

Chinese expert consensus on mediastinal lymph node dissection in esophagectomy for esophageal cancer (2017 edition)

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Submitted Mar 01, 2018. Accepted for publication Mar 23, 2018.

doi: 10.21037/jtd.2018.03.175

View this article at: <http://dx.doi.org/10.21037/jtd.2018.03.175>

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, English Edition Committee, Panelists (in alphabetical order according to the Pinyin of last names);

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Introduction

Esophageal cancer is an aggressive malignancy and a major cause of cancer-related deaths globally. In 2012, about 460,000 new cases of esophageal cancer were diagnosed worldwide, with 400,000 deaths attributed to the disease (1). In China, esophageal cancer is the fourth leading cause of cancer-related mortality, according to the China Cancer Registry, with approximately 270,000 new cases of esophageal cancer and about 200,000 deaths in 2013 (2). Surgery is still the most important and most effective way to treat resectable esophageal cancer. Despite advances in surgery and the development of multimodal therapy in recent years, patients with esophageal cancer continue to exhibit unfavorable clinical outcomes with a 5-year overall survival rate of less than 20% (3,4). Depth of carcinoma invasion and lymph node metastasis are the most important factors affecting esophageal cancer prognosis. Therefore, lymph node dissection is an essential part of radical surgery for esophageal cancer. Radical lymphadenectomy may help determine precise postoperative pathological staging, ensure the integrity and radicality of surgery, and more importantly, improve the survival of patients after surgery (5).

However, the indications, surgical approach, and extent of thoracic lymphadenectomy during esophagectomy for esophageal cancer are still under debate. Some studies suggested that radical lymphadenectomy could better control local lesions, remove undetectable micrometastases, and prolong patient survival (6-11), but others believed that the esophageal squamous cell carcinoma is a systemic disease (12) and radical lymphadenectomy would increase postoperative complications without prolonging the survival of patients (13-15). Therefore, in order to reach a consensus and to guide the clinical practice in China, the Esophageal Cancer Committee of the Chinese Anti-Cancer Association organized a group of experienced experts in the field to develop this consensus document.

Aim and scope of the consensus

The aim of the current consensus is to provide guidance to standardize mediastinal lymph node dissection in esophagectomy for esophageal cancer in China, to achieve accurate staging, reduce the local recurrence rate, and ultimately, to improve long-term survival. To achieve these goals, the committee took into consideration the experts' clinical experiences and carefully reviewed existing evidence

in the literature, most of the publications on this topic are from Chinese thoracic surgeons.

The scope of this consensus is limited to mediastinal lymph node dissection. Relevant contents about cervical and abdominal lymph node dissection involved in radical surgery for esophageal cancer will be described separately.

Chinese version of mediastinal lymph node map for thoracic esophageal squamous cell carcinoma

At present, both the lymph node maps of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) nomenclature (16-18) and the Japan Esophageal Society (JES) are commonly used in China for thoracic lymph nodes dissection in esophageal cancer (19,20). Major differences exist in N staging between the two systems; with the AJCC/UICC system, N staging is based on the number of lymph node metastases, while with the JES system, it is based on the region (i.e., the classified station) in which the metastatic lymph nodes are located. In clinical practice, AJCC/UICC N staging is simple and easy for surgeons and pathologists to apply. JES N staging may be better associated with the prognosis of esophageal cancer (21), but clinical application is relatively complicated. In Japan, this work is usually done by a surgeon (22). In addition, compared with the number of metastatic lymph nodes, the classification of metastatic lymph nodes does not always have a strong prognostic value. This is the main reason why JES standards are not widely used in countries outside of Japan.

Taking into consideration the international acceptance and the clinical practice in China, the Esophageal Cancer Committee of the Chinese Anti-Cancer Association now proposes this Chinese system for the classification of thoracic lymph nodes in esophageal cancer. The present version aims to ensure consistency with the AJCC/UICC and the JES systems as much as possible, and to reflect the latest advances in mediastinal lymph node dissection for esophageal cancer. However, significant modifications have been made based on the evidence collected in China, since both the AJCC/UICC TNM classification (8th) and the JES classification (11th) have their own limitations (*Figures 1,2*). This consensus should be easy to use and will facilitate standardization and unification of mediastinal lymph node dissection in China. The Chinese version of the mediastinal lymph node map and its differences with the AJCC/UICC and JES systems are shown in *Figure 1*.

Region	Chinese system	AJCC/UICC system (18)	JES system (19,20)
Upper mediastinum	Station C201*: Right recurrent laryngeal nerve nodes	Station 2R: Upper right paratracheal lymph nodes	Station 106recR: Right recurrent laryngeal nerve nodes
	Station C202: Left recurrent laryngeal nerve nodes	Station 2L: Upper left paratracheal lymph nodes	Station 106recL: Left recurrent laryngeal nerve nodes
	Station C203: Upper thoracic paraesophageal lymph nodes	Station 8U: Upper thoracic paraesophageal lymph nodes	Station 105: Upper thoracic paraesophageal lymph nodes
	Station C204: Right paratracheal lymph nodes	Station 4R: Right lower paratracheal lymph nodes	Station 106: Thoracic paratracheal lymph nodes ❖ Station 106pre: Pretracheal lymph nodes ❖ Station 106tbR: Right tracheobronchial lymph nodes
	N/A	Station 4L: Left lower paratracheal lymph nodes	Station 106tbL: Left tracheobronchial lymph nodes
		N/A	Station 113: Ligamentum arteriosum lymph nodes
		N/A	Station 114: Anterior mediastinal lymph nodes
Station C205: Subcarinal lymph nodes	Station 7: Subcarinal lymph nodes	Station 107: Subcarinal lymph nodes	
Lower mediastinum	Station C206: Middle thoracic paraesophageal lymph nodes	Station 8M: Middle thoracic paraesophageal lymph nodes	Station 108: Middle thoracic paraesophageal lymph nodes
	Station C207: Lower thoracic paraesophageal lymph nodes	Station 8Lo: Lower thoracic paraesophageal lymph nodes	Station 110: Lower thoracic paraesophageal lymph nodes
	Station C208: Inferior pulmonary ligament lymph nodes	Station 9L: Left lower pulmonary ligament lymph nodes	Station 112L: Posterior mediastinal lymph nodes
		Station 9R: Right inferior pulmonary ligament lymph nodes	Station 112R: Posterior mediastinal lymph nodes
	N/A	N/A	Station 109L: Left main bronchus lymph nodes
			Station 109R: Right main bronchus lymph nodes
	Station C209: Paradiaphragmatic lymph nodes	Station 15: Paradiaphragmatic lymph nodes	Station 111: Supradiaphragmatic lymph nodes

Figure 1 Comparison of the Chinese version of naming and grouping mediastinal lymph nodes with the AJCC/UICC and the JES systems for esophageal cancer. *, “C” represents Chinese standards and “2-” represents thoracic lymph nodes. AJCC, American Joint Committee of Cancer; UICC, Union for International Cancer Control; JES, Japan Esophageal Society.

Recommendation 1: the current consensus represents the first Chinese version of naming and grouping mediastinal lymph nodes for esophageal cancer. It is in line with the current clinical practice in China, with the advantages of being concise, clear, and easy to use. It is recommended that the name of a specific mediastinal lymph node station be recorded by using “C” plus the relative number, e.g., C201, as the right recurrent laryngeal nerve nodes.

Thoracic lymphadenectomy procedures in radical esophagectomy for esophageal cancer

Lymph node metastasis is an independent prognostic factor for esophageal cancer. Frequency and distribution of nodal metastases vary greatly depending on the location, size, and depth of invasion of the primary tumor (23-27). The esophagus has a complex and widespread lymphatic drainage system; in addition to transmural lymphatic vessels that flow to

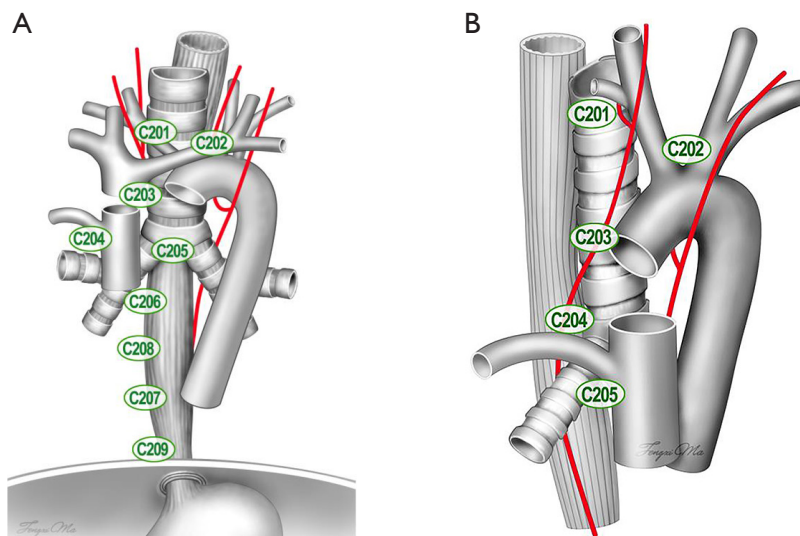


Figure 2 Diagram of the Chinese version of naming and grouping of mediastinal lymph nodes in esophageal cancer: (A) anterior view; (B) right side view. “C” represents Chinese nomenclature, and “2-” represents thoracic lymph nodes. Station C201, right recurrent laryngeal nerve nodes; Station C202, left recurrent laryngeal nerve nodes; Station C203, upper thoracic paraesophageal lymph nodes; Station C204, right thoracic paratracheal lymph nodes; Station C205, subcarinal lymph nodes; Station C206, middle thoracic paraesophageal lymph nodes; Station C207, lower thoracic paraesophageal lymph nodes; Station C208, inferior pulmonary ligament lymph nodes; Station C209, paradiaphragmatic lymph nodes.

the adjacent lymph nodes by penetrating the esophageal wall transversely, there are also abundant longitudinal lymphatic flows in the submucosal layer of the esophageal wall.

Surgical approaches to radical esophagectomy for esophageal cancer

The selection of the surgical approach greatly impacts the number and extent of lymph nodes that are dissected in radical surgery for esophageal cancer. The lower cervical and recurrent laryngeal nerve nodes are important drainage areas for thoracic esophageal cancer (28-30). Esophageal lymph node metastasis normally spreads along the bilateral recurrent laryngeal nerves beside the esophagus to cervical lymph nodes. Therefore, to ensure accurate pathological staging and complete tumor eradication, it is necessary to perform a radical dissection on the left and right recurrent laryngeal nerve nodes during thoracic surgery (31-33). Due to the obstacles presented by the aortic arch, left common carotid artery, and subclavian artery, it is extremely difficult, if not impossible, to completely remove lymph nodes in the aforementioned areas via the traditional surgical approach using a left posterolateral thoracic incision. Approaches through a right thoracic incision (Ivor Lewis and McKeown

procedures) can help overcome this shortcoming. Therefore, these two procedures have gradually become the preferred approaches for thoracic esophageal cancer (11,34-36). The Chinese Guidelines for Standardized Diagnosis and Treatment of Esophageal Cancer also recommended these procedures (37).

In recent years, minimally invasive esophagectomies (thoracoscopic or mediastinoscopic, or robotic-assisted) have been increasingly performed at home and abroad (38). These approaches are comparable to right thoracotomy in lymphadenectomy. No matter thoracotomy or minimally invasive surgery, similar standards in lymph node dissection should be followed to ensure the quality of surgery (39-42).

Recommendation 2: for radical esophagectomy with an intention to cure, a right transthoracic approach should be used for harvesting all the lymph nodes of the designated stations.

Number of lymph nodes removed in radical surgery for esophageal cancer

General information

According to the AJCC/UICC Staging of Cancers of the

Esophagus (8th Edition), N staging is determined by the number of positive lymph nodes resected. Therefore, number of lymph nodes resected is critical to postoperative pathological N staging (43). That is, the more lymph nodes resected, the less likely that metastatic nodes be missed, and the higher accuracy of N staging (44-47). Thus, a reliable node-negative staging (N0 stage) requires a sufficient number of resected lymph nodes (47-51).

The Chinese Guidelines for Standardized Diagnosis and Treatment of Esophageal Cancer (37), the AJCC/UICC Staging of Cancers of the Esophagus (8th Edition), and the NCCN Guidelines for the Treatment of Esophageal and Esophagogastric Junction Cancers [2016] all recommend that at least 11–15 nodes should be removed in radical surgery for esophageal cancer. Of course, this refers to the total number of nodes harvested in two- or three-field lymphadenectomy, not limited to the thoracic part of the dissection. Although a definitive number of nodes could not be decided for mediastinal dissection alone, systemic thoracic lymphadenectomy according to the proposed nodal map should always be performed for accurate N staging.

Recommendation 3: the mediastinal lymph nodes should be dissected as more as possible to ensure accurate pN staging and radical resection of the disease.

Special conditions

In clinical practice, multiple metastatic nodes may fuse into one, making it difficult to determine the exact number of lymph nodes. According to the AJCC/UICC Staging of Cancers of the Esophagus (8th Edition), fused nodes should be considered as one single node based on the principle that an uncertain stage will be determined as the earlier stage. Another common situation is that lymph nodes become fragmented during surgical dissection. If this is not documented in the pathology report, the number of metastatic nodes may be overestimated and this could lead to overstaging. Therefore, it is recommended that fragmented lymph nodes should be packed together and classified as one single node before it is sent for pathologic examination.

Neoadjuvant therapy has become the standard therapy for locally advanced esophageal cancer (52). However, little is known about the optimal number and extent of lymph nodes that should be removed after neoadjuvant therapy. Also, the number of lymph nodes removed has relatively low sensitivity for N staging in this scenario. Thus, the significance of lymphadenectomy after induction needs to be further confirmed. However, all of the suspected

metastatic lymph nodes should be resected to evaluate the response of induction therapy and to help decide the ypStage according to the 8th UICC/AJCC staging system (53).

Extent of thoracic lymphadenectomy in radical surgery for esophageal cancer

In addition to the number of nodes dissected, the extent of mediastinal lymph node dissection is even more important to the outcome of esophagectomy (54-56). As mentioned earlier, regional lymph node identification and dissection should be based on the understanding of the anatomy of esophageal lymphatic drainage in all 9 stations of mediastinal lymph nodes as defined in the current consensus, and they should be dissected systemically in a radical esophagectomy.

Recommendation 4: all 9 stations of mediastinal lymph nodes (C201–C209) proposed in the current consensus should be dissected during radical surgery for esophageal cancer, especially the left and right recurrent laryngeal nerve nodes and para-esophageal nodes.

Lymphadenectomy-related complications and prevention of complications

Radical lymphadenectomy for esophageal cancer involves extensive surgical dissection, and thus is associated with intensive trauma. In addition, preoperative co-morbidities, such as heart and lung diseases, that are commonly seen in esophageal cancer patients further increase the risk of postoperative complications. With the improvement in surgical techniques and instruments, anesthesia, and postoperative care, major complications are less frequent than they used to be but they still cannot be completely avoided.

Lymph nodes involved in esophageal cancer are widely spread in the thoracic cavity, from the entrance of the thorax to the diaphragm esophageal hiatus. Some of the lymph nodes are located deep in the mediastinum and adjacent to important organs. Precise dissection and careful exposure of these important neighboring organs, including the trachea, the aorta, pulmonary vessels, recurrent laryngeal nerve, and the thoracic duct, are mandatory to avoid unnecessary injury. Good exposure and lighting are always required to ensure a safe procedure.

The recurrent laryngeal nerves are prone to injury during lymphadenectomy due to their slenderness and

frequent variation in anatomy. Adequate exposure of the nerve is mandatory when dissecting the lymph nodes that are alongside it. To better protect these nerves, the dissection should begin from the starting point where the right recurrent laryngeal nerve branches off from the vagus nerve, and the left recurrent nerve curves around the aortic arch. To preserve the blood supply to the nerve, extensive dissection of the epineurium should be avoided when resecting the surrounding lymph nodes. If energy devices, such as electric cautery or harmonic scalpel, are used, they should be kept at a safe distance away from the nerve to avoid thermal damage to the nerve. “Cold weapons”, such as scissors or blunt dissection instruments, are helpful in this area.

Special care should be taken not to injure the membranous trachea or the main bronchus when removing the paratracheal and subcarinal lymph nodes. Again, when energy devices are used, efforts should be made to avoid thermal damage to the tracheal membrane. The working blade of the harmonic scalpel should be kept away from the trachea and bronchus, and the device should be used with intermittent cooling to avoid overheating. En bloc resection of the lymph nodes is recommended. In addition to the oncological principle of radical resection, a fragmented lymph node or bleeding may obscure the surgical vision field and lead to inadvertent injury to the neighboring structures (57). Similarly, branches of the esophageal and bronchial arteries often extend under the lower pulmonary ligament, tracheal carina, aortic arch, and right subclavian artery. Therefore, these small artery branches should be carefully handled before removing the lymph nodes so as to avoid bleeding and ensuring clear dissection.

Chylothorax, which happens more often after extensive lymphadenectomy, is an annoying or even life-threatening problem. Tiny lymphatic vessels can be closed with a harmonic scalpel, but injuries to larger lymphatics or the thoracic duct are the major causes of refractory chylothorax. Therefore, it is recommended that the thoracic duct should be clearly exposed during mediastinal lymphadenectomy and carefully examined upon the completion of dissection. If an injury is suspected, thoracic duct ligation near the hiatus should be performed.

Pulmonary complications are the most common functional morbidity and a leading cause of mortality immediately after esophagectomy. During surgery, care should be taken to avoid stretching or compressing of the lung parenchyma. It has been suggested that preserving the bronchial arteries and the pulmonary branches of the

vagus nerves during the dissection of the subcarinal nodes may help reduce pulmonary complications after surgery. Strict restriction of the amount and the rate of fluid input are extremely helpful in preventing the occurrence of pulmonary edema and respiratory insufficiency.

Recommendation 5: when ensuring the extent and number of lymph nodes involved in dissection, care should be taken to avoid any inadvertent injury associated with extensive lymphadenectomy.

Conclusions

Lymph node dissection is an important step of radical resection for esophageal cancer. An appropriate lymphadenectomy can be helpful in obtaining accurate pathological staging, reducing the local recurrence, and improving postoperative survival. Standardized and reasonable dissection of lymph nodes based on the characteristics of lymphatic metastasis and biological behavior of tumors is indispensable to improve the efficacy of esophageal cancer surgery.

Acknowledgements

None.

Footnote

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

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Cite this article as: Li H, Fang W, Yu Z, Mao Y, Chen L, He J, Rong T, Chen C, Chen H, Chen K, Du M, Han Y, Hu J, Fu J, Hou X, Gong T, Li Y, Liu J, Liu S, Tan L, Tian H, Wang Q, Xiang J, Xu M, Ye X, You B, Zhang R, Zhao Y; on behalf of The Society of Esophageal Tumor, Chinese Anti-Cancer Association. Chinese expert consensus on mediastinal lymph node dissection in esophagectomy for esophageal cancer (2017 edition). *J Thorac Dis* 2018;10(4):2481-2489. doi: 10.21037/jtd.2018.03.175