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.

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Footnote

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References


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