comparing EUS, CT and FDG-PET showed pooled sensitivities of EUS, CT, and FDG-PET for regional LN metastases were 0.80, 0.50, and 0.57, and specificities were 0.70, 0.83, and 0.85. For detection of celiac LN metastases by EUS, sensitivity and specificity were 0.85 and 0.96. For abdominal LN metastases by CT, these values were 0.42 and 0.93. For distant metastases, sensitivity and specificity were 0.71 and 0.93 for FDG-PET and 0.52 and 0.91 for CT. Diagnostic performance of FDG-PET for distant metastases was significantly higher than that of CT, which was not significantly affected by study and patient characteristics.19)

LN metastasis, beside the esophagus, is also diagnosed with EUS. The overall accuracy of EUS for T staging was 72%, and it was the only method for delineating the layers of the esophageal wall. The sensitivities for N staging were 42% for EUS, 49% for PET, and 35% for CT, and their specificities were 91, 87, and 93%. The accuracy for N staging was 66% for EUS, 68% for PET, and 63% for CT, and it did not differ significantly across the three tests. The author concluded that preoperative EUS for the loco-regional staging of esophageal cancer provides excellent T staging accuracy and similar accuracy for N staging, compared with PET and CT.20)

In the comparison of the diagnostic performance of EUS, CT, and FDG-PET in staging of esophageal cancer, EUS is the most sensitive in identifying the detection of regional LN metastases, whereas CT and FDG-PET are more specific tests.21)

Patients proven by endoscopy and biopsy with no evidence of distant metastatic disease on CT and FDG-PET were referred for EUS for locoregional staging. The results of N staging with CT, FDG-PET, and EUS were compared with surgical pathology or EUS-FNA cytology. Overall accuracy for N staging was 69% for CT, 56% for FDG-PET, and 81% for EUS. The combination of CT plus EUS appears to be accurate for locoregional staging in esophageal cancer.22) EUS is also the most accurate technique for preoperative local-regional staging of esophageal carcinoma, once CT and/or the FDG-PET scan have excluded the presence of distant metastasis. EUS-guided fine needle aspiration (EUS-FNA) might help improve diagnostic accuracy in esophageal cancer LN staging, and the therapeutic decision might be derived from such a practice.23) Omloo et al. emphasized an additional value of external US of the neck as a part of the routine diagnostic work-up in patients with esophageal cancer, even after normal CT and FDG-PET scanning.22)

**Modality for Distant Metastases**

For the evaluation of distant metastases, FDG-PET has probably a higher sensitivity than CT. Recent study showed FDG-PET staging was more accurate than CT in the preoperative staging of esophageal cancer.23) The combined use of these modalities could, however, be of clinical value, with FDG-PET detecting possible metastases and CT confirming or excluding their presence and precisely determining the locations (Fig. 3).

As for bone metastasis, there is a meta-analysis comparing FDG-PET and bone scintigraphy in the detection of osseous metastases in patients with breast cancer. The study evaluated the diagnostic accuracy between two modality by systematic surveillance of MEDLINE, CIA-NAL, EBM Review databases. The authors concluded that FDG-PET does have a higher specificity (95% vs. 79%) and may serve as a confirmatory test than bone scintigraphy and used to monitor response to therapy.24)

**New Therapeutic Strategy for Stage II, III Esophageal Cancer**

Results of phase II study which examined the efficacy of CRT for Stage II, III Esophageal cancer (Japan clinical oncology group: JCOG9906 study)25) could not show superior survival benefit compared with previous surgical result and high toxicity especially in the late phase was shown to be a critical problem.
Many patients needed a salvage operation, which brought about serious mortality and morbidity. The JCOG9204 study showed efficacy of adjuvant chemotherapy, with CDDP and 5FU increasing the five year survival rate (55% vs. 45%). A randomized study comparing adjuvant and neo-adjuvant chemotherapy (NAC) (JCOG9907) showed that NAC increased compliance of the therapy (85.4% vs. 75%), and down staging was achieved in some patients by NAC. The five-year overall survival rate was better in NAC group (55% vs 43%, p = 0.04); however, progression free survival did not reach the stopping boundary.

NAC with low dose of CDDP and 5-FU combined with weekly Docetaxel had obtained a better response rate and a more pathological complete response than the ordinary NAC with CDDP and 5FU (Fig. 4). Recently, our data showed that patients with positive EGFR had a poor prognosis without chemotherapy; however, the prognosis had improved with NAC. EGFR is a predictive factor in the patient’s prognosis and response to chemotherapy, and HER2 and HER3 also show similar behaviors. NAC with taxane was recommended for ESCC patients with positive for HER family members. These biomarkers will be candidates for the predictor of prognosis (recurrent risk) and choosing the therapeutic options. Molecular therapy targeting these biomarkers might improve the prognosis of esophageal cancer.

These data show that neoadjuvant therapy (NAT) becomes a common choice for treatment of ECSS in Japan, therefore, an accurate estimation of NAT is essential to decide the following therapy (Fig 5). But re-estimation of the advanced tumor is still controversial. Especially, diagnosis of invasion to neighboring organs is difficult after CRT even with EUS, enhanced CT scan and MRI.

**Evaluation of Primary Therapy and Restaging**

FDG-PET is a good modality for predicting the efficacy of NAT and neoadjuvant chemoradiotherapy (NACRT) for advanced esophageal cancer. An SUVmax reduction of more than 70% was classified as an FDG-PET responder and showed better prognosis, however, the response for the primary tumor (PT) or LN on CT evaluation was not a significant prognostic predictor. They concluded that FDG-PET was superior to CT for evaluating the CRT response, from the viewpoint of survival analysis. However, the response should be evaluated for both LN and PT because of their different behaviors during primary therapy. FDG-PET/CT has limited utility in T staging and relatively limited utility in detection of dissemination to locoregional lymph nodes. Interpretation of FDG-PET/CT results is optimized by an understanding of the diagnostic limitations and pitfalls that may be encountered together with knowledge of the natural history of esophageal cancer and the staging and treatment options available.

A recent systemic review concluded that PET was recommended to improve the accuracy of M staging for the staging work-up of patients who were potential candidates for
curative therapy; however, no recommendation was made for or against the use of PET for the assessment of treatment response and evaluation of suspected recurrence.\(^{36}\)

A 50% or more reduction of tumor thickness by EUS post chemotherapy continues to be the best measure for tumor downstaging survival, while FDG-PET/CT may be more accurate than EUS-FNA and CT scan for predicting nodal status and complete responders after NAT. The role of EUS in restaging following NAT remains controversial, with recent studies showing that FDG-PET/CT may be more accurate than EUS-FNA and CT scan for predicting nodal status and complete responders after NAT. Potential methylation analysis, digital image analysis, and fluorescence in-situ hybridization on EUS-FNA samples might increase the yield and prove to be better than routine cytology.\(^{37}\) It is also hard to recognize dissectability of the fibrotic tissue including tumor after definitive CRT. Dynamic study with MDCT or MRI, or EUS elastography might help to diagnosis for dissectability.\(^{38}\)

**New Strategy for Superficial Esophageal Cancer Diagnosis**

An accuracy of tumor depth for m1 m2 cancer was 95%, but it was 74% for m3 sm1, and 79% even with NBI scope. It is not satisfied because 20-30% of submucosal esophageal cancers which involves LN metastases are underestimated.\(^{39}\)

EMR and ESD have been developed in Japan. Pathological mapping and decision making for further treatment are feasible with those enhanced biopsy specimen. Phase II study of CRT for stage I (cT1bN0) esophageal cancer (JCOG9708) proved efficacy and safety of CRT from the viewpoint of organ preservation.\(^{40}\) Additional studies are necessary to further elucidate this multimodality approach.\(^{41}\) There is currently an ongoing phase II study evaluating the efficacy and the safety of combined treatment of EMR and CRT for clinical stage I esophageal cancer (JCOG0508). In this study, EMR was made for Tlb (sm 1, 2 suspected, <5 cm, <3/4, ≤2 accessory lesion) N0M0 patients. An additional CRT; two cycles of 5-FU/ cisplatin, with 41.4 Gy of radiation for negative resection margin or 50.4 Gy with boost on the primary site for positive margin is added if residual tumor is suspected after detailed pathological examination. The data from this trial will be expected to provide a non-surgical treatment option to clinical stage I (Tlb) esophageal cancer patients.\(^{42}\)

**Another Strategy for Measuring Tumor Extent of Superficial Esophageal Cancer**

The sentinel lymph node (SLN) concept has been developed by researchers in several different cancer centers and has become a widely accepted element in the routine surgical management of breast cancer.\(^{43}\) It has been reported that pN0 breast cancer patients diagnosed by SLN biopsy (SLNB) showed superior survival to pN0 patients diagnosed by axillary dissection. It is easily acceptable because SLNs are examined more carefully in thin sliced spacers compared with dissected lymph nodes samples are examined in one sliced specimen.\(^{44}\) Thus, SLNB provides strong evidence for an improvement in tumor staging on the basis of SLNB. At the moment, the available data does not justify reduced the extent of lymphadenectomy, but most recent result of phase III trial comparing SLNB alone and axillary lymph node dissection after SLNB for breast cancer patients with less than 2 node involvement showed no differences in local control and survival in breast cancer.\(^{45}\)

Introduction of SLN navigation to gastrointestinal (GI) tract is controversial. SLNB using available techniques have suggested that the lymphatic drainage of GI tract is much more complicated than other sites, skip metastasis being rather frequent because of an aberrant lymphatic drainage outside of the basin exist. Recent studies have shown favorable results for identification of SLN in esophageal cancer.\(^{46}\) Uenosono et al. performed SLN navigation surgery for T1, T2 and T3 patients with esophageal cancer after (99m) Tc-Tin colloid endoscopical injection into the esophageal wall around the tumor 1 day before surgery. They concluded SLN mapping could be applied to patients with cT1 and cN0 esophageal cancer.\(^{47}\) The SLN concept might enable surgeons to perform less invasive surgery, with a reduction in the number of lymphadenectomies performed. However, SLN navigation with radioisotope and blue dye are the intra-operative technique. Radio-scintigraphy cannot supply preoperative detailed anatomical information, especially SLN neighboring the tumor cannot detect because of the shine-through phenomenon. Tumor-occupied lymph nodes could not be detected preoperatively, and they were also missed during the operation.\(^{48}\) We developed a new strategy of SLN mapping with CT scan. Lymph flows from the tumor was visualized on a 3D CT image, with the surrounding anatomy during the preoperative, routine CT examination for tumor infiltration and metastasis.\(^{49}\)

CT lymphography (CTLG) with endoscopic mucosal injection of iopamidol was applicable for SLN navigation of
superficial esophageal cancer. The multiple-angle views of 3D, CT image sets provided a comprehensive anatomy of these lymphatic pathways (Fig. 6A and 6B). Our recent study about preoperative CTLG and intraoperative fluorescent navigation with ICG (indocyanine green) with Infrared Endoscopic Camera System (OLIMPUS, Tokyo, Japan) completed the precise detection of SLN with lymphatic routes from the tumor (Fig. 7A–7C). Tumor-occupied metastases were translated in unstained swollen, mottled stain pattern, or stain defect with rerouting lymph routes from CTLG images.

The aim of surgical treatment for cancer is complete resection of the tumor-infiltrated organ including the regional lymph nodes. Accurate detection of SLN can achieve a selection of a more sophisticated tailor made approach.

We developed mediastinoscope assisted transhiatal esophagectomy (MATHE). Esophagectomy can be performed with this procedure under clear visualization of the mediastinum, and LN sampling is feasible. If the sampled LN proved to be metastasis, conversion to a transthoracic radical operation with LN dissection is very easy.

The patient can make an individualized choice from a
broader spectrum of therapeutic options including EMR, laparoscopic, thoracoscopic, MATHE, modified radical surgery, and typical, radical surgery with lymph node dissections. Ultra-staging, by the detection of micrometastasis, and the choice of an adequate adjuvant therapy improve the postoperative quality of life and survival. However, these issues require further investigation.

Conclusion

FDG-PET and CT scan are the gold standard to detect distant metastases of ESSC, but the metastatic node is difficult to diagnose from its size and SUV. After diagnosis with high resolution NBI endoscopy, the neighboring node should be examined with UES. US is also available for screening the neck and abdomen. Exact staging will be determined by the fine needle aspiration biopsy (FNAB) under EUS and US. For superficial cancers, indications for EMR and ESD should be sensitive because of the difficulty in making the diagnosis of T1b cancer. A detailed examination for finding residual tumor in the dissected specimen will predict an appropriate additional therapy. A new strategy like SLN navigation, in which CTLG is used, will supply more information about lymphatic routes and metastatic nodes. SLN navigation with ESD or MATHE might become a new, less invasive strategy for superficial esophageal cancer.

References


