



The impact of neoadjuvant therapy on postoperative outcomes following sleeve lobectomy for locally advanced non-small cell lung cancer: a call for future investigation

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The identification of optimal treatment strategies for patients with locally advanced non-small cell lung cancer (NSCLC) remains an ongoing challenge. There is a consensus that pneumonectomy should be avoided whenever possible, given its associated morbidity and detrimental effects on quality of life (1). An alternative surgical approach to pneumonectomy for central tumors is sleeve lobectomy, a lung-sparing approach which has been associated with superior outcomes with regard to postoperative complications and long-term survival (2). Sleeve lobectomy has classically been performed as an upfront treatment given concerns over neoadjuvant treatment-associated fibrosis. However, this practice will likely change with the increased utilization of neoadjuvant therapy for patients with locally advanced NSCLC. Novel targeted therapy and immunotherapy drugs are increasingly utilized in neoadjuvant regimens (3). The integration of neoadjuvant therapy into the treatment paradigm has proven to downstage tumors, increase complete resection rates, and improve long-term patient outcomes after surgical resection (4). Importantly, several contemporary small series and case reports encompassing diverse patient cohorts have consistently demonstrated that sleeve lobectomy can be

safely performed following neoadjuvant treatment (5-7). Despite this, whether new neoadjuvant modalities increase surgical risks or postoperative complications after sleeve lobectomy is still a question that remains to be definitively answered in larger patient cohorts.

In *The Journal of Thoracic and Cardiovascular Surgery*, Li *et al.* conducted a retrospective analysis of patients who underwent sleeve lobectomy after neoadjuvant therapy for NSCLC from January 2018 to December 2021 at a single large-volume center. About one third of patients received neoadjuvant immunotherapy or targeted therapy as part of their treatment regimen. The authors assessed perioperative outcomes and postoperative morbidity to evaluate the feasibility and safety of such a strategy (8). A critical examination of the study's scope, methodology, and conclusions brings to light nuances for consideration. Factors associated with a higher likelihood of receiving neoadjuvant therapy were younger age, higher rates of smoking history, larger tumors, N2 nodal metastases, and more advanced clinical tumor, node, metastasis (TNM) stage. In a balanced, propensity-matched cohort, their key finding was that no significant difference was observed in perioperative factors (blood loss, utilization of minimally

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invasive surgery, conversion rates) or in postoperative morbidity.

The authors conclude that neoadjuvant therapy does not increase postoperative morbidity following sleeve lobectomy for locally advanced NSCLC. This is an important finding in this group of patients undergoing modern neoadjuvant treatment regimens. The focus on postoperative morbidity prompts the question of whether there are subtler, yet equally significant, long-term complications related to neoadjuvant therapy that extend beyond the immediate postoperative period. Long-term survival rates, disease recurrence patterns, and patients' quality of life are essential aspects that deserve attention in the evaluation of neoadjuvant therapy's overall impact prior to sleeve lobectomy. A previous study from the same group has already demonstrated that sleeve lobectomy was associated with decreased postoperative morbidity and improved long-term survival (9). However, as the authors point out, such outcomes eventually also need to be queried after neoadjuvant therapy, an analysis which was unfortunately outside the scope of the current paper. Ultimately, a comprehensive assessment of these factors is paramount in guiding treatment decisions, as the surgeon's goal is not only to ensure immediate surgical success, but also to optimize the long-term well-being of patients with locally advanced NSCLC. The integration of health-related quality of life measures in clinical trials can be used to identify specific needs and perspectives of patients (10).

While this remarkably large series contributes valuable insights into short-term surgical outcomes, it is crucial to acknowledge certain limitations that may impact the broader interpretation of these findings. The retrospective nature of the analysis and the relatively short follow-up period might not fully capture the intricacies of long-term morbidity and survival outcomes associated with neoadjuvant therapy. Additionally, the single-center study cohort and predominance of squamous cell carcinoma may not be entirely representative of the diverse patient population encountered in all clinical practices, raising questions about the generalizability of the results. A recent National Cancer Database (NCDB) study showed only 21.4% of eligible patients with NSCLC in the United States from 2006–2017 received neoadjuvant therapy (11). Significant barriers to receipt of neoadjuvant therapy were identified in this study, including racial, socioeconomic, and geographic disparities. Despite evidence suggesting that neoadjuvant therapy leads to superior outcomes, in practice surgeon preferences as well as individual patient tumor

and socioeconomic factors have historically contributed to low utilization of this approach (12). The lack of access to neoadjuvant therapy to certain high-risk populations and the challenges of selection bias, as the authors point out, could significantly affect the post-operative outcomes described. Future research endeavors should aim to bridge gaps in knowledge, providing a more holistic understanding of the outcomes associated with neoadjuvant therapy in the context of sleeve lobectomy for NSCLC.

By this analysis of the study put forth by Dr. Li and colleagues, we hope to add to the discourse surrounding treatment decisions for locally advanced NSCLC. Their publication urges a nuanced perspective that considers both immediate surgical outcomes and the broader spectrum of patient-centric long-term implications. To draw more robust conclusions and guide clinical decision-making, further prospective studies with larger and more diverse cohorts, extended follow-up periods, and comprehensive assessments of both 30-day morbidity and mortality and 5-year survival are warranted. We may be able to analyze data from the large number of neoadjuvant trials for patients with locally advanced NSCLC which have recently been reported or published. Future research endeavors should prioritize comprehensive assessments, encompassing not only immediate postoperative outcomes, but also long-term survival rates, disease recurrence patterns, and patients' quality of life. Given the remarkable series described by Li *et al.*, it seems likely that neoadjuvant therapy is safe to deliver prior to sleeve lobectomy and that surgeons should continue to pursue lung-sparing surgical options when oncologically feasible. This has been our own practice, in which we have employed sleeve resection after neoadjuvant chemotherapy and immunotherapy even for tumors which initially only appeared to be resectable by pneumonectomy.

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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.

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