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Lymph Node Metastases in Esophageal Carcinoma: An Endoscopist's View

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One of the most important prognostic factors in esophageal carcinoma is lymph node metastasis, and in particular, the number of affected lymph nodes, which influences long-term outcomes. The esophageal lymphatic system is connected longitudinally and transversally; thus, the pattern of lymph node metastases is very complex. Early esophageal cancer frequently exhibits skipped metastasis, and minimal surgery using sentinel node navigation cannot be performed. In Korea, most esophageal cancer cases are squamous cell carcinoma (SCC), although the incidence of adenocarcinoma has started to increase recently. Most previous reports have failed to differentiate between SCC and adenocarcinoma, despite the fact that the Union for International Cancer Control (7th edition) and American Joint Committee on Cancer staging systems both consider these separately because they differ in cause, biology, lymph node metastasis, and outcome. Endoscopic tumor resection is an effective and safe treatment for lesions with no associated lymph node metastasis. Esophageal mucosal cancer confined to the lamina propria is an absolute indication for endoscopic resection, and a lesion that has invaded the muscularis mucosae can be cured by local resection if invasion to the lymphatic system has not occurred.

Key Words: Esophageal neoplasms; Lymph node metastasis; Endoscopic resection

INTRODUCTION

The incidence of esophageal cancer is increasing more rapidly than that of most other gastrointestinal malignancies, and the disease has a very poor prognosis. In particular, the 5-year survival rate for patients with lymph node metastasis is exceptionally low. The treatment of patients with early-stage disease is relatively straightforward via curative surgery, whereas patients with advanced esophageal cancer are often managed by palliative chemoradiotherapy.[1] Currently, the most pressing problem in esophageal cancer treatment is that the postoperative mortality and morbidity rates are consistently higher than those for other gastrointestinal cancers.[2]

The prognosis of esophageal cancer depends on the extent of both the primary tumor and lymph node metastasis.[3] Lymph node status is the single most important prognostic factor in esophageal cancer, with an increasing number of metastatic lymph nodes being associated with a progressively poor prognosis. To date, no standardized surgical protocol for esophageal cancer or a consensus on the optimal range of lymph node dissection is available. Many patients undergo surgery at low-

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volume centers that manage fewer than 20 cases of esophageal cancer resection per year.[3] There are also significant differences in the number of metastatic lymph nodes as well as surgical short- and long-term outcomes.

Current management options for superficially invading lesions include endoscopic resection, ablation, and a number of less invasive surgical techniques. Cases showing invasion to the mucosa but no lymph node metastasis are always treated using endoscopic resection, a method that has advanced through the development of endoscopic devices and techniques, including endoscopic submucosal dissection or mucosal resection. The optimal treatment is often decided on a case-by-case basis, in consideration of the lesion's invasion depth and the patient's underlying diseases.

In the present review, we describe the pattern of lymph node metastasis in esophageal cancer and the rate of lymph node metastasis with respect to a lesion's invasion depth. We also clarify the indication for endoscopic resection in esophageal cancer.

UNDERSTANDING LYMPH NODE METASTASIS IN ESOPHAGEAL CANCER

Pathways of lymph node metastasis

All lymph node metastases occur along the lymphatic chain. The sentinel node is the first lymphatic drainage area from the primary tumor, and could be the first site of micrometastasis. Recently, several centers have attempted minimally invasive curative resection for esophageal cancer, including resection of regional lymph nodes through sentinel node navigation.[4]

In early esophageal cancer, skipped metastasis is observed in 60% of cases.[4] The lymphatic drainage system in the submucosa is very complex, with an abundant lymph-capillary network, which not only penetrates the esophageal wall transversally and drains to the adjacent lymph nodes, but also has a longitudinal communicating drainage system.[3,5,6] The pattern of lymph node metastasis is indiscriminate, irrespective of the primary tumor site.

Esophageal cancer metastasizes to different regional and distant lymph nodes depending on the primary site,[1] and early esophageal cancer invading the muscularis mucosae may have more than one lymph node metastasis.[7] In a Japanese nationwide study on three-field lymph node dissection, the prevalence of metastasis among esophageal cancer cases showing muscularis mucosae invasion was 7.5% in the abdominal and cervical nodes and 15% in the mediastinal node, whereas the risk of lymph node metastasis in submucosal cancer increased to 15.2%, 32.2%, and 23.5% in the cervical, mediastinal, and abdominal nodes, respectively.[2]

Extended lymph node dissection is not indicated for esophageal cancer owing to the disease's low prevalence of lymph node metastasis. Furthermore, lower thoracic esophageal cancer does not exhibit cervico-upper thoracic lymph node metastases in the absence of regional lymph node metastasis; therefore, patients with negative upper thoracic lymph nodes do not necessarily require three-field lymphadenectomy.[8]

Tumor-node-metastasis classification

The 7th tumor-node-metastasis (TNM) classification, devised in 2010 following an analysis of 4,627 patients who received only surgical treatment for esophageal cancer, differs from the 6th classification published in 2002 in a number of aspects. One of the most important changes is that the new classification includes separate staging systems for squamous cell carcinoma (SCC) and adenocarcinoma. In addition, with respect to the degree of invasion by the primary tumor, stage T4 is divided into T4a (resectable) and T4b (unresectable), and staging also considers histological grade and tumor location.[9,10] Another significant change involves the classification of lymph node metastasis. In the 6th TNM classification, lymph node metastasis is based on the site of the metastatic lymph node, and it is defined as regional or distant. Conversely, the main determinant of lymph node staging in the seventh TNM classification is the number of metastatic lymph nodes.

In the 6th TNM classification, lymph node status is classified into three stages (N0, N1, and M1), in which N1 denotes regional lymph node metastasis, and M1 indicates distant metastasis (to the celiac or cervical lymph nodes).[10] The disadvantages of this classification are that it does not take into consideration the relationship between the number of metastatic lymph nodes and long-term outcomes of the disease, and that it provides the same prognostic weighting to cervical and intra-abdominal lymph node metastasis.

In the 7th TNM classification, lymph node status is classified into four stages (N0, N1, N2, and N3) according to the number of lymph node metastases, regardless of the location.[11] Regional lymph node status is classified as N0 if none of the lymph nodes exhibits metastatic involvement; it is classified as N1 if one or two lymph nodes show metastatic involvement, N2 if three to six lymph nodes show metastatic involvement, and N3 if seven or more lymph nodes show metastatic involvement.

According to the 6th TNM classification, celiac lymph node metastasis from an intrathoracic tumor is classified as distant metastasis (M1a), whereas according to the seventh TNM classification, the condition is considered simply as regional node metastasis, regardless of the primary tumor site, and is associated with a low 5-year survival rate.[2]

Prognostic significance of lymph node metastasis

Lymph node metastasis is the single most important prognostic factor in esophageal cancer, and the condition is associated with poor survival,[12] whereby an increasing number of metastatic lymph nodes is related to a progressively bad prognosis. On average, patients with a single lymph node metastasis survive significantly longer than those with two or more lymph node metastases.[13,14] Likewise, Zhang et al.[15] reported that the number of positive lymph nodes was significantly associated with survival in patients with esophageal SCC, and that patients with 0, 1, and ≥2 positive nodes had 5-year survival rates of 59.8%, 33.4%, and 9.4%, respectively. Correspondingly, esophageal cancer patients with a high "LN ratio" (i.e., metastatic lymph nodes as a proportion of the total number of lymph nodes removed) have a poor prognosis, and an LN ratio of less than 0.2 is associated with a significantly better prognosis. Patients with an LN ratio of less than 0.2 have a 5-year survival rate of 22% and a recurrence risk of 44%; the figures increase to 54% and 69%, respectively, for those with an LN ratio equal to or higher than 0.2.[12,16,17]

Although several studies have concluded that the number of resected lymph nodes is an important determinant of overall survival, the optimal resection strategy remains unclear, and still no guidelines have been established for the number of lymph nodes that should be resected during curative surgery. The 6th TNM classification published by the Union for International Cancer Control and American Joint Committee on Cancer (AJCC) in 2002 proposes that at least six lymph nodes should be removed for an accurate and reliable N classification of esophageal cancer.[18,19] However, several reports have suggested that for an adequate lymphadenectomy, at least 18 lymph nodes should be resected.[2,13,20,21]

The 7th TNM classification defined N3 as the presence of metastasis in seven or more regional lymph nodes, which implies that previously reported data, including cases without a minimum number of resected lymph nodes necessary for an adequate lymphadenectomy, might have an inaccurate N classification. In Japan, patients who undergo three-field lymphadenectomy tend to have a better prognosis, and many centers have considered adopting it as their standard protocol. It is possible that patients who undergo nonradical esophagectomy show downstaging owing to an insufficient number of lymph nodes being resected, compared to those undergoing two- or three-field extended lymphadenectomy.[2,22]

Micrometastasis and isolated tumor cells

Lymph node metastasis in breast cancer has been described as isolated tumor cells (pN0i+), micrometastasis (pN1mi), or metastasis, according to the 6th AJCC TNM classification. Micrometastases are detected using immunohistochemical techniques and range from 0.2 to 2 mm in size. They are usually found in 21% to 40% of the resected lymph nodes, and are the reported stage in 25% to 65% of patients undergoing radical esophagectomy with lymph node dissection.[4,8,23] It has been suggested that radical excision should include micrometastatic lymph nodes as well.[24] McGuill et al.[25] reported that a low 5-year survival rate was associated with occult lymph node metastasis in esophageal cancer cases previously diagnosed as being lymph node negative on conventional staining. However, there is currently no consensus about the importance of resection of micrometastasis because the number of resected lymph nodes in previous studies differs significantly, and the immunohistochemical methods have not been standardized with respect to the antibodies, staining technique, and scoring system used.[23,26] Isolated tumor cells covering an area with the longest dimension of less than 0.2 mm should be distinguished from micrometastasis, and it is unclear whether they represent clinically relevant metastases.[23]

RISK AND CHARACTERISTICS OF LYMPH NODE METASTASIS

Adenocarcinoma vs. squamous cell carcinoma

Esophageal cancer comprises SCC and adenocarcinoma. Previously, most esophageal cancer cases were found to be SCC, but the incidence of both types is now equal in the United States, implicating an explosive increase in adenocarcinoma cases over the last 20 years.[12] Similarly, in Korea, more than 90% of esophageal cancer cases were diagnosed as SCC, and adenocarcinoma cases were rare. However, the incidence of adenocarcinoma seems to be increasing with a rapid growth in the number of patients with gastroesophageal reflux disease and Barrett esophagus.

The question remains whether it is accurate to describe both SCC and adenocarcinoma of the esophagus as the same disease. These conditions have different outcomes because they differ in etiology, tumor biology, and tumor location. Nonetheless, only a few studies have differentiated between the two. The 7th TNM classification applies separate staging systems for esophageal SCC and adenocarcinoma.[11,27,28] Distant metastasis of SCC occurs most commonly in the intrathoracic area, whereas adenocarcinoma more frequently metastasizes to the intra-abdominal sites, as esophageal adenocarcinomas are usually located in the distal third of the esophagus, including the esophagogastric junction.

In superficial esophageal cancer cases, adenocarcinoma carries a lower risk of lymph node metastasis than SCC, which is more locoregional, and consequently has a better prognosis.[27,29] Siewert et al.[27] compared adenocarcinoma and SCC of the esophagus and found that the overall 5-year survival rate

was significantly higher in adenocarcinoma than in SCC cases (42.3% vs. 30.3%). In addition, skipped metastasis occurs less frequently in esophageal adenocarcinoma.[27] Stein et al.[28] compared lymph node metastasis between early esophageal adenocarcinoma and SCC, and found that in patients with submucosal cancer, the prevalence of lymph node metastasis differed significantly between adenocarcinoma and SCC cases (21% vs. 36%), and that none of the adenocarcinoma cases involved skipped metastasis.

Tumor invasion depth

The prognosis of esophageal cancer patients without nodal involvement is related to the tumor T stage, histology, grade, and location.[30] One of the changes in the 7th TNM classification is that T4 (tumor invasion of an adjacent structure) is subclassified as T4a (resectable) and T4b (unresectable). Siewert et al.[27] reported R0 resection in 59.3% of adenocarcinoma cases and 48.5% of SCC cases in which the tumor was classified as T4.

Most preoperatively diagnosed as T2 to T3NoMo lesions are found to involve lymph node metastasis when the resected specimen was examined.[31] Patients with stage T3 tumors that invade the adventitia also have a poor prognosis, and the cure rate is approximately 15%. Siewert et al.[27] analyzed 1,059 consecutive resections for esophageal cancer. The prevalence of lymph node metastasis in cases where the lesion was at least pT2 was more than 50%, regardless of histology, and almost all patients with T4 tumors had lymph node metastasis (Table 1).[27,32]

Superficial cancer: submucosal vs. mucosal

Superficial esophageal cancer refers to a tumor that is limited to the submucosa, and localized resection by endoscopy or ablation is an option when these cases do not involve lymph node metastasis. According to the TNM classification, superficial esophageal cancer is classified as Tis (high-grade dysplasia), T1a (invasion of the muscularis mucosae), or T1b (invasion of the submucosa). Evaluation of the lymph node metastasis risk in association with the invasion depth was previously deemed necessary to predict prognosis and decide upon the therapeutic modality.[7,18,30] Mucosal layer invasion in the esophagus is classified as M1 (limited to the epithelial layer), M2 (invasion of the lamina propria), or M3 (invasion of the muscularis mucosae). The submucosal layer is divided into three layers of equal thickness that are classified as SM1 (superficial one-third), SM2 (middle one-third), and SM3 (deep one-third) (Tables 2, 3).[7,18,22,33,34]

Esophageal SCC invading the mucosal layer (T1a) also involves lymph node metastasis in 0% to 3% of cases; however, there are no cases of M1 and M2 lesions that involve the lymph nodes.[27,28] The prevalence of nodal involvement in M3 lesions is 0% to 18%.[7,33,35] In cases where the lesion is associated with lymphatic invasion, there is a higher probability of lymph node metastasis. The incidence of nodal metastasis in esophageal SCC invading the submucosa (T1b) is reportedly 26% to 50%, while that of lesions limited to SM1 is 8% to 50%, and cases involving skipped metastasis are rare.[7,21,33,36]

The rate of nodal involvement is 0% to 2% in cases of esophageal adenocarcinoma invading the mucosa (T1a) with an M1 or M2 lesion, which have no significant risk of lymph node metastasis. Adenocarcinoma with submucosal invasion (T1b) involves metastatic lymph nodes in 27% to 41% of cases, and SM1 lesions are associated with nodal involvement in 0% to 22% of cases.[18,22,27,28,36] Leers et al.[18] studied the prevalence of lymph node metastasis in patients with T1 esophageal adenocarcinoma and found that lymphovascular invasion, a tumor equal to or greater than 2 cm in size, and poor differentiation were all associated with an increased risk of submucosal invasion and lymph node metastasis.

Sgourakis et al.[36] found that lymphovascular invasion was a principal predictor of lymph node metastasis in T1b esophageal cancer, and that the best predictors of lymph node metastasis were SM3 invasion and vascular invasion for submucosal SCC and lymphatic invasion for adenocarcinoma. However, they found no association between lymph node metastasis and invasion depth (SM1 vs. SM2 vs. SM3) in submucosal cancer.[36]

Table 1. Prevalence of Lymph Node Metastasis according to Tumor Invasion Depth

Reference	T_1	T_2	T_3	T_4
Squamous cell carcinoma				
Rice et al. (1998)[32]	5 (20)	12 (33)	29 (48)	7 (57)
Siewert et al. (2001)[27]	117 (20)[a)]	75 (52)	195 (74)	33 (100)
Adenocarcinoma				
Rice et al. (1998)[32]	60 (10)	24 (45)	182 (83)	2 (100)
Siewert et al. (2001)[27]	107 (10)[a)]	70 (69)	104 (81)	27 (93)

Values are presented as number (%).
[a)]Number of esophageal cancer cases in which the tumor invaded the mucosa and submucosa, including high-grade dysplasia.

Histological grade and other classifications

In the seventh TNM classification, histological grade is classified as G1 (well differentiated), G2 (moderately differentiated), G3 (poorly differentiated), or G4 (undifferentiated), and it partly determines the tumor stage. Histological grade is a predictor of lymph node metastasis. Bollschweiler et al.[22] reported that G1/G2 histology was associated with a lower rate of lymph node metastasis compared with G3 in early esophageal cancer. In T1 esophageal adenocarcinoma, Leers et al.[18] found that poor differentiation was associated with an increased risk of lymph node metastasis and submucosal invasion. A number of biochemical markers may also predict lymph node metastasis in esophageal cancer. In particular, vascular endothelial growth factor C has been shown to be associated with lymph node metastasis and a poor prognosis.[37]

The appearance of lesions during endoscopy is also helpful in assessing the likelihood of lymph node metastasis. In particular, a flat lesion is less likely to have metastasized to a lymph node than a depressed or elevated lesion.[30]

THERAPEUTIC ENDOSCOPY

Although esophagectomy is the treatment of choice for esophageal cancer, the number of endoscopic resections for superficial esophageal cancer has recently increased. Nonetheless, surgical therapy for esophageal cancer is still an operation with high perioperative risks. Even at a high-volume center, the perioperative mortality rate is 1% to 5%, and the perioperative morbidity rate is also high. In a Japanese nationwide study, postoperative complications were observed in more than 50% of cases.[2] Therefore, a lesion without lymph node metastasis should be treated using minimally invasive approaches. Both the nature of a tumor and the patient's performance status need to be evaluated when deciding upon the optimal treatment method because operative risk is considerably greater in patients with severe underlying diseases.

The absolute indications for the use of endoscopic resection in esophageal cancer are when the lesion is limited to the lamina propria (M1 and M2) in SCC or to the mucosa, including the muscularis mucosae, in adenocarcinoma. Endoscopic mucosal resection or submucosal dissection for lesions confined to the mucosa is performed regardless of the histology because preoperative histological evaluation cannot accurately differentiate between M2 and M3.[38,39] M3 lesions without lymphovascular invasion have a very low risk of lymph node metastasis, and they may be treated using an endoscopic method. Moriya et al.[35] assessed the prognostic value of lymphatic tumor emboli detected by D2-40 immunostaining to predict the risk of lymph node metastasis. They found that in SCC cases, M3 and submucosal lesions with an invasion depth no greater than 200 μm from the lower margin of the muscularis mucosae had no associated lymph node metastasis if they were negative for lymphatic tumor emboli.[35] Accurate pathologic evaluation of the resected specimen after endoscopic resection,

Table 2. Risk of Lymph Node Metastasis in Mucosal (T1a) Esophageal Cancer

Reference	M_1	M_2	M_3	M
Squamous cell carcinoma				
Araki et al. (2002)[33]	8 (0)	10 (0)	22 (0)	40 (0)
Endo et al. (2000)[7]	29 (0)	47 (0)	36 (8)	112 (3)
Adenocarcinoma				
Westerterp et al. (2005)[34]	13 (0)	18 (0)	22 (4.5)	54 (2)
Leers et al. (2011)[18]	0	18 (0)	57 (1.8)	75 (1.3)

Values are presented as number (%).

Table 3. Risk of Lymph Node Metastasis in Submucosal (T1b) Esophageal Cancer

Reference	SM_1	SM_2	SM_3	SM
Squamous cell carcinoma				
Bollschweiler et al. (2006)[22]	3 (33)	6 (17)	13 (69)	22 (50)
Araki et al. (2002)[33]	12 (8)	18 (22)	28 (36)	58 (26)
Endo et al. (2000)[7]	18 (11)	50 (30)	56 (61)	124 (41)
Adenocarcinoma				
Bollschweiler et al. (2006)[22]	9 (22)	4 (0)	9 (78)	22 (41)
Westerterp et al. (2005)[34]	25 (0)	23 (35)	18 (67)	66 (27)
Leers et al. (2011)[18]	19 (21)	9 (11)	23 (26)	51 (22)

Values are presented as number (%).

including the use of D2-40 immunostaining, is essential. Furthermore, the decision to perform additional surgery or chemoradiation therapy must be taken after considering tumor invasion depth, lymphovascular invasion, and a patient's underlying diseases.

CONCLUSIONS

One of the most important prognostic factors in esophageal cancer is lymph node metastasis. SCC and adenocarcinoma differ in their etiology, tumor biology, tumor location, and long-term outcomes. In superficial esophageal cancer cases, adenocarcinoma carries a lower risk of lymph node metastasis than SCC, which is more locoregional.

Surgical treatment is the treatment of choice for esophageal cancer, despite high rates of perioperative mortality and morbidity. Endoscopic resection is a safe and effective treatment for superficial esophageal cancer without lymph node metastasis. Both the nature of a tumor and the patient's performance status need to be evaluated when deciding upon the optimal treatment method.

Conflicts of Interest

The authors have no financial conflicts of interest.

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