



Neoadjuvant therapy and sleeve lobectomy for locally advanced non-small cell lung cancer: morbidity and survival balancing

Alessio Campisi^{1,2^}, Giorgio Cannone^{3^}, Vincenzo Verzeletti^{3^}, Andrea Dell'Amore^{3^}

¹Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; ²Thoracic Surgery Department, University and Hospital Trust-Ospedale Borgo Trento, Verona, Italy; ³Department of Cardiothoracic Surgery and Vascular Sciences, Padua University Hospital, University of Padua, Padua, Italy

Correspondence to: Andrea Dell'Amore, MD, PhD. Department of Cardiothoracic Surgery and Vascular Sciences, Padua University Hospital, University of Padua, Via Giustiniani 2, 35128 Padua, Italy. Email: andrea.dellamore@unipd.it.

Comment on: Li X, Li Q, Yang F, *et al.* Neoadjuvant therapy does not increase postoperative morbidity of sleeve lobectomy in locally advanced non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2023;166:1234-1244.e13.

Keywords: Induction therapy; sleeve lobectomy; bronchoplasty; complications; advanced lung cancer

Submitted Jan 04, 2024. Accepted for publication Mar 04, 2024. Published online Apr 10, 2024.

doi: 10.21037/jtd-24-23

View this article at: <https://dx.doi.org/10.21037/jtd-24-23>

Lung cancer stands as the predominant cause of global cancer-related mortality, with an annual incidence approaching 2 million new cases (1). Non-small cell lung cancer (NSCLC) constitutes 80% of these cases, and merely 26% of NSCLC patients survive beyond 5 years post-diagnosis, often due to delayed identification (2). Substantial strides have been made in comprehending NSCLC and formulating effective treatment approaches, particularly for centrally situated or advanced-stage NSCLC.

The management of centrally located NSCLC frequently involves extensive removal of lung tissue and is associated with a grim prognosis, primarily attributable to elevated rates of hilar and mediastinal lymph node metastases. Modern surgical protocols for these tumors prioritize complete tumor excision while concurrently preserving parenchyma to preclude the need for pneumonectomy, which carries a reported mortality rate ranging from 4.6% to 9.2% (3). Presently, sleeve resection emerges as the recommended procedure for centrally located tumors, safeguarding against pneumonectomy without compromising the surgical outcomes from an oncological perspective (4-6).

Recent attention has been directed toward refining

surgical approaches for locally advanced NSCLC, with neoadjuvant therapy assuming a pivotal role. However, the tangible advantages of induction therapy remain underutilized and not universally demonstrated (7). The efficacy of neoadjuvant therapies lies in their ability to address tumors in a multifaceted manner before surgical intervention. By administering chemotherapy, immunotherapy, or targeted therapy prior to surgery, neoadjuvant treatment aims to downsize tumors, reduce tumor burden, and eradicate micrometastases, thus increasing the likelihood of successful surgical resection (8,9). Moreover, neoadjuvant therapy can enhance the feasibility of complete tumor removal (R0 resection) by reducing tumor size and improving surgical margins. Additionally, it allows for early assessment of tumor response, providing valuable information about tumor biology and guiding subsequent treatment decisions. The incorporation of neoadjuvant therapy into treatment protocols has been associated with improved long-term outcomes, including enhanced disease-free survival and overall survival rates. Furthermore, neoadjuvant therapy offers the opportunity to tailor adjuvant treatment strategies based on the tumor's response to preoperative therapy, optimizing personalized care for each patient. Overall,

[^] ORCID: Alessio Campisi, 0000-0002-1384-7441; Giorgio Cannone, 0000-0003-4242-6168; Vincenzo Verzeletti, 0000-0001-7239-1248; Andrea Dell'Amore, 0000-0002-1384-7441.

neoadjuvant therapy represents a promising approach in the pursuit of better outcomes and improved quality of life for cancer patients. Conversely, induction therapy introduces potential challenges during surgery and may escalate postoperative complications, which may be a catastrophic event in case of bronchoplasty (10-12). The potential loss of tissue vitality associated with these drugs further delays tissue healing, posing a particular risk at the level of bronchial anastomosis. Additionally, it has been reported that chemotherapy induces both transient and relatively permanent immunodeficiency in patients, increasing the risk of postoperative infections and impacting patient prognosis (11).

In this context, a recent article authored by Li *et al.* (13), published in the October 2023 issue of the *Journal of Thoracic and Cardiovascular Surgery*, seamlessly aligns with the imperative to explore the correlation between neoadjuvant therapy and postoperative morbidity in individuals undergoing sleeve lobectomy for locally advanced NSCLC. The authors conducted a retrospective analysis of patients who underwent sleeve lobectomy for locally advanced NSCLC, aiming to evaluate the impact of neoadjuvant therapy on postoperative morbidity. The study included a cohort of 613 patients and yielded several notable findings.

The study unfolds within a rapidly advancing field, particularly following the publication of the Checkmate 816 and AEGEAN studies (9,14), which demonstrated that patients who underwent neoadjuvant therapy experienced enhanced disease-free and overall survival in contrast to those who did not receive such treatment. This observation is underpinned by the understanding that neoadjuvant therapy can effectively downsize tumors, facilitate R0 resection, and ultimately lead to improved long-term outcomes. This finding reaffirms the importance of incorporating neoadjuvant therapy into the treatment paradigm for locally advanced NSCLC, considering it a standard of care for eligible patients, and makes the article of Li *et al.* of great value (13). The potential to enhance long-term outcomes is particularly relevant for patients with stage IIIA NSCLC, for whom neoadjuvant therapy may convert unresectable tumors into resectable ones, potentially resulting in an increased number of patients undergoing induction therapies in the near future.

The population treated with neoadjuvant intent exhibited different baseline characteristics compared to the upfront surgery control group: larger neoplasm size, a higher rate of N2 metastasis, and a more advanced clinical

tumor, node, metastasis (TNM) stage. To mitigate this bias, the authors employed propensity score matching (PSM), creating two new groups, each consisting of 97 patients with similar features. Following PSM, of paramount interest, the study revealed that neoadjuvant therapy did not result in a statistically significant increase in postoperative morbidity. This finding is crucial, as concerns about the potential rise in surgical complications following neoadjuvant therapy have been a subject of debate and hesitation among clinicians. The authors' ability to dispel these concerns is a significant contribution to the field and supports the momentum to incorporate neoadjuvant therapy into treatment plans. Secondary, an interesting aspect is the comparison of perioperative outcomes during different periods of the study. The authors divided the 4-year study period into two 2-year subperiods: the first 2 years and the last 2 years. This analysis revealed a 16.9% increase in the number of patients eligible for neoadjuvant treatment in the last 2 years group, along with a reduction in postoperative complications, albeit without statistical significance. While no statistical analysis was performed to substantiate this observation, there seems to be a noticeable decreasing trend in operative time over the last 2 years. These trends could be attributed to the growing expertise of the surgeons in handling these challenging cases. This observation is crucial as an increasing number of patients are expected to undergo this type of treatment before surgery in the present and near future. With an expanding patient pool, future research should focus on clinical trials examining the efficacy of different drugs and their impact on both efficacy and the onset of postoperative complications.

Li *et al.* (13) also investigated the potential risk factors associated with postoperative morbidity. While the study initially identified factors such as smoking history, open thoracotomy, and operation time exceeding 150 minutes as potential risk factors for postoperative complications during univariate analysis, only open thoracotomy emerged as an independent risk factor during multivariable logistic regression analysis. Consequently, the utilization of neoadjuvant therapy did not emerge as a significant risk factor. Therefore, on one hand, their results further strengthen the argument in favor of neoadjuvant therapy for locally advanced NSCLC, especially for patients who may benefit from tumor downstaging or improved resectability. On the other hand, depending on the type of induction, the effects may challenge the procedure and necessitate performing surgery via thoracotomy, thereby increasing the risk for complications. Nevertheless, not all of the patients

may be a suitable candidate for this approach. The results underscore the importance of careful patient selection, taking into account these factors. A multidisciplinary approach, involving oncologists, surgeons, and other specialists, is critical to making informed treatment decisions. In fact, the research results of Li *et al.* (13) further emphasized the need for personalized treatment plans. Each patient's clinical characteristics and tumor biology should be taken into account when determining the most appropriate treatment sequence. For some patients, neoadjuvant therapy may be the optimal choice, while others may benefit more from upfront surgery or other approaches.

Despite the valuable insights provided by the article, it is important to acknowledge certain limitations that warrant consideration. Firstly, the study's retrospective design may introduce inherent biases and limit the establishment of causal relationships. Additionally, the absence of detailed preoperative information, such as the rationale for choosing induction therapy or upfront surgery and the specific type of induction therapy employed, poses a notable constraint. Different modalities may have distinct impacts on outcomes. Furthermore, the generalizability of the findings may be influenced by the single-center nature of the study, potentially limiting the extrapolation of the results to broader populations and diverse clinical settings. Moreover, the high-volume center, in one sense, accommodated a large number of patients; on the other hand, it may have contributed to improved patient outcomes, reduced complication rates, and enhanced overall quality of care which may not be representative of real world experience.

The study by Li *et al.* (13) is a valuable addition to the growing body of literature on the treatment of locally advanced NSCLC. The authors have provided compelling evidence that neoadjuvant therapy does not increase postoperative morbidity in patients undergoing sleeve lobectomy for this challenging disease. Their findings underscore the importance of incorporating neoadjuvant therapy into the treatment paradigm for eligible patients, with a focus on achieving improved long-term outcomes without compromising safety. As we move forward in the fight against lung cancer, studies like this serve as a reminder of the ever-evolving landscape of oncology and the critical role that research plays in shaping clinical practice.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease*. The article has undergone external peer review.

Peer Review File: Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-24-23/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-24-23/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Vansteenkiste J, Crinò L, Doooms C, et al. 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. *Ann Oncol* 2014;25:1462-74.
2. Ettinger DS, Wood DE, Aisner DL, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 2.2021. *J Natl Compr Canc Netw* 2021;19:254-66.
3. Park JS, Yang HC, Kim HK, et al. Sleeve lobectomy as an alternative procedure to pneumonectomy for non-small cell lung cancer. *J Thorac Oncol* 2010;5:517-20.
4. Dell'Amore A, Chen L, Monaci N, et al. Total Lung-sparing Surgery for Tracheobronchial Low-grade Malignancies. *Ann Thorac Surg* 2021;112:450-8.
5. Pagès PB, Mordant P, Renaud S, et al. Sleeve lobectomy may provide better outcomes than pneumonectomy for non-small cell lung cancer. A decade in a nationwide study. *J Thorac Cardiovasc Surg* 2017;153:184-195.e3.

6. Deslauriers J, Grégoire J, Jacques LF, et al. Sleeve lobectomy versus pneumonectomy for lung cancer: a comparative analysis of survival and sites or recurrences. *Ann Thorac Surg* 2004;77:1152-6; discussion 1156.
7. Song WA, Zhou NK, Wang W, et al. Survival benefit of neoadjuvant chemotherapy in non-small cell lung cancer: an updated meta-analysis of 13 randomized control trials. *J Thorac Oncol* 2010;5:510-6.
8. Decaluwé H, De Leyn P, Vansteenkiste J, et al. Surgical multimodality treatment for baseline resectable stage IIIA-N2 non-small cell lung cancer. Degree of mediastinal lymph node involvement and impact on survival. *Eur J Cardiothorac Surg* 2009;36:433-9.
9. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. *N Engl J Med* 2022;386:1973-85.
10. Cannone G, Comacchio GM, Pasello G, et al. Precision Surgery in NSCLC. *Cancers (Basel)* 2023;15:1571.
11. Mammana M, Sella N, Giraud C, et al. Postoperative hypoxaemic acute respiratory failure after neoadjuvant treatment for lung cancer: radiologic findings and risk factors. *Eur J Cardiothorac Surg* 2022;63:ezac569.
12. Allaeys T, Berzenji L, Van Schil PE. Surgery after Induction Targeted Therapy and Immunotherapy for Lung Cancer. *Cancers (Basel)* 2021;13:2603.
13. Li X, Li Q, Yang F, et al. Neoadjuvant therapy does not increase postoperative morbidity of sleeve lobectomy in locally advanced non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2023;166:1234-1244.e13.
14. Heymach JV, Harpole D, Mitsudomi T, et al. Perioperative Durvalumab for Resectable Non-Small-Cell Lung Cancer. *N Engl J Med* 2023;389:1672-84.

Cite this article as: Campisi A, Cannone G, Verzeletti V, Dell'Amore A. Neoadjuvant therapy and sleeve lobectomy for locally advanced non-small cell lung cancer: morbidity and survival balancing. *J Thorac Dis* 2024;16(4):2690-2693. doi: 10.21037/jtd-24-23