Editorial

Editorial on "upfront surgery as first-line therapy in selected patients with stage IIIA non-small cell lung cancer"

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In many countries, lung cancer is still the leading cause of cancer deaths, as many patients are diagnosed with cancer at an advanced stage (III or IV). Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer cases. Treatment for patients with stage IIIA NSCLC remains one of the most challenging areas in thoracic surgery. During the last two decades, many clinical studies have focused on chemotherapy, radiotherapy, or chemoradiotherapy combined with or without surgery. However, optimal management of clinical stage IIIA NSCLC is still controversial in clinical practice (1).

Surgical indications of stage IIIA NSCLC have not been exactly proved and in a general way, only those who have had a complete resection will have a long-term survival (2). Even without induction therapy, some patients with discovered occasionally microscopic N2 lymph node metastasis could benefit from initial surgical resection (3). However, no definite and universally accepted guidelines exist for treating these patients. Therefore, it is necessary to the discover the certain patients with stage IIIA NSCLC who have better outcomes and who have the best chance of long-term survival with surgery. The article by Zheng and colleagues entitled "Upfront surgery as first-line therapy in selected patients with stage IIIA non–small cell lung cancer" is an important single-arm study to show that upfront surgery followed by adjuvant therapy may provide favorable survival outcomes for selected patients with IIIA NSCLC, especially for patients with adenocarcinoma (AD) or patients with clinical N0 and pathologic single-station N2 diseases (4).

The authors performed a retrospective analysis and obtained the records for patients with pIIIA (including T1-3N2, T3-4N1, T4N0) NSCLC from August 2006 to December 2013. A total of 668 patients with pIIIA NSCLC was employed who performed the surgery as first-line therapy. They provided an analysis of these patients' progression-free survival (PFS) and overall survival (OS), comparisons of the outcomes between patients with lung AD and SCC, also the clinical N2 and pathologic N2 Diseases and so on. It was surprising that the results showed the median PFS and OS were 17.0 and 44.0 months, respectively. Multivariate analysis showed age, smoking status, pathologic N2 status, margin, and adjuvant chemotherapy were independent prognostic factors with OS. The authors conclude that this high OS rate compared with some previous reports may provide evidence that upfront surgery play an important role in this the selected patients (5,6). But we should realize that their strategy was slightly different from the current guidelines (7). Based on these strict criteria, those patients who received neoadjuvant chemotherapy and/or radiotherapy prior to surgical resection were excluded from this study but these patients may lead to a worse prognosis.

The study showed that patients with single-station N2 had the significantly better PFS and OS than those with multistation N2. This result supports the eighth edition

of the TNM classification for lung cancer (8). The new edition of the TNM classification has proposed that N1 disease is subdivided into N1a and N1b, while N2 disease is subdivided into N2a1, N2a2 and N2b, which is according to single or multiple station involvement and with or without skip involvement because of obviously different effect on the prognosis. But to our knowledge, it should be clear that clinical N2 status does not always correspond with pathologic true N2 status. Many previous studies have already reported induction treatment followed by surgery maybe benefit the survival for some selected patients with IIIA/N2 NSCLC, especially for multi-station N2 involvement. Furthermore, stage pIIIA (T3N2) in the old edition of the TNM classification has already been classified into pIIIB in the new one, which may predict poor prognosis. So whether this subgroup of patients in this study should be treated with induction chemotherapy (9)?

This study is also subject to several other limitations. First, the comparison of median survival between present and previous studies is of little relevance, because most previous studies mainly concerned extensive N2 involvement while Zhang and colleagues included a majority of occult N2 disease, which has been demonstrated to have better survival (10). Second, the number of patients with T3–4N1 and T4N0 is extremely small (less than 10% of total population) in this study, and therefore, the conclusion may not be extrapolated to these patients. Third, the study revealed that postoperative adjuvant chemotherapy and radiotherapy were absolutely necessary for these patients. But it is lack of detailed therapeutic strategy like chemotherapy regiments and radiotherapy dose for patients which would impact tumor recurrence and the result of this study. Fourth, the study found that patients with AD had better 5-year OS than those with SCC and they found that patients with AD had a much better post recurrent-free survival (PRS) than those with SCC. But it is lack of post-recurrent treatment modality makes the comparison of PRS untenable.

In conclusion since patients with stage IIIA NSCLC represent several intrinsically heterogeneous subgroups, and the results of the study by Zheng and colleagues demonstrated that a subgroup of patients with pIIIA NSCLC who underwent upfront surgery as first-line therapy could greatly benefit from initial surgical resection even without induction treatment. How to identify and conduct these certain patients who may benefit most from upfront surgery may be of upmost importance. However, this is a retrospective and single-institution study without control groups as stated by the authors (4). Conclusions of this study are needed to be confirmed. So a prospective randomized trial and multicenter studies on this topic are warranted and further studies are still needed.

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Footnote

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

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