Technical Note

Current status and future direction of lymph node dissection in radical surgery for esophageal cancer

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Abstract: Surgical resection is the main treatment for esophageal cancer. Lymph node dissection is an essential part of radical surgery for esophageal cancer. However, the extent of dissection, numbers of lymph nodes, and sentinel lymph nodes in lymphadenectomy are still under debate. However, a clinical practice consensus has gradually formed despite this dispute.

Keywords: Esophageal cancer; lymph node dissection

Submitted Feb 12, 2019. Accepted for publication May 16, 2019.
doi: 10.21037/jtd.2019.05.51
View this article at: http://dx.doi.org/10.21037/jtd.2019.05.51

Surgical treatment of esophageal cancer is aimed at achieving accurate tumor staging, reducing the local recurrence rate, and improving patient quality of life and long-term survival. While developing surgical strategies, it is important to carry out a reasonable lymphadenectomy procedure in addition to radical surgery. The Chinese Society of Esophageal Cancer of the Chinese Anti-Cancer Association has issued the 2017 edition of the Chinese Expert Consensus on Mediastinal Lymph Node Dissection in Esophagectomy for Esophageal Cancer, which provides guidance to standardize thoracic lymph node dissection (1). However, the discussions of lymph node dissection in radical surgery for esophageal cancer have been controversial. This article summarizes and discusses the details and consensus of the debate, and proposes some suggestions on related issues.

Two- and three-field

As early as the 1980s, Japanese scholars demonstrated a negative correlation between cervical and mediastinal lymph node metastasis and long-term survival after esophageal cancer surgery (2). Therefore, it was recommended that a wide range of three-field lymph node dissections in radical surgeries should be performed to improve survival rates (3). In the 1990s, Japanese scholars conducted a multicenter, prospective, randomized, controlled study to confirm the impact of three-field lymph node dissection on patient survival in esophageal cancer (4). They found that esophageal cancers can metastasize to bilateral recurrent laryngeal nerve lymph nodes and paracardial lymph nodes regardless of the original location. It was suggested that the three-field lymph node dissection in radical surgery for esophageal cancer is consistent with the tumor treatment principle. Altorki also found that three-field lymph node dissection can increase the detection rate of metastases to the recurrent laryngeal nerve chain and the cervical lymph nodes by 36%, thereby improving pathological staging (5). The study also found that three-field lymph node dissection can significantly improve the long-term survival of patients. Akiyam *et al.* retrospectively analyzed 1,298 cases of esophageal cancer that had occurred over 20 years (6). They found that the 5-year survival rate of the three-field lymph node dissection was 55.0%, significantly higher than the rate of two-field lymph node dissection, which was 38.3% (P=0.0013). Two meta-analyses showed that the three-field lymph node dissection was superior to the two-field lymph node dissection in improving overall survival (7,8). However, there were also oppositions to the three-field lymph node dissection. First of all, European and American scholars believed that cervical lymph node metastases were distant metastases rather than local lesions. The practical value of three-field lymph node dissection is questionable.

In addition, three-field lymph node dissection resulted in higher surgical-related complications. The incidence of anastomotic leakage and vocal cord paralysis was significantly higher in the three-field lymph node dissection group than in the two-field lymph node dissection group (8,9). Most importantly, some studies have found that there was no significant difference in long-term survival rates between patients with two- and three-field lymph node dissections (10).

In agreement with the current viewpoint, we believe that the scope of lymph node dissection should be treated differently according to esophageal cancer location.

For upper thoracic esophageal cancer, a recent study found a high rate of cervical and upper mediastinal lymph node metastasis. Thus, lymph node dissection should include the neck. Although lymphatic metastasis rarely occurs in the lower mediastinum and the abdominal cavity, we recommend performing a three-field lymph node dissection, in which the abdominal cavity area dissection should include the left gastric lymph node.

For middle thoracic esophageal cancer, lymph node metastasis mainly occurs in the neck and the upper, middle, and lower mediastinum as well as the abdominal cavity. The extent of lymph node dissection includes the neck and supraclavicular area. However, in addition to the cervical esophageal lymph nodes, lymph nodes in other areas of the neck are rarely involved. Therefore, some scholars suggest that the cervical lymph nodes (cervical esophagus) can be cleared through the chest path. If the thoracic approach is not enough to clear the cervical lymph nodes, it is important to add a neck path to approach from the bilateral parapharyngeal recurrent nerve lymph nodes to the upper thyroid gland.

For the lower thoracic esophageal cancer, lymph node metastasis mainly occurs in the mediastinum and abdomen. Cervical metastasis is relatively low. It is generally believed that two-field lymph node dissections are suitable. At present, the best method of lymph node dissection is still under debate. Some scholars believe that cervical lymph nodes should also be cleared, but a majority believe that only thoracic lymph nodes should be cleared.

Number or region

In lymph node dissection, whether the number or the region is more important is also under debate. This divergence is mainly reflected in the N-staging criteria of the Tumor-Node-Metastasis/American Joint Committee on Cancer (TNM/AJCC) system and the Japan Esophageal Society (JES) system (11-13). In the TNM/AJCC system, N staging is based on the number of lymph node metastases, while in the JES system, the N staging is based on the region in which the metastatic lymph nodes are located. In clinical practice, the TNM/AJCC N staging is simple and easy to apply. In particular, the pathologist can easily determine the number of metastatic lymph nodes in the resected specimen. However, the clinical application of the JES N staging is more complicated. Nevertheless, almost all Japanese oncologists believe that regional lymph node metastasis may still belong to the category of local disease, and should be cleared for the purpose of radical surgery. Conversely, Western tumor surgeons believe that lymph node metastasis is a systemic disease and difficult to be cured by surgery. Therefore, the difference in the concept of lymph node metastasis is the crux of the N staging differences.

In terms of clinical practice, we advocate extensive lymph node dissection, regardless of the number of lymph nodes or the region. The best choice of an N-staging system will depend on long-term prospective studies. Meanwhile, the standards for minimum number of lymph nodes and the classification of the station in the chest need to be further explored.

In 2017, the "*Chinese Expert Consensus for Thoracic Lymph Node Dissection for Esophageal Carcinoma*" emphasized that the scope of lymphadenectomy should cover as many classified lymph nodes as possible in addition to defining the number of lymph nodes (1). The bilateral para-laryngeal recurrent nerve lymph node dissection should be given more attention in the future.

The value of lymph node dissection

A large number of clinical studies have shown that the value of lymph node dissection in esophageal cancer is reflected in the following ways:

(I) Improve the accuracy of surgical pathological staging. In particular, the Union for International Cancer Control (UICC) published the seventh edition of the staging manual for esophageal cancer in 2009. The manual proposed N-staging according to the number of metastatic lymph nodes. In this system, it is necessary to clear more than 12 lymph nodes to ensure the accuracy of staging (11). Studies have shown that the 5-year survival rates of patients with N0 (no lymph node

metastasis), N1 (1–2 lymph node metastases), N2 (3–6 lymph node metastases), and N3 (≥7 lymph node metastases) were 71.0%, 52.2%, 31.6%, and 12.3%, respectively (14).

(II) Gain in-depth understanding of the lymphatic metastasis path of esophageal cancer (15,16). For thoracic esophageal cancer, the main metastasis lymph node groups are the recurrent laryngeal nerve chains located in the neck-thoracic junction. Intraoperative pathological investigation of recurrent nerve nodal metastasis can guide the decision whether to perform cervical lymph node dissection in thoracic esophageal cancer.

(III) Improve the effect of radical surgery, reduce local recurrence after surgery, and improve long-term survival. The study found that the local recurrence rate after two- or three-field lymph node dissection is generally less than 20%. The recurrence rate of conventional surgery can be as high as 30% to 40% (17,18). The 5-year survival rate of patients after three-field dissection can reach 40% to 50%, while the rate of conventional surgery rarely reaches 30% (4,5).

How to diagnose lymph node metastasis

The esophagus has a widespread lymphatic drainage system. The lymph node status is the most important factor in predicting the prognosis of esophageal cancer patients (19). The metastasis and distribution of lymph nodes vary depending on the location, size, and depth of invasion of the primary tumor. Therefore, it is important to use CT, ultrasound, MRI, or positron emission computed tomography (PET) methods to determine a reasonable lymph node dissection range.

At present, the commonly used examination methods are enhanced CT and endoscopic ultrasonography (EUS). The most common lymph node metastasis sites that can be found by CT and EUS are the mediastinum and lymph nodes around the celiac trunk. In the detection of lymph node metastasis, EUS is generally considered to be superior to CT (20). However, EUS can find lymph nodes only if they are close to the esophageal wall, whereas CT can detect local and distant metastatic lymph nodes.

For esophageal cancer cases in which EUS cannot pass due to stenosis of the lumen, CT is superior to EUS in the diagnosis of abdominal lymph node metastases. The CT features of metastatic lymph nodes mainly depend on the size of the lymph nodes (size standard). The lymph nodes with a short axis size greater than 1 cm are more likely to be metastatic lymph nodes (21). However, the size is not a sensitive indicator of lymph node metastasis, and some metastatic lymph nodes can be less than 1 cm across. When the mediastinal and abdominal lymph nodes have a maximum diameter of >1 cm, they are generally abnormal lymph nodes. Mediastinal lymph nodes with a short axis diameter of >1 cm are abnormal (except for the subcarinal lymph nodes), while 1.4 cm is the upper limit of the normal value of the mediastinal lymph nodes. Most studies use 1 cm as the standard to determine whether there is lymph node metastasis, with a sensitivity of 30% to 60% and a specificity of 60% to 80% (22). We must recognize that lymphadenopathy is non-specific. Reactive or inflammatory lymph nodes often increase in size, while some early metastatic lymph nodes do not significantly enlarge. Enlarged lymph nodes around the esophagus are difficult to distinguish from direct tumor invasion. Therefore, the absence of primary lesions around the esophagus is a reliable indication of lymph node metastasis, even if the lymph nodes are not significantly enlarged (20).

The sensitivity of CT in the diagnosis of mediastinal lymph node metastasis of esophageal cancer is not high. Comprehensive consideration of lymph node shape, size, internal density, edge characteristics, and three-dimensional reconstruction techniques is necessary to determine metastasis and improve the accuracy of diagnosis (23).

Is there a sentinel lymph node in esophageal cancer?

There have been many criticisms of extensive lymph node dissection through the thoracic path for esophageal cancer. The most common reason for opposing enlarged lymphadenectomy is that it increases mortality and complications. The destructive effects on patients' quality of life after surgery are obvious. In order to improve the cure rate and postoperative quality of life, more attention should be paid to individualized treatment. The intraoperative sentinel lymph node localization and sentinel lymph node biopsy both seem to be attractive. The identification of sentinel lymph nodes can be confirmed by observing the first drainage point of the primary lesion. This method of identification can be used for personalized lymph node dissection for esophageal squamous cell carcinoma. The pathological state of the sentinel lymph nodes can be used to predict the condition of all regional lymph nodes, thereby

avoiding unnecessary radical lymph node dissection. These techniques can benefit patients and avoid unnecessary complications from radical lymph node dissection. Takeuchi has reported radiation-guided techniques to locate sentinel lymph nodes in esophageal cancer (24). A total of 75 patients with primary esophageal cancer with preoperative stage T1N0M0 or T2N0M0 were included in that study. In 71 cases (95%), the patients were diagnosed with sentinel lymph nodes. In 33 patients with lymph node metastasis, 29 of them had sentinel lymph nodes (88%). The accuracy of sentinel lymph node diagnosis was 94%. Studies have shown that a parapharyngeal recurrent nerve lymph node metastasis can be considered a sentinel lymph node to predict cervical lymph node metastasis (25,26) and provide guidance for two- or three-field lymph node dissections. We believe this will help to make accurate intraoperative diagnosis and individualized minimally invasive surgery approaches for patients with esophageal cancer in the future. The extent of lymph node dissection can be determined by the distribution of sentinel lymph nodes. The location of the sentinel lymph nodes may play a very crucial role in the process of adjusting and correcting the surgical procedure for each patient by obtaining specific information about the patient, thereby avoiding unnecessary traumatic surgery.

Conclusions

In summary, lymph node dissection is an important means of surgical treatment for esophageal cancer, but there are still many controversies. The numbers of new esophageal cancer cases and deaths from esophageal cancer in China are the highest in the world. Therefore, we have the greatest clinical resources and research potential. The surgical skills of thoracic surgeons in China are well recognized worldwide. The incidence of postoperative complications is also lower than the world average. However, we lack high-quality clinical data. We should overcome impetuosity and anxiety for quick success and instant benefit and choose to launch large multi-center prospective randomized clinical trials in spite of needing to undertake massive surgeries. We need to build our own accurate, objective, and convincing database and lay a solid foundation for the development of standardized diagnostic and treatment systems that adequately address the characteristics of esophageal cancer in China. It will take a few years to do this and to do it well. Only in this way can Chinese esophageal surgery have a solid position and a pivotal voice in the international arena.

Acknowledgments

None.

Footnote

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

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Cite this article as: Li H, Zhang ZR. Current status and future direction of lymph node dissection in radical surgery for esophageal cancer. J Thorac Dis 2019;11(Suppl 13):S1678-S1682. doi: 10.21037/jtd.2019.05.51

