Editorial

Treatment of resectable stage IIIA non-small cell lung cancer

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Surgical treatment of stage IIIA non-small cell lung cancer (NSCLC) remains a controversial area in the management of lung cancer despite being considered as part of combined modality therapy over the last two decades (1). The heterogeneity of stage III disease and the need for a multidisciplinary approach adds complexity to the treatment of resectable stage III NSCLC. Prospective randomized trials including surgery have consistently faced problems in recruiting. Multicenter trials in different countries: the United Kingdom (2), USA (3), France (4) or Japan (5) were terminated early as a result of poor accrual. This may in part be due to the low frequency of suitable patients for surgical treatment. Two modern randomized studies have been published comparing concurrent chemoradiotherapy (CRT) treatments with and without surgery. In the Intergroup 0139 trial (6), patients with stage III N2 disease were treated with concurrent induction chemotherapy plus radiotherapy. If no progression occurred, patients in the surgical group underwent resection and those in the chemoradiation group continued radiotherapy. A total of 396 eligible patients were randomized and there were no differences in overall survival (OS) between the two groups. However, in an exploratory analysis, survival was improved for the patients who underwent lobectomy, but not pneumonectomy, compared with definitive concurrent chemoradiation. In the ESPATUE trial (7) patients with resectable stage IIIA N2 and selected stage IIIB NSCLC were randomized to surgery or definitive concurrent CRT boost after induction chemotherapy followed by concurrent CRT. A total of 245 eligible patients were recruited to induction therapy over a 10-year period, 161 of them were finally randomized to surgery or tailored dose-scaled CRT. It should be pointed out that 63% of those patients were stage IIIB. There was no difference in OS between the arms. Although both trials were planned to demonstrate superiority in the surgery arm, they failed to show any benefit from surgery in terms of OS. Consequently, definitive concurrent CRT is the only strategy which can be given category 1 recommendation for most stage III NSCLC patients.

The induction strategy for patients with stage III NSCLC who are deemed candidates for surgery is not well established. There is controversy on the benefit of the addition of radiation therapy to chemotherapy as part of induction therapy before surgery. Two large randomized phase III trials performed in Europe evaluate this issue. The German Lung Cancer Cooperative Group (8) randomized 524 stage IIIA/IIIB eligible NSCLC patients (36% of whom were T4N2 or TanyN3) to an induction treatment of sequential chemotherapy and concurrent CRT or to chemotherapy alone. Fifty four percent of the patients in the interventional group underwent resection versus 59% in the control group, but only 37% and 34% respectively, underwent complete resection. The addition of CRT to preoperative treatment resulted in an increase in pathological response rate (60% *vs.* 20%) and mediastinal downstaging (49% *vs.* 29%) in those patients completely resected but did not improve either disease-free survival (DFS), which was the primary end-point (median DFS: 9.5 *vs.* 10.0 months), or OS (median OS: 15.7 *vs.* 17.6 months). In another study the Swiss

Lung Cancer Project Group (9) randomized 232 patients with pathologically proven stage IIIA N2 NSCLC over an 11-year period. Patients were randomly assigned preoperative chemotherapy and sequential radiotherapy or preoperative chemotherapy alone. Eighty five percent of the patients in the interventional group and 82% in the control group underwent surgery. Complete resection, nodal downstaging and pathologic complete response were achieved in a similar proportion of patients who underwent surgery in the two groups (91% and 81%; 64% and 53% and 16% and 12%). There was no statistically significant difference in event-free survival (median EFS: 12.8 *vs.* 11.6 months) or OS (median OS: 37.1 *vs.* 26.2 months; HR =1.0) between the two induction treatments. Therefore, the survival benefit of the addition of radiation therapy to chemotherapy before surgery has not been substantiated in randomized controlled trials. A recent meta-analysis (10) involving 2,724 patients from 12 studies also showed that neoadjuvant chemoradiation (NCRT) improved pathological response and mediastinal tumor downstaging when compared with neoadjuvant chemotherapy alone in patients with resectable stage III NSCLC but could not demonstrate an increase in progression-free survival or OS.

Another meta-analysis (11) included 868 patients from six randomized controlled trials and compared definitive concurrent CRT to induction chemotherapy or concurrent CRT followed by surgery (bimodal or trimodal therapy) in patients with N2 disease. The HR for patients randomized to surgery after CRT was 0.87 (0.75–1.01, P=0.068), showing a survival benefit for trimodal therapy that did not reach the statistical level of significance.

Although in all patients with stage III considered for an induction approach followed by surgery it is imperative to obtain a pre-treatment surgical opinion on resectability, in some of these patients ultimately surgery becomes unfeasible. The probability of this event favors induction CRT over induction chemotherapy alone, since these patients will not have received local treatment and the delivery of adequate definitive CRT at this juncture may be compromised by the prior chemotherapy. Moreover, the optimal postoperative management of patients treated with bimodal or trimodal therapy has not been prospectively studied. In the majority of prospective randomized trials of induction chemotherapy, a high percentage of patients receive PORT, but there are no comparative data supporting its role.

The Intergroup 0139 trial (6) has been the base of current clinical practice with trimodal therapy for patients who present with stage IIIA N2 with limited or one level mediastinal disease and can be treated with a lobectomy, and this has been the preferred approach in this setting (12).

The optimal time interval from completion of chemoradiation therapy to surgery has not been established. The development of pulmonary injury associated with neoadjuvant concurrent CRT may result in early and late morbidity from surgery. The interval to surgery (ITS) following induction concurrent CRT has been empirically established as 4–6 weeks, short enough to reduce the likelihood of having developed pneumonitis or fibrosis at the time of surgery, but with a necessary interval of recovery to enable the patient to undergo surgery.

Gao *et al.* (13) studied the influence of different time intervals on the outcome of patients with stage IIIA N2 NSCLC and concluded that a time interval longer than 6 weeks was detrimental in terms of OS. The study was based on the National Cancer Data Base (NCDB), where they identified 1,623 patients with stage IIIA N2 NSCLC who underwent NCRT followed by surgery between 2004 and 2012. They categorized the study cohort in four intervals in weeks (from 0 to 12 weeks) between completion of NCRT (end of radiotherapy) and surgery: ITS quartiles. Median OS decreased significantly in the 9–12-week interval in the univariate analysis compared to the 0–3-week interval, and for both the 6–9-week interval and the 9–12-week interval in the multivariate analysis, which was adjusted for the surgical procedure (pneumonectomy or lobectomy) and radiation therapy dose, among other prognostic factors. Interestingly, there was no difference in 30 day-mortality between the first quartile and the other three, but there was a non-significant increase in 90-day mortality in patients with an ITS greater than 6 weeks.

This is the first study demonstrating a negative impact of prolonged ITS on survival, and advices against unnecessary delays in surgery. The results of this study should be interpreted with caution due to its retrospective nature which does not allow to control the selection in treatment allocation. In addition there is a lack of information on some tumor and treatment factors, as the mediastinal tumor burden or type and intensity of chemotherapy. These unknown variables may not be balanced among time interval groups.

Management of stage IIIA NSCLC continues to be challenging, there are no definitively proven optimal approaches and treatment selection in a multidisciplinary conference is of paramount importance. As we will not be able to rely on randomized controlled data to obtain evidence for every relevant detail of the complex trimodality

approach we will need to learn from large retrospective series and detailed comprehensive databases to improve treatment decisions.

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Footnote

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

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