

## Lymphatic spreading and lymphadenectomy for esophageal carcinoma

Xiang Ji, Jie Cai, Yao Chen, Long-Qi Chen

Xiang Ji, Jie Cai, Yao Chen, Long-Qi Chen, Department of Thoracic Surgery, West China Hospital of Sichuan University, Chengdu 610041, Sichuan Province, China

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**Correspondence to:** Dr. Long-Qi Chen, Department of Thoracic Surgery, West China Hospital of Sichuan University, No. 37 Guo Xue Xiang, Wuhou District, Chengdu 610041, Sichuan Province, China. [drchenlq@gmail.com](mailto:drchenlq@gmail.com)  
Telephone: +86-28-85422494  
Fax: +86-28-85422494

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### Abstract

Esophageal carcinoma (EC) is a highly lethal malignancy

with a poor prognosis. One of the most important prognostic factors in EC is lymph node status. Therefore, lymphadenectomy has been recognized as a key that influences the outcome of surgical treatment for EC. However, the lymphatic drainage system of the esophagus, including an abundant lymph-capillary network in the lamina propria and muscularis mucosa, is very complex with cervical, mediastinal and celiac node spreading. The extent of lymphadenectomy for EC has always been controversial because of the very complex pattern of lymph node spreading. In this article, published literature regarding lymphatic spreading was reviewed and the current lymphadenectomy trends for EC are discussed.

**Key words:** Lymphadenectomy; Lymphatic spreading; Anatomical lymphatic system; Lymph node metastasis; Esophageal cancer

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**Core tip:** Esophageal carcinoma (EC) is a highly lethal malignancy with a poor prognosis. One of the most important prognostic factors in EC is lymph node status. Therefore, lymphadenectomy has been recognized as a key that influences the outcome of surgical treatment for EC. However, the lymphatic drainage system of the esophagus is very complex, with cervical, mediastinal and celiac node spreading. The extent of lymphadenectomy for EC has always been controversial because of the very complex pattern of lymph node spreading. In this article, published literature regarding lymphatic spreading was reviewed and the current lymphadenectomy trends for EC are discussed.

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## INTRODUCTION

Esophageal carcinoma (EC) is one of the most common cancers and an important cause of cancer-related deaths in the world. It is an aggressive disease with a poor prognosis and a rapidly increasing incidence. The overall 5 years survival is 10%, ranging from 15% to 40% after surgery. Although multimodal therapy, including neoadjuvant chemotherapy or chemoradiotherapy with esophagectomy, has improved the long-term survival, surgery is also regarded as the standard treatment for resectable EC<sup>[1-4]</sup>. Lymph node status has been recognized as the most important independent factor that influences the prognosis of EC. The 7<sup>th</sup> edition of the TNM staging system showed that an increasing number of metastatic lymph nodes is associated with a poorer prognosis<sup>[5,6]</sup>. Therefore, the outcome of surgery depends on lymphadenectomy as well as the primary tumor invasion in EC.

However, the extent of lymphadenectomy in EC is still considerably controversial. There have been two primary opinions in recent years. Some agree with a three-field lymphadenectomy and hold that it is essential to achieve improved postoperative survival by resectioning adequate lymph nodes in the neck because cervical lymph node metastases have been documented as approximately 20% to 40%. Others argue that two-field lymphadenectomy is enough to dissect all the possible metastatic lymph nodes, including recurrent nerve chain lymph nodes from the superior mediastinum up to the neck, with less perioperative complications and the same outcome<sup>[7-10]</sup>. A consistent lymphadenectomy strategy has yet to be established.

In this review, we hope to offer some references about the extent of lymphadenectomy through describing the pattern of the lymphatic spreading.

## THE ANATOMICAL LYMPHATIC SYSTEM OF THE ESOPHAGUS

The lymphatic drainage system of the esophagus is very complex because of an abundant lymph-capillary network in the lamina propria and muscularis mucosa, deep to the basement membrane. In total, lymphatic spreading has two modes, including penetrating the esophageal wall transversally and shifting longitudinally upwards (cervical lymph glands) and downwards (abdominal lymph glands). However, the longitudinal lymphatic flow is much more abundant than the transverse flow<sup>[11,12]</sup>. In detail, there are three pathways for lymph node metastasis in EC. One is spreading longitudinally along the submucosal lymphatic networks to regional and non-regional lymph nodes; another passes transversely through the muscularis propria to regional lymph nodes; and the last penetrates perpendicularly through the muscularis mucosa to the thoracic duct and the venous system<sup>[13]</sup>. Moreover, some studies show the presence of lymphatic drainage

and an anatomical correlation between the right recurrent laryngeal nerve nodes and cervical lymph nodes in EC, which suggests that tumor cells from the midthoracic level reach the right recurrent laryngeal nerve nodes through submucosal lymphatic vessels in the early stage. Meanwhile, it seems that lymphatic routes communicating with periesophageal lymph nodes generally originate from the intermuscular area of the muscularis propria and connections between the submucosal and intermuscular areas do not exist. Thus, once the primary tumor infiltrates the submucosa of the esophagus, the lymph node metastasis might apparently increase<sup>[14-16]</sup>.

## PATHWAYS OF ESOPHAGEAL LYMPHATIC SPREADING

According to many published data, the upper mediastinal and perigastric areas are the most common areas for lymph node metastasis in EC. However, lymph node metastasis in different areas may vary with the location of the primary tumor<sup>[17,18]</sup>.

For upper thoracic EC, tumor cells usually spread upwards to upper mediastinal and cervical nodes. As for middle thoracic EC, lymphatic flow drains primarily both up and down into the cervical, upper mediastinal, periesophageal and perigastric nodes. With regard to lower thoracic EC, the perigastric area is the most important<sup>[17,18]</sup>. Another study of endoscopic injection of technetium-labeled rhenium colloid into the esophageal wall also demonstrated that lymphatic flow of the upper and middle third of the esophagus drains mainly to the neck and upper mediastinum, with the lower third draining mainly into the abdomen<sup>[19]</sup>. These studies generally reach a consensus.

On the other hand, Akiyama *et al*<sup>[20]</sup> showed that the frequency of cervical and upper mediastinal lymph node metastasis, including recurrent laryngeal nerve chains, was 46.3% in cases of thoracic EC. Shiozaki *et al*<sup>[21]</sup> reported that the rates of cervical lymph node metastasis with positive recurrent laryngeal nerve nodes was 22.2%, 51.9% and 50.0% in upper, middle and lower third thoracic EC, respectively. The rate of the recurrent laryngeal nerve lymph node metastasis with positive cervical lymph nodes was 51.2%, in contrast to 13.9% of patients with negative cervical nodes<sup>[22]</sup>. Tabira *et al*<sup>[23]</sup> demonstrated that the 5 years survival was 21% with recurrent laryngeal nerve nodes metastasis, in contrast to 47% with negative recurrent nerve nodes. Therefore, it is generally accepted that recurrent laryngeal nerve chain nodes, especially the right side, should be intensively dissected in surgery for EC to improve survival, regardless of the location of the tumor<sup>[20-24]</sup>.

In addition to the location, the tumor histological type and invasion depth may be worth considering, well known as influencing factors on the prognosis for EC<sup>[25-29]</sup>. In contrast to esophageal squamous cell carcinoma

ma with lymphatic spreading more widely, the lymphatic flow of esophageal adenocarcinoma is primarily into the lower posterior mediastinum, the pericardial region and along the lesser gastric curvature. Distant metastasis is rarely found<sup>[28,30]</sup>. Based on the anatomical lymphatic drainage system, lymph node metastasis in EC is usually present in the upper mediastinum and perigastric area, known as skip metastasis, with the tumor not penetrating through the submucosa. If the tumor reaches the muscularis propria, the rate of periesophageal lymph node metastasis will increase rapidly for the middle and lower thirds of the mediastinum<sup>[18]</sup>.

## LYMPHADENECTOMY FOR EC

Lymph node metastasis is the most important prognostic factor in EC and the number of metastatic nodes is closely related to survival. More and more studies have reported that the number of positive nodes independently determines survival rather than the area of metastatic lymph node in EC<sup>[5,31-35]</sup>. Tachimori *et al.*<sup>[18]</sup> showed that the overall postoperative survival did not differ between the areas of metastatic lymph nodes. According to their multivariate analyses, the number of metastatic nodes was the most predictive factor for survival, not the area. Similarly, Zhang *et al.*<sup>[31]</sup> reported that the number of metastatic lymph nodes was significantly associated with survival for esophageal squamous cell carcinoma. The 5 years survival rates of patients with none, one and two or more positive lymph nodes were 59.8%, 33.4% and 9.4%, respectively. Therefore, the 7<sup>th</sup> edition of the TNM staging system identified the number of metastatic lymph nodes for N stage in EC<sup>[6]</sup>. Apparently, the more lymph nodes are dissected, the lower the possibility of missing positive lymph nodes. The 7<sup>th</sup> edition also intensively requested that at least twelve lymph nodes should be removed for an accurate and reliable N classification in EC on account of several detailed research outcomes<sup>[36,37]</sup>. However, only considering the number regardless of the area of metastatic lymph nodes is not enough. For the same number of positive lymph nodes, the prognosis between one and more distribution areas is different<sup>[38,39]</sup>.

Considering both outcome of lymphadenectomy and perioperative complications, the controversy about the extent of lymphadenectomy for EC has developed: Two or three-field?

The three-field lymphadenectomy was initiated in Japan. According to a prospective randomized trial, high neck recurrence rates in patients with esophageal squamous cell cancer were reported, suggesting that it was necessary to add neck dissection<sup>[40]</sup>. After that, it was known that lymph from the upper third of the esophagus mainly flows upwards to the superior mediastinum and neck, whereas lymph from the middle and lower third of the esophagus flows downwards *via* the mid and inferior mediastinum to the left gastric and celiac nodes<sup>[41]</sup>. A nationwide study showed that

the rate of lymph node metastasis was significantly increased with adding cervical dissection of three-field lymphadenectomy (58.7% of two-field vs 72.9% of three-field). Moreover, not only the rate of cervical nodes metastasis, but also the rate of mediastinal nodes metastasis was evidently increased<sup>[42]</sup>. Meanwhile, Lerut *et al.*<sup>[8]</sup> showed that the overall morbidity was 58%, 5 years disease-free survival was 46.3% and 5 years overall survival was 41.9% after three-field lymphadenectomy. Other research reported that the 5 years survival rate after three-field dissection was in the range of 40%-50%<sup>[42,43]</sup>. However, some demonstrated that no survival benefit was found in patients undergoing cervical nodal dissection compared to esophagectomy with three-field vs two-field lymphadenectomy<sup>[44]</sup>. Several recent meta-analyses suggested a priority of three-field lymphadenectomy for EC, especially for tumors with lymph node metastasis. However, the incidence of complications such as anastomotic leakage and recurrent laryngeal nerve palsy increased following three-field lymphadenectomy<sup>[45,46]</sup>.

## CONCLUSION

Lymph node metastasis is a key factor that affects both surgical treatment and prognosis in patients with EC. Thus, reasonable lymphadenectomy becomes very important, offering a better treatment outcome and accurate staging. However, lymphatic channels within the esophagus are very complex, resulting in variable lymphatic spread and skip metastases in EC. Generally, upper mediastinal and perigastric areas are worth more consideration. Based on current studies, it seems that three-field lymphadenectomy for EC is being gradually accepted by more and more people, with more extensive lymphadenectomy and higher survival. However, there are more postoperative complications in three-field lymphadenectomy compared to two-field. Therefore, more studies have recently focused on identifying optimal patients for each pattern of lymphadenectomy. Considering complications, tumor stage and lymphatic spreading of the esophagus, limiting factors in the application of three-field lymphadenectomy, may be a poor physical condition, systemic disease stage and lower mediastinal, including the esophagogastric junction, carcinoma of the esophagus. Although more strict clinical trials are needed to compare two and three-field lymphadenectomy, it is essential to attempt to decrease surgical traumatic injury of esophagectomy with lymphadenectomy while ensuring the extent of lymph node dissection in EC.

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