Letter to the Editor

Upfront surgery is essential in selected patients with stage IIIA non-small cell lung cancer

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Treatment strategy of stage IIIA non-small cell lung cancer (NSCLC) is one of the most challenging domains in thoracic oncology. Surgical interventions play a very important role in the multidisciplinary treatment strategy of stage IIIA NSCLC. In Fudan University Shanghai Cancer Center, from 2006, we developed an accurate and thorough diagnosis and treatment strategy for patients with locally advanced NSCLCs. Appropriate patients with stage IIIA were selected to receive upfront surgery followed by adjuvant therapy. Our data showed that these patients could achieve favorable surgical outcomes. The median progression-free survival (PFS) and overall survival (OS) were 17 months and 44 months, respectively. The 5-year PFS was 21% and the 5-year OS was 43%.

We publish our excellent results titled "Upfront surgery as first-line therapy in selected patients with stage IIIA non-small cell lung cancer" in *The Journal of Thoracic and Cardiovascular Surgery* (*JTCVS*) in 2017 (1). This article was widely spread and this topic has aroused extensive discussions. Professor Gaetano Rocco in Istituto Nazionale Tumori, IRCCS, Fondazione G. Pascale wrote an editorial commentary in *JTCVS* titled "Against the tide" to show that "*It is time to reconsider the role of upfront surgery in the multimodality treatment of locally advanced non-small cell lung cancer*". "*It shines a new light on the important role of surgery in the management of locally advanced lung cancer.*" He also emphasized "*the importance of the analyses of the resected mediastinal lymph nodes and the immunohistochemical profile of the tumor*". More importantly, "*our research questioned the old standards of care in oncology and forced thoracic surgeons to swim against the tide to propose and collaborate on new clinical trials focused on primary surgery for locally advanced lung cancer*" (2).

After this essential research, we further explored the complexity and heterogeneity of stage IIIA NSCLCs. Firstly, we constructed a quantitative tool (nomogram) to predict the prognosis of post-chemotherapy patients with resected stage IIIA NSCLC. In this research, we found that tumor size and positive lymph node count in both N1 group and N2 group were very important independent prognostic factors. And the count of the positive lymph nodes in N2 group was more important than that in N1 group. Nomograms including these factors could help doctors more easily estimate the prognosis and choose optimal decisions for the individual during clinical practices (3). Secondly, in the stage IIIA–N2 NSCLC subgroup, we investigate the role of post-operative radiotherapy (PORT). Using propensity score matching (PSM) method to balance the patients' characteristics, our data showed that for completely resected IIIA-N2 NSCLC, mediastinal lymph node metastasis and histologic subtypes could influence the effect of PORT. Single N2 station involvement and papillary predominant lung adenocarcinoma were predictors of benefit from PORT. In the same stage IIIA–N2 NSCLC subgroup, we also found that positive subcarinal

lymph node was an independent prognostic factor of OS. Patients with positive subcarinal lymph node had worse surgical outcomes. Therefore, we built a quantitative model which can preoperatively predict the subcarinal lymph node metastasis. This model can successfully select proper patients for upfront surgery which can bring more favorable surgical outcomes. On the other side, since neoadjuvant chemotherapy for stage IIIA NSCLC remained controversial, we extended our exploration areas and paid attention to compare the survival outcomes between neoadjuvant chemotherapy and adjuvant chemotherapy in stage IIIA NSCLC. We collected patients in the stage IIIA NSCLC subgroup who received preoperative chemotherapy followed by surgery and who received upfront surgery followed by adjuvant chemotherapy. After PSM analyses, our data demonstrated that both long-term and short-term clinical outcomes of neoadjuvant chemotherapy and adjuvant chemotherapy represented non-significant difference.

These researches derived from our primary research enriched our understanding of stage IIIA NSCLC, filled some gaps of stage IIIA NSCLC in this area, and further extended our research perspectives and topics on stage IIIA NSCLC. Although there is a lot of clinical evidence that contributed to developing the diagnosis and treatment strategy of stage IIIA NSCLC to date, we still hope that there will be more multi-center, large-sample, prospective randomized clinical trials to further confirm our findings and further refining the management of stage IIIA NSCLC in clinical practice.

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Footnote

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