Two-field lymph node dissection or three-field lymph node dissection. What's in a name?

Nasser Altorki, MD

Feature Editor Note—The staging system for esophageal cancer is complex because the spread of esophageal cancer is complex. There are many variables considered in the staging of esophageal cancer, which even include histology (adenocarcinoma or squamous cell carcinoma) and the affected region of the esophagus. However, to more accurately represent the biology of a disease with aggressive locoregional and distant metastatic potential, there could be major variables that still require parsing into additional subcomponents. For example, nodal staging is currently based on the number of metastatic regional nodes from the upper esophageal sphincter to the celiac artery (N1: metastases in 1-2 regional lymph nodes, N2: 3-6 regional nodes, N3: ≥ 7 regional nodes). Recognition of the importance of cervical lymph nodes in esophageal cancer effective drove the adoption of the “3-field lymphadenectomy” and has fueled the debates on its impact relative to “2-field lymphadenectomy.” In this Feature Expert Opinion article in the *Journal of Thoracic and Cardiovascular Surgery*, we invited an enduring leader in this field to comment on a recently reported clinical trial. This trial, which he describes as likely to be the most definitive trial in this arena, reported overall and disease-free survival in patients with esophageal cancer randomly assigned to 2- or 3-field nodal dissection. In the following distillation of decades of work, you can expect to gain enlightenment on the basis of this field, appreciation for the nuances of esophageal cancer staging and surgery, and inspiration to contribute to the advancement of what may still be a very young field.

Bryan M. Burt, MD, FACS

In 1991, a nationwide Japanese study reported the results of nearly 1800 esophagectomies with 3-field lymph node dissection (TFD) performed for squamous cell cancer of the esophagus at 35 institutions across Japan.¹ Approximately 25% of patients were found to have previously unsuspected metastases to the cervical nodes. The authors also reported that TFD was associated with significantly better survival

Nasser Altorki, MD

CENTRAL MESSAGE

A randomized trial shows no difference between 2- and 3-field dissection for esophageal cancer but implies survival benefit of lymphadenectomy.

This Invited Expert Opinion provides a perspective on the following paper: *J Thorac Oncol*. 2021 Feb;16(2):310-317. <https://doi.org/10.1016/j.jtho.2020.10.157>. Epub 2020 Dec 8.

See Commentaries on pages 1698 and 1700.

compared with that after lymph node dissection limited to the abdomen and mediastinum. Significantly, most Japanese studies reported a 5-year survival of 25% to 30% in patients with metastatic carcinoma to the cervical lymph nodes.^{2,3} These impressive survival rates seemed to argue that the recurrent laryngeal and cervical lymph nodes should be considered as regional (N1) rather than distant sites of disease for squamous cell carcinoma of the intrathoracic esophagus. However, until recently, Level 1 evidence supporting the use of TFD was limited to 2 randomized trials that were either underpowered and/or suboptimally designed.^{4,5} The recently reported randomized trial from the Fudan University group will likely be the most definitive trial evaluating the difference in survival between 2- and 3-field lymph node dissection for squamous cell cancer of the thoracic esophagus.⁶ In a little over 3½ years, the investigators randomly assigned 400 patients with cT1-T3/N0-N1 squamous cell carcinoma of the middle and lower thirds of the esophagus to either 2-field or 3-field lymphadenectomy. All procedures were performed using open surgical approaches. The authors had previously reported

From the Department of Cardiothoracic Surgery, Weill Cornell Medicine-New York Presbyterian Hospital, New York, NY.

Received for publication March 2, 2021; revisions received April 26, 2021; accepted for publication June 9, 2021; available ahead of print July 15, 2021.

Address for reprints: Nasser Altorki, MD, Department of Cardiothoracic Surgery, Weill Cornell Medicine-New York Presbyterian Hospital, 1300 York Ave, New York, NY 10023 (E-mail: nkaltork@med.cornell.edu).

J Thorac Cardiovasc Surg 2022;163:1695-7

0022-5223/\$36.00

Copyright © 2021 by The American Association for Thoracic Surgery

<https://doi.org/10.1016/j.jtcvs.2021.06.063>

that there was no difference in morbidity between the 2 arms of the trial.⁷ Complications of any Clavien–Dindo grade occurred in 28% of patients after TFD and 30.5% after 2-field dissection. Remarkably, there were no deaths within 90 days in the 3-field group and 1 death (0.5%) in the 2-field group. Occult cervical nodal metastases were observed in 21% of the patients in the 3-field arm. There was no difference between the 2 arms of the trial in either overall survival (hazard ratio, 1.019; 95% confidence interval, 0.727–1.428) or disease-free survival (hazard ratio, 0.868; 95% confidence interval, 0.636–1.184). Cumulative 5-year overall survival, the primary end point, was 63% in both arms of the trial. Disease-free 5-year survival, the secondary end point, was 59% in the 3-field arm and 53% in the 2-field arm. Interestingly, patients with metastases to the cervical nodes who also had mediastinal or abdominal nodal disease had a 5-year survival of approximately 40%. Regardless of treatment assignment, these survival figures are extremely impressive, especially when one considers that enrollment was restricted to patients who did not receive neoadjuvant therapy. Regardless of any potential limitations of the trial, it is an impressive undertaking and will likely be the last and most definitive statement on this topic.

However, in my opinion there are important limitations that should be considered. For starters, the authors based their sample size calculation on the assumption that 3-field lymphadenectomy would increase 5-year survival from the 30% expected after 2-field dissection to 45%. At first glance that appears reasonable; however, it represents a 50% relative improvement in survival, which I believe is a “heavy lift” for a surgical procedure alone to achieve. A more reasonable assumption would have been to assume a more realistic 20% to 25% relative improvement in survival but that would have significantly increased the sample size. As it turned out, both arms performed spectacularly better than historical controls.

Another potential limitation is that the investigators did not stratify patients based on clinical stage, and therefore one cannot be confident that a significant imbalance in stage distribution may underlie the lack of a survival difference. Lastly but perhaps most importantly, the 2-field dissection performed by the authors included dissection of the lymph nodes along both recurrent laryngeal lymph nodes such that the third field essentially comprised the deep cervical nodes. In the transcendental words of the Bard: “what’s in a name? That which we call a rose by any other name would smell as sweet.” The author’s 2-field dissection is in fact a “rose” by another name. Should we then be surprised that the 2 arms are comparable? To be fair, the nomenclatures describing the extent of node dissection for esophageal cancer are confusing. At inception, TFD included the nodes along the course of both recurrent nerves in the superior mediastinum and neck plus the deep cervical nodes. I refer to these as the cervicothoracic nodes. In contrast, 2-field dissection was limited to an infracarinal and abdominal node

dissection. It soon became apparent that one can effectively resect the nodes along both recurrent nerves through a right thoracotomy without the need for a cervical incision and that became referred to as the extended 2-field dissection. Therefore, it would not be surprising if the purists among us suggest that the Fudan trial should more precisely be described as 3-field versus extended 2-field (rather than 2-field) dissection. Some, myself included, believe that the best-available evidence suggests that, at least for thoracic esophageal squamous cell carcinoma, the recurrent nodes are essentially periesophageal nodes and not distant M1 nodes. These nodes are a frequent site of metastatic disease in squamous cell carcinoma and are more critical to remove than the deep cervical nodes. In fact, when the latter are involved, they signal a particularly poor prognosis, especially in patients with adenocarcinoma. Ultimately, we need to develop specific parameters defining the extent of lymph node dissection in each field so that one can reasonably compare outcomes between studies and trials. A description of the fields of node dissection using numerals similar to those employed for gastric cancer may be useful. An example of a potential nomenclature is shown in Table 1.

One might wonder; what is the relevance of these findings to a Western patient population in whom adenocarcinoma is the predominant cell type? Several years ago, both the Cornell and Leuven groups independently reported their results after TFD in patients with esophageal adenocarcinoma.^{2,3} The frequency of occult nodal metastases to the recurrent laryngeal nodes were similar to those reported in Japanese series; 36% of patients in the Cornell series and 26% in the series from Leuven. Patients with lower-third esophageal adenocarcinoma who had recurrent laryngeal nodal disease had 3- and 5-year survival that were essentially identical at 30% and 15% in the Cornell series and 35% and 12% for the Leuven series.^{8,9} To date, neither the Cornell nor the Leuven group have reported their results comparing 2- and 3-field dissection. However, given the results of the Fudan trial, it is entirely plausible that there may also be no difference in survival between the 2 techniques in patients with adenocarcinoma. A topline message from the results of Fudan trial should be that an adequate lymph node dissection, whether 2- or 3-field, is associated with a clinically meaningful improvement in overall and disease-free survival. That is a message that needs to be more fully embraced when

TABLE 1. Field designation (F) and extent of node dissection

F ₀	Perigastric, left gastric, periesophageal (thoracic and/or abdominal)
F ₁	Left gastric, celiac, hepatic, proximal, splenic
F ₂	Subcarinal, hilar, bronchial (right and left), thoracic periesophageal and para-aortic lymphatics +/- thoracic duct, mediastinal pleura
F ₃	F ₁ + F ₂ + Bilateral recurrent laryngeal nodes
F ₄	F ₁ + F ₂ + F ₃ + Cervical nodes

treating patients with esophageal adenocarcinoma. Years ago, an editorial accompanying the first report on TFD in patients with adenocarcinoma, stated that “the majority of Western esophageal surgeons have for the most part removed readily accessible regional lymph nodes at the time of esophagectomy for the purpose of staging rather than with any expectation of improving survival.”¹⁰ Although the association between lymph node dissection and survival still remains a matter of some debate, most studies from national and international registries as well as numerous case series show that the total number of lymph nodes retrieved during esophagectomy is associated with improved survival even after preoperative chemotherapy or chemoradiation.¹¹⁻¹⁶ Today, the challenge for esophageal surgeons caring for patients with esophageal adenocarcinoma is not whether to do 2- or 3-field dissection but rather the lack of a precise definition of an “adequate” 2-field lymphadenectomy. The TIGER trial (NCT03222895), an ongoing multicenter international observational study, will enroll 5000 patients with esophageal cancer undergoing esophagectomy and will collect such variables as the total number of nodes removed and examined, the locations of various nodal stations dissected, as well as disease recurrence and survival.¹⁷ The study may result in a data-driven esophageal cancer nodal map and specific recommendations for the minimum requirements for an adequate 2-field lymph node dissection such as total number of nodes to be removed and nodal stations to dissect based on tumor type, location, and use of neoadjuvant therapy. The current National Comprehensive Cancer Network Guidelines recommend that a thorough dissection be performed to identify all lymph nodes with at least 15 lymph nodes submitted for pathologic evaluation and adequate nodal staging in patients undergoing esophagectomy without preoperative chemoradiation.¹⁸ Unfortunately, the median number of lymph nodes examined after esophagectomy remains below the very low bar set by the National Comprehensive Cancer Network guidelines. A report by Merkow and colleagues¹⁹ on the variation in lymph node examination after esophagectomy showed that although there was significant improvement over time, only 39% of academic centers and 28% of community hospitals met the minimum requirement of 15 lymph nodes examined. The authors also reported data from the National Cancer Database that showed a significant increase over time both in the median number of lymph nodes removed and the in the number of centers in compliance with guidelines. As I see it, the tide is turning slowly but surely toward more adequate lymphadenectomy. That is good for patients.

Conflict of Interest Statement

Dr Altorki reports support from Astra Zeneca LLC (research grant), NCI Moonshot (UG3CA244697), DoD grant (W81XWH-21-1-0309), and Janssen Pharmaceuticals (research grant).

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

References

- Isono K, Sato H, Nakayama K. Results of a nationwide study on three-field lymph node dissection of esophageal cancer. *Oncology*. 1991;48:411-20.
- Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y. Radical lymph node dissection for cancer of the thoracic esophagus. *Ann Surg*. 1994;220:364-74.
- Tachibana M, Kinugasa S, Yoshimura H, Shibakita M, Tonomoto Y, Dhar DK, et al. Clinical outcomes of extended esophagectomy with three-field lymph node dissection for esophageal squamous cell carcinoma. *Am J Surg*. 2005; 189:98-109.
- Kato H, Watanabe H, Tachimori Y, Iizuka T. Evaluation of neck lymph node dissection for thoracic esophageal carcinoma. *Ann Thorac Surg*. 1991;51:931-5.
- Nishihira T, Hirayama K, Mori S. A prospective randomized trial of extended cervical and superior mediastinal lymphadenectomy for carcinoma of the thoracic esophagus. *Am J Surg*. 1998;175:47-51.
- Li B, Zhang Y, Miao L, Ma L, Luo X, Zhang Y, et al. Esophagectomy with three-field versus two-field lymphadenectomy for middle and lower thoracic esophageal cancer: long-term outcomes of a randomized clinical trial. *J Thorac Oncol*. 2021;16:310-7.
- Li B, Hu H, Zhang Y, Zhang J, Miao L, Ma L, et al. Three-field versus two-field lymphadenectomy in transthoracic oesophagectomy for oesophageal squamous cell carcinoma: short-term outcomes of a randomized clinical trial. *Br J Surg*. 2020;107:647-54.
- Altorki N, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. *Ann Surg*. 2002;236:177-83.
- Lerut T, Naftoux P, Moons J, Coosemans W, Decker G, De Leyn P, et al. Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. *Ann Surg*. 2004;240:962-72.
- Orringer MB. Occult cervical nodal metastases in esophageal cancer: preliminary results of three-field lymphadenectomy. *J Thorac Cardiovasc Surg*. 1997; 113:538-9.
- Groth SS, Virnig BA, Whitson BA, DeFor TE, Li ZZ, Tuttle TM, et al. Determination of the minimum number of lymph nodes to examine to maximize survival in patients with esophageal carcinoma: data from the surveillance epidemiology and end results database. *J Thorac Cardiovasc Surg*. 2010;139:612-20.
- Rizk NP, Ishwaran H, Rice TW, Chen LQ, Schipper PH, Kesler KA, et al. Optimum lymphadenectomy for esophageal cancer. *Ann Surg*. 2010;251:46-50.
- Peyre CG, Hagen JA, DeMeester SR, Van Lanschot JJ, Hölcher A, Law S, et al. Predicting systemic disease in patients with esophageal cancer after esophagectomy: a multinational study on the significance of the number of involved lymph nodes. *Ann Surg*. 2008;248:979-85.
- Altorki NK, Zhou XK, Stiles B, Port JL, Paul S, Lee PC, et al. Total number of resected lymph nodes predicts survival in esophageal cancer. *Ann Surg*. 2008; 248:221-6.
- Visser E, van Rossum PSN, Ruurda JP, van Hillegersberg R. Impact of lymph node yield on overall survival in patients treated with neoadjuvant chemoradiotherapy followed by esophagectomy for cancer: a population-based cohort study in The Netherlands. *Ann Surg*. 2017;266:863-9.
- Samson P, Puri V, Broderick S, Patterson GA, Meyers B, Crabtree T. Extent of lymphadenectomy is associated with improved overall survival after esophagectomy with or without induction therapy. *Ann Thorac Surg*. 2017;103:406-15.
- Hagens ERC, van Berge Henegouwen MI, van Sandick JW, Cuesta MA, van der Peet DL, Heisterkamp J, et al. Distribution of lymph node metastases in esophageal carcinoma [TIGER study]: study protocol of a multinational observational study. *BMC Cancer*. 2019;19:662.
- Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, et al. Esophageal and esophagogastric junction cancers, version 2.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2019;17:855-83.
- Merkow RP, Bilimoria KY, Chow WB, Merkow JS, Weyant MJ, Ko CY, et al. Variation in lymph node examination after esophagectomy for cancer in the United States. *Arch Surg*. 2012;147:505-11.

Key Words: three-field node dissection, esophageal cancer