We appreciate the kind comments provided by Dr. Yalman regarding our recently published article examining the impact of timing of surgery following neoadjuvant chemoradiation therapy in locally advanced non-small cell lung cancer (NSCLC) (1). As the readership of the Journal is aware, stage III NSCLC encompasses patients with a wide variety of tumor characteristics. The 7th edition of the TNM Staging Manual defined stage III NSCLC as tumors that invade into local structures and/or have mediastinal nodal involvement (2). For stage III patients with N2 involvement, the decision between treating with definitive chemoradiotherapy or neoadjuvant chemoradiotherapy followed by surgery has been extensively debated (3-5). Retrospective and phase II trials have suggested that the addition of surgery after chemoradiotherapy may lead to improved survival (6-9). However, phase III trials have showed that while local control and progression free survival is improved with trimodality therapy, overall survival does not appear to be significantly prolonged compared to definitive chemoradiotherapy (2,5). Despite this gap in knowledge, it is important to note that the success of surgery after neoadjuvant chemoradiation therapy may heavily depend on a number of factors that were not adequately controlled for in previous studies, including the selection of appropriate patients, the surgical approach taken, and the details of the protocol for trimodality therapy. For each of these factors, there is room for potential further optimization, and as such, there is hope that a subset of patients who will significantly benefit from the use of surgery after neoadjuvant treatment can be identified.

In an attempt to understand the impact of differences among protocols for trimodality therapy, we investigated the effect of the timing of surgery after neoadjuvant chemoradiotherapy in our study (1). Previously, the time interval between neoadjuvant therapy and surgery had not been well studied, although there has been much speculation regarding its impact on outcomes. Radiotherapy has been known to impair DLCO, and observational data has suggested that a recovery period of 4–6 weeks is needed in order to proceed safely to surgery (10). Additionally, as Dr. Yalman astutely noted, reducing this recovery period poses the theoretical risk of experiencing complications, such as copious bleeding and organ failure. Alternatively, waiting for an extended period of time following neoadjuvant chemoradiation therapy prior to surgery may increase the risk of fibrosis and pneumonitis, which can greatly complicate a resection (11,12). Our study of 1,623 patients who had surgery following neoadjuvant chemoradiation therapy showed that overall survival decreased significantly in patients who waited longer than 6 weeks to have surgery (1). These results suggest that timing may indeed play an important role in patient outcomes and discourage delaying surgery beyond 6 weeks after the completion of neoadjuvant therapy.
chemoradiotherapy.

A limitation to our study, which also exists to a lesser degree in the randomized control trials that compared definitive chemoradiotherapy to trimodality therapy, was that not all patients in our sample population were ideal candidates for trimodality therapy. This is partly due to the fact that no rigorous set of guidelines exist to guide clinicians in determining which candidates are ideally suited for surgery following neoadjuvant chemoradiotherapy. As of now, there is some evidence suggesting that that patients with single-station, non-bulky N2 disease with a good response to induction therapy may experience improved survival with surgery (13). However even in this context, patients with N2 disease demonstrating a poor response to induction therapy may have a high likelihood of recurrence after surgery; questioning the value of adding surgical therapy (7). Additionally, patients with multi-station and/or bulky N2 disease should not be operated on due to the difficulty of achieving a complete resection in these cases. Finally, considering that in the Intergroup 0139 trial, the incidence of 30-day mortality for patients who underwent pneumonectomies was very high (26%) and that in their post-hoc analysis there was a survival benefit observed for patients undergoing lobectomy, patients who are eligible for lobectomy and not pneumonectomy should be considered for trimodality therapy (2). Stricter implementation of these selection criteria may lead to an improvement in survival outcomes for patients who get trimodality therapy. In an era where medicine is increasingly personalized, it is paramount to assign the appropriate treatment to the appropriate group of patients, especially for a disease as heterogeneous as stage III NSCLC.

In summary, there is still much work to be done to improve the outcomes associated with stage IIIA-N2 NSCLC and trimodality therapy. Given the current body of evidence, improving outcomes may be achieved through being more selective in choosing patients for trimodality therapy, performing lobectomies instead of pneumonectomies, and reducing the number of patients who unnecessarily wait longer than 6 weeks to undergo surgery after neoadjuvant chemoradiotherapy. While Dr. Yalman perceptively noted that it will be difficult for the results of our study to be validated in a prospective randomized trial, we invite our colleagues to pay greater attention to the timing of surgery in the context of trimodality therapy, as this may be a relatively straightforward way of optimizing outcomes.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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