Letter to the Editor

Controversy and perspective in the management of marginally operable stage IIIA non-small cell lung cancer: response to Editorial by Charlotte Billiet and Dirk De Ruysscher and Editorial by Dr. Wanpu Yan and Dr. David R. Jones

Kai-Lin Yang[1,2,3], Jiunn-Song Jiang[2,4], Kwan-Hwa Chi[1,3]

[1]Department of Radiation Therapy and Oncology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan; [2]School of Medicine, Fu Jen Catholic University, New Taipei, Taiwan; [3]Department of Biomedical Imaging and Radiological Sciences, National Yang-Ming University, Taipei, Taiwan; [4]Department of Chest Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

Correspondence to: Kwan-Hwa Chi, MD. Department of Radiation Therapy and Oncology, Shin Kong Wu Ho-Su Memorial Hospital, 95 Wen-Chang Road, Shih-Lin, Taipei 111, Taiwan. Email: M006565@ms.skh.org.tw.

Provenance: This is an invited article commissioned by Section Editor Dr. Jie Dai (Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China).

Response to: Billiet C, De Ruysscher D. Optimized local therapy for locally advanced non-small cell lung cancer. J Thorac Dis 2017;9:1783-5; Yan W, Jones DR. Editorial on: multidisciplinary therapy of marginally operable stage IIIA non-small cell lung cancer. J Thorac Dis 2017;9:1826-7.

Submitted Aug 07, 2017. Accepted for publication Aug 16, 2017.
doi: 10.21037/jtd.2017.08.112
View this article at: http://dx.doi.org/10.21037/jtd.2017.08.112

Physicians in the world never stop pursuing the best approach for patients. We are pleased to participate in a debate on what is the most optimal management for stage IIIA non-small cell lung cancer (NSCLC), which is well known for heterogeneity of diseases and complexity of treatment options. Indeed, our study had some limitations, which was inevitable for a retrospective design. The detailed staging work-up including chest CT scan, invasive mediastinal staging, PET/CT, bone scan and brain MRI were available, and the clinical stage were determined in the combined conference. A substantial part of our patients were evaluated by PET/CT before and after treatment. Whether to undergo surgery or not is determined by complicated factors, including tumor response, the status of vessel invasion or adhesion, pulmonary function tests, surgeon's opinion and willingness of patients, etc. The patients who were eligible for surgery may be those with good response, better performance status and thus better prognosis, but this also suggests that surgical intervention should be tailored for a substantial group of the patients since optimized survival could possibly be achieved in surgically treated patients (lobectomy, but not pneumonectomy). As for the possible reasons of suboptimal dose in our group C were already discussed in our publication. For lung cancer, the standard dose of definitive CCRT is 60 Gy, which is determined by clinical trials. However, in the real world, total prescribed doses are sometimes limited by normal tissue tolerance, especially for those advanced diseases. A retrospective study should be interpreted carefully, and the results should be confirmed in a prospective well-designed study.

Our research focused on the "*marginally operable stage IIIA NSCLC*" since the management of this group of patients is much more challenging (1). Our responses to comments from Billiet *et al.* and Yan *et al.* involve the following issues besides their concerns about our study: firstly, definitive chemoradiotherapy versus neoadjuvant therapy followed by surgery; secondly, neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy for surgical candidate.

Definitive chemoradiotherapy is undoubtedly the category 1 suggestion for stage III NSCLC, but neoadjuvant chemotherapy with or without radiotherapy followed by surgery for those without progression is still an alive option for stage IIIA NSCLC according to randomized trials and NCCN guideline (2-4). Our phased CCRT protocol in this

work followed the latter treatment policy for patients who could benefit from surgery. To our best knowledge, there is no consensus regarding definition of marginally operable NSCLC. Clinical scenarios typically considered marginally operable usually involve the patients with locally advanced NSCLC that might be resectable if induction therapy shrinks the tumors and makes a less morbid surgery possible (5). We define marginally operable diseases by respecting opinions of chest surgeons. All our patients in this study were informed about what alternative options they could choose. The raised issue was about the patients who did not undergo surgery as initially planned. According to NCCN guideline, these patients would be treated with systemic therapy only, but typically most of them were still stage III cases that a local treatment should still be emphasized. In principle, offering only systemic therapy to local-regional diseases is not enough for local-regional tumor control. This is why we offered split-course CCRT boost. One of the purposes of our study is exactly to raise the issue about how to take care of these patients.

On the other hand, an alternative approach may be neoadjuvant chemotherapy followed by surgery, and if the tumor was reassessed inoperable, then salvage CCRT with curative standard doses of 60 Gy could be delivered. This is definitely a practical approach to adapt to common clinical situations. However, "marginally operable diseases" may require higher response rates to convert into deemed operable disease. A Japanese study ever reported neoadjuvant CCRT with 50 Gy for cN2-3 NSCLC achieved response rate of 78% and pCR rate of 17.1% (6), which was higher than historical results of neoadjuvant chemotherapy (7). A higher response rate may allow better downstaging and respectability. A Swiss randomized study found higher objective response rate, lower progressive disease rate, more R0 resection, more nodal downstaging and more pCR in neoadjuvant chemoradiotherapy group than neoadjuvant chemotherapy group, although no statistically difference in survival was demonstrated between the 2 groups (8). This may be because this study mostly enrolled initially deemed operable patients. Marginally operable patients could possibly benefit more from the higher response rate of neoadjuvant chemoradiotherapy, since their operability was determined by a more effective response to induction therapy. For example, superior sulcus tumor typically is marginally operable and is a scenario that neoadjuvant chemoradiotherapy proved clinical benefit (9). Additionally, neoadjuvant chemoradiotherapy may have its advantage in stimulating anti-cancer immunity as compared to neoadjuvant chemotherapy alone (10).

In conclusion, the management of stage IIIA NSCLC remains controversial. A small retrospective study could not answer big questions. However, our treatment options were real-world personalized and safer. The phased CCRT protocol may suggest a more conservative radiation program in era of good systemic treatment and multimodality team approach. For instance, the dose of neoadjuvant CCRT may not need to exceed 40 Gy if surgery is scheduled, and a one-stage CCRT to 60Gy may not be better than a split-course program. We totally agree that incorporation of newer systemic agents (pemetrexed, targeted therapy, and immunotherapy) should be evaluated. Perhaps the story of further studies combining immunotherapy and other modalities may be encouraging.

Acknowledgements

Funding: The work was supported in part by a research grant (SKH-8302-106-DR-27) from the Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan.

Footnote

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

References

1. Yang KL, Chang YC, Ko HL, et al. Optimizing Survival of Patients With Marginally Operable Stage IIIA Non-Small-Cell Lung Cancer Receiving Chemoradiotherapy With or Without Surgery. Clin Lung Cancer 2016;17:550-7.
2. Ettinger DS, Wood DE, Akerley W, et al. Non-small cell lung cancer, version 1.2015. J Natl Compr Canc Netw 2014;12:1738-61.
3. Eberhardt WE, Pöttgen C, Gauler TC, et al. Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients With Resectable Stage IIIA(N2) and Selected IIIB Non-Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPATUE). J Clin Oncol 2015;33:4194-201.
4. Albain KS, Swann RS, Rusch VR, et al. Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for stage IIIA (pN2) non-small cell lung cancer (NSCLC): outcomes update of North American Intergroup 0139 (RTOG 9309). J Clin

Oncol 2005;23:7014.
5. Hoppe R, Phillips T, Roach M. Leibel and Phillips Textbook of Radiation On-cology-E-Book. Editors. Expert Consult: Elsevier Health Sciences, 2010.
6. Yokomise H, Gotoh M, Okamoto T, et al. Induction chemoradiotherapy (carboplatin-taxane and concurrent 50-Gy radiation) for bulky cN2, N3 non-small cell lung cancer. J Thorac Cardiovasc Surg 2007;133:1179-85.
7. Gottfried M, Ramlau R, Krzakowski M, et al. Cisplatin-based three drugs combination (NIP) as induction and adjuvant treatment in locally advanced non-small cell lung cancer: final results. J Thorac Oncol 2008;3:152-7.
8. Pless M, Stupp R, Ris HB, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. Lancet 2015;386:1049-56.
9. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol 2007;25:313-8.
10. Golden EB, Apetoh L. Radiotherapy and immunogenic cell death. Semin Radiat Oncol 2015;25:11-7.

Cite this article as: Yang KL, Jiang JS, Chi KH. Controversy and perspective in the management of marginally operable stage IIIA non-small cell lung cancer: response to Editorial by Charlotte Billiet and Dirk De Ruysscher and Editorial by Dr. Wanpu Yan and Dr. David R. Jones. J Thorac Dis 2017;9(9):E881-E883. doi: 10.21037/jtd.2017.08.112

