Ann Surg Oncol (2019) 26:1959–1960
https://doi.org/10.1245/s10434-019-07382-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – THORACIC ONCOLOGY

Better Survival After 4L Lymph Node Dissection for Early-Stage, Left-Sided, Non-small Cell Lung Cancer: Are We Debating a False Duality?

J. Matthew Reinersman, MD

Division of Cardiac, Thoracic and Vascular Surgery, Department of Surgery, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Lung cancer remains the leading cause of cancer death worldwide.[1] Improvements have been made in recent years in systemic therapy for advanced stage; however, surgical resection is the best chance for cure in early stage. Resection requires a systematic lymph node assessment; yet there has remained intense debate regarding this assessment, i.e., extent of assessment, how many lymph nodes, or how many nodal stations. The article by Zhao and colleagues, "Survival Benefit of Left Lower Paratracheal (4L) Lymph Nodes Dissection for Patients with Left-Sided Non-Small Cell Lung Cancer: Once Neglected but of Great Importance," attempts to clarify a portion of this debate.[2] The study is a retrospective analysis of a large database of patients undergoing resection for early-stage, left-sided non-small cell lung cancer, comparing outcomes of selected 4L lymph node dissection to selected matched controls with lymph node dissection of at least three lymph node stations excluding 4L. Disease-free survival and overall survival were the primary end points. The authors found that patients undergoing a 4L lymph node dissection had an improved overall survival (65.8% vs. 56.3%, $p = 0.006$), suggesting that 4L lymphadenectomy is superior. The authors did a further subgroup analysis according to N stage and found that the 4L lymphadenectomy group had a better overall survival in patients with N2 disease as well [hazard ratio (HR) = 1.53; $p = 0.008$], which they interpreted as providing therapeutic value to the 4L lymphadenectomy.

The American College of Surgeons Oncology Group Z0030 trial has provided the best quality data in the debate on lymph node evaluation with a randomized trial of systematic lymph node sampling versus lymph node dissection.[3] The trial was rigorously performed, and the data has been highly scrutinized. The findings from this trial showed no difference in survival in the two practices of systematic sampling versus lymph node dissection. The key finding is that all patients should undergo a very thorough lymph node evaluation. Often, due to the anatomic location of the 4L station, it is not sampled during lung cancer resection out of concern for recurrent laryngeal nerve injury. Guidelines from other organizations also make the debate on the evaluation of the mediastinum less clear. The National Comprehensive Cancer Network (NCCN) guidelines require a minimum of three N2 stations be evaluated but do not differentiate sampling versus dissection. The American College of Surgeons Commission on Cancer does not have any guidelines regarding sampling versus dissection or even specific lymph node station requirements but rather requires evaluation of ten or more regional lymph nodes.[4] The European Society of Thoracic Surgeons expert consensus guidelines for lymph node staging does recommend systematic nodal dissection, with a minimum of three hilar and interlobar nodes and three mediastinal nodes from three stations in which the subcarinal station is always included.[5] Therefore, a wide variety of potential possibilities is recommended for "quality" care, depending on which guidelines one chooses to follow.

First Received: 4 April 2019;
Published Online: 23 April 2019

J. M. Reinersman, MD
e-mail: Matthew-reinersman@ouhsc.edu

The study by Zhao and colleagues comes from a large database with a large sample size to draw from but is limited due to its retrospective nature and the need to match patients for comparison. A major liability is the very high rate of N2 disease in this study of purported early-stage patients—26.6%—which calls into question the preoperative evaluation. Comparatively, only 4.4% of patients in the Z0030 trial were found to have stage IIIA or IIIB disease at time of resection.[3] The Z0030 trial did not include dissection of the 4L nodal station, so some patients could be missing from this analysis. The ESTS guidelines do recommend 4L nodal evaluation for left-sided tumors except in select circumstances.[5] However, if the patients were known to have N2 disease before surgery, then the paradigm of management changes significantly. The NCCN guidelines recommend complete lymph node dissection if resection is undertaken for N2 positive stage IIIA disease.[6]

The real question at the crux of this issue of improved survival due to lymphadenectomy is whether this represents instead a "false duality" or "false dichotomy." False dichotomy refers to the error of evaluating for two outcomes for a problem when in fact there are likely many other possible answers. I would argue that this is in fact the case. Rather than focusing on the 4L lymph node dissection providing therapeutic value or not, we should consider what is the optimal evaluation of the 4L lymph node station, as well as the other stations. This stems from what was found in the Z0030 trial. The most important consideration the trial found is the thoroughness of the mediastinal evaluation rather than better/worse survival with extent of lymphadenectomy. Improved evaluation leads to more accurate pathologic staging.[7] The authors attempt to utilize a subgroup analysis to show therapeutic value for the lymphadenectomy of a single lymph node station. This could be true, but unrelated, particularly given the high number of patients with N2 disease in this study, which calls into question what stage patients we are evaluating. Applying therapeutic value to lymph node dissection may be erroneous when we are likely only identifying patients with advanced disease.

The study by Zhao and colleagues opens the question for a more thorough evaluation of the 4L station in patients undergoing resection for early-stage, left-sided lung cancers, particularly given current societal guidelines. However, the recommendation that this provides therapeutic value may represent a false dichotomy where the true meaning is not in survival advantage from the lymphadenectomy itself but rather from more accurate pathologic staging. Further long-term, randomized studies are clearly warranted to provide closure to this debate.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87–108.
2. Zhao K, Wei S, Mei J, Guo C, Hai Y, Chen N, Lie L. Survival benefit of left lower paratracheal (4L) lymph node dissection for patient with left-sided non-small cell lung cancer: once neglected but of great importance. *Ann Surg Oncol*. 2019. https://doi.org/10.1245/s10434-019-07368-x.
3. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 trial. *J Thorac Cardiovasc Surg*. 2011;141:662–70.
4. CoC Quality of Care Measures. *Non-small cell lung cancer*. Revised November 30, 2018. https://www.facs.org/quality-programs/cancer/ncdb/qualitymeasures. Accessed 1 Mar 2019.
5. Lardinois D, De Leyn P, Van Schil P, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. *Eur J Cardio-thorac Surg*. 2006;30:787–92.
6. National Comprehensive Cancer Network. *NCCN clinical practice guidelines in oncology: non-small cell lung cancer. Version 3*. 2019. https://www.nccn.org/professionals/physician_gls/pdf/nscl_blocks.pdf. Accessed 20 Mar 2019.
7. Osarogiagbon RU, Decker PA, Ballman K, Wigle D, Allen, MS, Darling GE. Survival implications of variation in the thoroughness of pathologic lymph node examination in American College of Surgeons Oncology Group Z0030 (Alliance). *Ann Thorac Surg*. 2016;102:363–9.