

From Uniformed Treatment to Individualized Treatment for Superficial Esophageal Cancer —What Is Potentially a New Approach?—

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Esophageal squamous cell carcinoma (ESCC) is among the most aggressive gastrointestinal tumors. The surgical procedure for esophageal cancer is difficult and complicated. According to the history of esophageal cancer treatment, the view of a surgical method has been changed, in consideration of such factors as attention to safety, importance of curability, and consideration of quality of life (QOL).^{1,2} Because of improved imaging diagnoses and the development of surgical devices, treatments of esophageal cancer have gradually improved. Recent developments of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have enabled patients with early-stage ESCC to maintain QOL by preservation of the esophagus.³ The conventional strategy following EMR/ESD for superficial ESCC is radical surgery. From the viewpoint of QOL, the discrepancy of invasiveness is too different between EMR/ESD and radical surgery. Thus an intermediate treatment between them should be devised from another concept.

At present, since the treatment plan for superficial ESCC is based on tumor depth and lymph node metastasis, a detailed diagnosis should be required. According to guidelines for clinical and pathological studies on carcinoma of the esophagus by the Japan Esophageal Society,⁴ the depth of mucosal invasion was histologically subdivided as T1a-EP (M1), T1a-LPM (M2), and T1a-MM (M3). The depth of submucosal invasion was histologically subdivided as SM1, SM2, and SM3. This subclassification is very important for determining the treatment strategy. As the result

of analyses of superficial ESCCs in Japan, the incidence of lymph node metastasis in M1, M2, and M3 was 0%, 3.3%, and 12.2%, respectively. In submucosal cancer, nodal metastasis was found in 26.5% of SM1, 35.8% of SM2, and 45.9% of SM3, respectively.⁵ According to Japanese guidelines based on these results, absolute indication of EMR or ESD is an M1 or M2 tumor, and relative indication is an M3 or SM1 tumor. In fact, almost half of the Japanese patients with superficial ESCCs underwent EMR or ESD, and the remaining half underwent surgical treatment.⁶

Recently, the sentinel node (SN) concept has been introduced to gastrointestinal cancer.^{7,8} If this concept is applicable to patients with esophageal cancer, it would prove useful in identifying sites for lymph node dissection. SN navigation surgery (SNNS) would therefore appear to benefit esophageal cancer patients by not only allowing reduced lymphadenectomy, but also reduced esophagectomy. However, a clinical application of SNNS for esophageal cancer has not yet been established. Some researchers have subsequently studied SNNS by using various methods.^{9–11} In esophageal cancer, detecting SNs by the use of dye methods is difficult because of anatomical limitations and the anthoracosis of lymph nodes. Generally, radioisotopic methods have been used to identify SNs. The SN concept is a worthwhile approach to detecting lymph node metastases according to the individual situation. Based on preliminary studies, including our own, the SN concept is applicable to superficial ESCCs, especially in patients clinically diagnosed as T1 and N0.^{12,13}

What potentially is a new approach to superficial ESCCs? Extended indication of EMR/ESD is acceptable in some patients with clinical M3 and SM1 tumors. With it, however, correctly diagnosing both tumor depth and nodal metastasis is more difficult. Because about 20% of patients have lymph node metastasis, the problem is how to detect these patients. We currently try to preserve the

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esophagus by EMR/ESD and SN dissection for clinical M3 and SM1 tumors. We consider that such methods are crucial to preserving QOL. If SN is positive for metastasis, additional treatment is necessary, such as surgery or chemotherapy and/or radiation therapy.

Extended lymph node dissection is applicable to SM2 and SM3 tumors because the incidence of nodal metastasis, including micrometastasis, is high. More than half of the patients, however, do not have nodal metastasis, and even if it is found, the number of lymph node metastases is relatively few in comparison with advanced ESCC.¹⁴⁾ Especially in patients without clinical metastasis, a reduction of lymphadenectomy may be possible by the device of detection for the presence or absence of nodal metastasis. In such cases, SNNS seems to be ideal for detecting nodal metastasis. Thus if SN is negative for metastasis, limited lymph node dissection can be performed.

Among the most important problems in SNNS is the ability to accurately diagnose lymph node metastasis. The accuracy rate of preoperative diagnosis is around 80% by various imaging methods. Furthermore, in approximately 15% of pN0 patients, lymph node micrometastasis is detected by a detailed immunohistochemistry examination and RT-PCR methods even in superficial ESCC.¹⁵⁾ If we can detect lymph node metastasis more accurately during surgery, we will have a new treatment strategy that is different from conventional treatments. Thus when SNNS is performed, a diagnosis of lymph node micrometastasis during surgery is essential. When we apply rapid immunohistochemical diagnosis during SNNS, we will have the result in about 30 minutes.¹⁶⁾ Rapid RT-PCR will also be available to detect micrometastasis.¹⁷⁾ Recent studies have revealed the close relationship between lymph node metastasis, including micrometastasis and lymph nodes along the recurrent nerve and cervical regions. If lymph node metastasis, including micrometastasis, is absent in the SN along the recurrent nerve, it may be possible to omit cervical lymph node dissection.¹⁸⁾

Some patients do not undergo surgery because of advanced age or serious preoperative complications. Because the distribution of lymph node metastasis is seen in extended regions, it is often difficult to set the radiation field for lymph node metastasis. The SN concept is available for patients who receive chemoradiation therapy. If SN is detected, radiation therapy can focus on the limited region by SN identification. Even in patients with SM2 or SM3 tumors, EMR/ESD with chemoradiation therapy is permitted.

As the ultimate aim of surgical treatment for superfi-

cial ESCC is curability and the preservation of function as much as possible, esophageal surgeons should have used a wide variety of approaches to this disease. Individual patients have individual presurgical conditions and individual characteristic tumors. Thus individual treatment of superficial ESCCs should be established with such methods as analysis of past data, clinical diagnosis of lymph node metastasis by imaging, and SNNS, including the diagnosis of micrometastasis. In the future, according to both the patient's condition and the tumor factor, treatment strategy for superficial esophageal cancer will be changed from a uniform type of treatment to an individual type of treatment.

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