Editorial

Tri-modality treatment in N2 stage IIIa non-small cell lung cancer: proper sequence remains unknown

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Provenance: This is an invited Editorial commissioned by the Section Editor Mong-Wei Lin (Division of Thoracic Surgery, Department of Surgery, National Taiwan University Hospital and Taiwan University College of Medicine, Taipei).

Comment on: Francis S, Orton A, Stoddard G, *et al.* Sequencing of Postoperative Radiotherapy and Chemotherapy for Locally Advanced or Incompletely Resected Non-Small-Cell Lung Cancer. J Clin Oncol 2018;36:333-41.

Submitted Mar 02, 2018. Accepted for publication Mar 08, 2018.

doi: 10.21037/jtd.2018.03.69

View this article at: http://dx.doi.org/10.21037/jtd.2018.03.69

Pathologic stage IIIA non-small cell lung cancer (NSCLC) is a challenging disease to treat and the role of postoperative radiotherapy (PORT) in patients following resection remains controversial. The American Society for Radiation Oncology 2015 guideline stated the indication for adjuvant PORT in R0 resected N2 NSCLCs as it improves local control compared with observation strategy (1). Subsequently, an analysis of the National Cancer Data Base (NCDB) that was also published in the same year demonstrated an improved overall survival (OS) in pN2 patients who received PORT following complete resection and adjuvant chemotherapy (2). However, according to the up-to-date meta-analysis of this issue which reviewed patients from 11 trials, the addition of PORT to surgery brings detrimental effects to OS (3). Interestingly, there were no differences in outcomes of PORT by different nodal status (e.g., N2 disease), which makes the implication of PORT less compelling until further evidence shows up.

Besides, the optimal sequence is also not well established in the setting of PORT. By investigating the NCDB database, Francis *et al.* found that the median OS was significantly higher in R0 resected pN2 NSCLCs who received adjuvant chemotherapy and subsequent PORT when compared with those who received concurrent chemoradiation (CRT) (58.8 *vs.* 40.4 months) (4). However, such difference was not found in patients with R1 or R2 resection. Though anecdotal report had mentioned the use of PORT-first strategy before adjuvant chemotherapy, delivering PORT sequentially after chemotherapy remains the mainstream practice to avoid interfering with the well-established standard of care with adjuvant chemotherapy in node-positive NSCLCs (1,5). Moreover, starting PORT first may lead to delaying or even not performing postoperative chemotherapy due to related toxicity.

Modern radiation technique indicated that the 4 years actuarial intercurrent disease death rate of patients following PORT was 12.9%, which was insignificant from the expected rate of 10.1% (6). In the largest published randomised trial, Dautzenberg found that the use of fraction sizes >2 Gy resulted in a high risk of late toxicity (7). The National Comprehensive Cancer Network (NCCN) guideline currently recommends 50 to 54 Gy in 1.8 to 2 Gy fractions in PORT, compared with 60–70 Gy (2 Gy daily) for gross residual tumour (R2) undergoing CRT. To the best of our knowledge, there is no report on the comparison of postoperative concurrent CRT with postoperative sequential CRT. The reasons that CRT is inferior to sequential C→PORT strategy regarding OS for NSCLCs following R0 resection in Francis's report may derive from the higher rate of intercurrent disease death in the CRT arm, though this was not shown in such retrospective analysis (4). CRT appears to be a reasonable option in R1–2 patients since the risk of local failure is more significant in these patients, hence a definite treatment is warranted. Interestingly, the author noted an increasing trend of C→PORT for R0 pN2 patients whereas a decreasing trend

of CRT (4). On the contrary, a different pattern was noticed in R1–2 pN2 patients with concordance to the changes from guidelines.

There are problems that remain in the field of PORT. One of the frequently discussed issues is that the clinical target volume (CTV) varies widely among radiation-oncologists (8). One study from China had indicated that ipsilateral superior mediastinal recurrence was the dominated pattern of locoregional failure (9). However, for a left-side tumour, bilateral superior mediastinum was frequently involved. Such findings may have implications on the design of CTV for PORT. It seems reasonable to treat pathologically involved lymph node stations and uninvolved stations considered as high risk according to tumour location, to better protect surrounding normal structures and consequently minimise treatment-related mortality. In the ongoing Lung Adjuvant Radiotherapy Trial (LungART) trial (NCT00410683), the CTV includes the bronchial stump, the ipsilateral hilar node region, and any possible extension to the mediastinal pleura adjacent to the resected tumour bed (10). Also, the mediastinal CTV is to include all the lymph nodes that lie between two non-contiguous nodal stations that have contained metastases at any stage. In detail, subcarinal and ipsilateral paratracheal nodes are always included in the CTV. In the case of left-sided tumours, the sub- and para-aortic nodes should also be included. Interestingly, the proposed new staging system for lung cancer introduces three subgroups for the N2 category: N2 at a single station without N1 involvement, N2 at a single station with N1 involvement, and N2 at multiple stations (11). Further study is needed to determine if these would affect the elective nodal irradiation strategy of PORT.

For locally advanced NSCLCs who received neoadjuvant chemotherapy, questions remain upon the role of PORT following a successful operation, especially for those with histologically proven N2 disease before chemotherapy. If the mediastinal nodes achieved down-staging to pN0 or N1, will the PORT cause a detrimental effect on survival? Furthermore, with the recent trial proving the adjuvant application of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor following chemotherapy, the role of PORT for pN2 EGFR mutant NSCLCs could also be challenged in future studies.

Though CTV definition variation is inevitable in retrospective series, Francis *et al.* should be praised for drawing attention to the comparison of sequential versus concurrent PORT strategy. The results from LungART trial with modern PORT techniques are still awaiting and a positive impact of PORT on outcomes for patients with surgically resected pN2 could be expected to change the practice for this controversial stage.

Acknowledgements

None.

Footnote

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

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Cite this article as: Zhao ZR, Ng CS. Tri-modality treatment in N2 stage IIIa non-small cell lung cancer: proper sequence remains unknown. J Thorac Dis 2018;10(Suppl 9):S1096-S1098. doi: 10.21037/jtd.2018.03.69

