



# Does it matter that lymphadenectomy through right or left side thoracotomy during esophagectomy?

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*Comment on:* Li B, Hu H, Zhang Y, *et al.* Extended Right Thoracic Approach Compared With Limited Left Thoracic Approach for Patients With Middle and Lower Esophageal Squamous Cell Carcinoma: Three-year Survival of a Prospective, Randomized, Open-label Trial. *Ann Surg* 2017. [Epub ahead of print].

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Lymph node metastasis is one of the critical determinants in the prognosis of esophageal cancer. Many lymph node-associated parameters, such as regional or nonregional location (1,2), number of positive nodes (3-6), number of total harvested nodes (7), ratio of positive to total nodes (5,6,8), and even number of negative nodes (9), have been reported to have prognostic relevance. There are also abundant studies assessing the diagnostic and therapeutic value of lymphadenectomy (10,11). The diagnostic purpose of lymphadenectomy is to identify the presence of lymphatic spread, which can be a surrogate of systemic disease. Although lymph node dissection itself may not have a survival benefit, the adjuvant treatments for lymph node metastasis are expected to. However, if viable malignant cells initially nest in lymph nodes and gradually spread to systemic metastases, lymphadenectomy would be an opportunity to cure patients, especially those with early phase of lymphatic dissemination.

Even though lymph node metastasis is such a crucial factor, the procedure of lymphadenectomy is not standardized. Various types of lymphadenectomy have been proposed. The Consensus Conference of the International Society for Diseases of the Esophagus (ISDE), held in Munich in 1994, has defined four types of lymphadenectomies: standard lymphadenectomy, extended lymphadenectomy, total lymphadenectomy, and 3-field lymphadenectomy (12). Whereas standard lymphadenectomy refers to dissection of the infracarinal nodes, extended lymphadenectomy includes the right upper mediastinal nodes in addition to

the standard procedure; total lymphadenectomy involves bilateral upper mediastinal nodes in addition to standard procedure; and 3-field lymphadenectomy adds resection of the bilateral cervical nodes to total lymphadenectomy. In 2009, Jamieson classified lymphadenectomy into nonradical lymphadenectomy, which includes only peritumoral nodes; and radical lymphadenectomy, which could be subclassified into 3-field, 2-field, and infracarinal 2-field lymphadenectomy (11). In the Japan Classification of Esophageal Cancer, regional lymph nodes are classified as “compartment 1 to 3” according to tumor location, while distant lymph nodes are categorized as “compartment 4” (13). Based on this lymph node grading classification, the N category is defined as N0–N4 and the extent of lymphadenectomy is defined as D0–D3. Whereas D0 is incomplete dissection of Group 1 lymph nodes, D1, 2 and 3 refer to complete dissection of Group 1, 2, and 3 lymph nodes.

To investigate the impact of types of surgical procedure, Li *et al.* randomized 300 patients with middle and lower thoracic esophageal carcinoma into esophagectomy through the right (Ivor Lewis, right thoracic plus upper midline incisions) or left (Sweet, left thoracic incision) thoracic approach (14). The 3-year disease-free survival rates were 62% and 52% and the 3-year overall survival rates were 74% and 60%, favoring right side approach. Although Li *et al.* stated that the differences were owing to the extent, i.e., radical or limited, of lymphadenectomy, rather than simply right or left side incisions, their results should be carefully interpreted especially when many factors were not well controlled. First, the incision

itself may affect patient outcome. For example, in the recent open *vs.* laparoscopically-assisted esophagectomy for cancer: a multicentric phase III prospective randomized controlled trial (the MIRO trial), which compared hybrid minimally invasive esophagectomy (laparoscopic plus thoracotomy) to open esophagectomy (laparotomy plus thoracotomy), not only 69% reduction in major intra- and post-operative morbidity, but improved outcomes in the laparoscopic group were noted (15). Laparoscopic group was also associated with slightly better overall survival and disease-free survival (67% *vs.* 55%,  $P=0.05$  and 57% *vs.* 48%,  $P=0.15$ ). Thus, surgical incisions (right thoracic and upper midline abdominal *vs.* left thoracic) itself may be with prognostic impact. In addition, the lymph node dissection fields were not well controlled. Whereas Ivor Lewis procedure included upper mediastinal and intraabdominal lymph node dissection, the Sweet procedure was difficult in upper mediastinal, common hepatic and celiac lymphadenectomies. Although higher upper mediastinal recurrence was noted in Sweet procedure, it is difficult to attribute survival difference to lymphadenectomy in this area since there were many unequal factors between two groups. With regard to the significance of upper (right side) mediastinal lymph node dissection, retrospective analysis by Hsu *et al.* has shown that 30% of right upper mediastinal lymphadenectomy for esophageal squamous cell carcinoma would have positive results (2). However, the survival difference was not significant between patients with or without right upper mediastinal lymphadenectomy, implicating the diagnostic, rather than therapeutic value of right upper mediastinal lymph node dissection. Moreover, despite the fact that this is a prospective randomized trial, the application of postoperative adjuvant treatments is not protocolized. Substantial percentage of patients were with poor prognostic factor, such as pT3/4 (52%), pN(+) (45%), and non-R0 resection (36%); however, less than half received postoperative adjuvant treatments. Postoperative chemoradiation, which has been reported to associate with better outcome by nation wide database studies, was used in only 12% of patients (16,17). Lack of protocolized indications for postoperative adjuvant treatments is one of the major concerns.

Last but not least, their results, which are based on patients after upfront esophagectomy, may not be applicable to those after neoadjuvant treatments. The Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) group has studied the impact of surgical approach on survival in esophageal cancer patients with or without neoadjuvant chemoradiotherapy (18). The transthoracic esophagectomy with extended 2-field lymphadenectomy had differential effects on overall survival

in patients who received surgery alone compared with patients who had neoadjuvant chemoradiotherapy and surgery. In patients treated with surgery alone, the transthoracic approach was associated with would have a better prognosis; however, its favorable prognostic effect over transhiatal esophagectomy with limited lymphadenectomy was absent in the neoadjuvant group. They concluded that the downstaging effect of neoadjuvant therapy may reduce the potential positive impact of extended lymphadenectomy on survival. Using the total number of resected lymph nodes as a surrogate for the radicalness of lymphadenectomy, the same group also studied the lymph node dissection during esophagectomy with and without neoadjuvant chemoradiotherapy (19). Similarly, the number of resected nodes had a prognostic effect only in patients who received surgery alone, but not in those after neoadjuvant treatments. Their data question the indication for maximization of lymphadenectomy in patients already have been treated with neoadjuvant treatments. Considering the effect of chemotherapy and radiotherapy, the tumor biology may change after neoadjuvant treatments. Accordingly, the optimal extent of lymphadenectomy and surgical approach may be different in patients with or without neoadjuvant treatments. Thus, the differences between Ivor Lewis and Sweet procedures shown in the study from Li *et al.* may not present in patients after neoadjuvant treatment followed by surgery, which is the current standard.

In sum, Li *et al.* tried to highlight the impact of “right side”, “radical” lymphadenectomy; however, the results were biased many hidden factors, which are not balanced and standardized between two groups. However, Li *et al.* made a conclusion that right side approach is associated with better outcome compared to left side approach. As nearly 70% of esophagectomies in China were done via left side thoracic approaches, the finding of the study from Li *et al.* will potentially change many China thoracic surgeon’s practice.

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