Letter to the Editor

Examining the ınterval between radiation therapy and surgery in trimodality therapy: Try Tri Again

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Provenance: This is an invited Letter to the Editor commissioned by the Section Editor Gang Shen, MMSC (The Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China).

Response to: Yalman D. Invited Editorial on "the timing of surgery after neoadjuvant chemoradiation in locally advanced non-small cell lung cancer". J Thorac Dis 2017;9:E299-E300.

Submitted Jun 07, 2017. Accepted for publication Jun 26, 2017.
doi: 10.21037/jtd.2017.07.17
View this article at: http://dx.doi.org/10.21037/jtd.2017.07.17

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

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.

Acknowledgements

None.

Footnote

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

References

1. Gao SJ, Corso CD, Wang EH, et al. Timing of Surgery after Neoadjuvant Chemoradiation in Locally Advanced Non-Small Cell Lung Cancer. J Thorac Oncol 2017;12:314-22.
2. Groome PA, Bolejack V, Crowley JJ, et al. The IASLC Lung Cancer Staging Project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2007;2:694-705.
3. Zheng Y, Jaklitsch MT, Bueno R. Neoadjuvant Therapy in Non-Small Cell Lung Cancer. Surg Oncol Clin N Am 2016;25:567-84.
4. Gillaspie EA, Wigle DA. Management of Stage IIIA (N2) Non-Small Cell Lung Cancer. Thorac Surg Clin 2016;26:271-85.
5. Saha SP, Kalathiya RJ, Davenport DL, et al. Survival after Pneumonectomy for Stage III Non-small Cell Lung Cancer. Oman Med J 2014;29:24-7.
6. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009;374:379-86.
7. Burkes RL, Shepherd FA, Blackstein ME, et al. Induction chemotherapy with mitomycin, vindesine, and cisplatin for stage IIIA (T1-3, N2) unresectable non-small-cell lung cancer: final results of the Toronto phase II trial. Lung Cancer 2005;47:103-9.
8. Koshy M, Fedewa SA, Malik R, et al. Improved survival associated with neoadjuvant chemoradiation in patients with clinical stage IIIA(N2) non-small-cell lung cancer. J Thorac Oncol 2013;8:915-22.
9. Thomas M, Rube C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. Lancet Oncol 2008;9:636-48.
10. Loor G, Ferguson MK. Pulmonary Function Alterations

After Induction Therapy for Lung Cancer: Preoperative Considerations. In: Ferguson MK. editor. Difficult Decisions in Thoracic Surgery: An Evidence Based Approach. New York: Springer, 2007.
11. Lingos TI, Recht A, Vicini F, et al. Radiation pneumonitis in breast cancer patients treated with conservative surgery and radiation therapy. Int J Radiat Oncol Biol Phys 1991;21:355-60.
12. Theise ND, Henegariu O, Grove J, et al. Radiation pneumonitis in mice: a severe injury model for pneumocyte engraftment from bone marrow. Exp Hematol 2002;30:1333-8.
13. Friedel G, Budach W, Dippon J, et al. Phase II trial of a trimodality regimen for stage III non-small-cell lung cancer using chemotherapy as induction treatment with concurrent hyperfractionated chemoradiation with carboplatin and paclitaxel followed by subsequent resection: a single-center study. J Clin Oncol 2010;28:942-8.

Cite this article as: Gao SJ, Kim AW. Examining the ınterval between radiation therapy and surgery in trimodality therapy: Try Tri Again. J Thorac Dis 2017;9(8):E730-E732. doi: 10.21037/jtd.2017.07.17

