Editorial

Neoadjuvant strategy for stage IIIA-N2 non-small cell lung cancer: chemoradiation or chemotherapy alone?

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This pooled study of two phase II trials (RTOG 0229 and 0839) aimed to assess safety and feasibility of anatomic resection following induction therapy with platinum-based chemotherapy and full-dose thoracic radiation for resectable N2 positive stage IIIA non-small cell lung cancer (NSCLC). And it concluded that lobectomy could be performed safely after full-dose concurrent chemoradiation. We would like to discuss this topic further from surgical point of view in the real world.

Stage III NSCLC comprises the most heterogeneous population of tumors in terms of clinical presentation and treatment options (1). There were tremendous debates and controversies regarding standard treatment strategy for potentially resectable stage IIIA-N2 disease (2,3). Before we could address which is the better neoadjuvant modality, the actual role of surgery in the multimodality treatment of stage IIIA-N2 NSCLC should be clarified. Given that the survival outcomes following chemoradiation have improved, surgery has faced a great challenge.

So far, three major randomized controlled trials which were performed in North America and Europe have compared surgery to radiation therapy after induction therapy. The first one was the EORTC 08941 trial, in which 579 patients with unresectable stage IIIA NSCLCs were first treated with 3 cycles of platinum-based chemotherapy before randomization into surgery or 6 weeks of radiotherapy (60 Gy) (4). Only 332 patients who responded to induction chemotherapy were included into the study. The results showed 5-year survivals between the two groups were of no difference (approximately 15%), but the locoregional relapse seemed to be more frequent in radiation group than surgery group (55% *vs.* 32%). Interestingly, pneumonectomy was performed in 47% of the patients in surgery group, and the 30-day mortality rates were 4% for the whole cohort and 7% after pneumonectomy. Complete resection rate was only achieved in 50% of the patients, while 40% received salvage radiation therapy. The North American Intergroup 0139 trial enrolled patients with T1-3N2M0 NSCLCs which were technically resectable. The patients were randomized into neoadjuvant chemoradiation followed by surgery and definitive chemoradiation (5). Finally, 202 patients were recruited in surgery group and 194 with definitive chemoradiation. Again, no significant survival benefit was provided by surgery. The 5-year survivals were 20.3% and 27.2% for radiotherapy and surgery, respectively. However, a further match pair analysis for this study was carried out, and it concluded that lobectomy actually offered better survival than radiotherapy, but pneumonectomy did not. The reason for this was that operative mortality was high, especially after right pneumonectomy (26%). The last trial was done in Germany, which was prematurely closed after just enrolling half of the patients. According to the protocol, patients with proven N2 disease in either stage IIIA or IIIB firstly received 3 cycles of induction chemotherapy followed by concurrent chemoradiation (45 Gy). And then, only the patients who were deemed to be resectable were randomly assigned into surgery or additional chemoradiation up to 65–71 Gy. In line with the previous two studies, there was no survival difference between the two arms, with 5-year survivals of 44% with surgery and 40% with chemoradiation respectively (6).

The current data did not provide us a clear message whether or not surgery was an indispensable component in the multimodality treatment for stage IIIA-N2 NSCLC. While there was no survival benefit identified, surgery was superior to radiation in terms of local control when complete resection was achieved. Furthermore, preliminary results demonstrated complete resection with lobectomy rather than pneumonectomy might lead to a better survival when compared with radiotherapy. Finally, incomplete resection is considered to be futile and should be avoided, since salvage radiotherapy has limited efficacy and increased toxicity. Therefore, the current consensus is induction therapy followed by surgery should be offered to a select subset of patients, after discussion in a multidisciplinary setting, incorporating input from medical, radiation, and surgical oncologists; the selection factors for this subset of patients include single-station N2 disease that was <3 cm prior to induction therapy, disease that can be resected via lobectomy rather than pneumonectomy, and disease that responded to induction therapy, as evidenced by clearance of mediastinal lymph nodes.

The next issue that needs to be addressed is the options for neoadjuvant strategy, chemoradiation or chemotherapy alone? There were several essential phase III clinical trials that attempted to answer this question. The first trial was reported by Thomas *et al.* in 2008. They enrolled 524 patients with stage IIIA or IIIB NSCLC, and randomized them into induction chemotherapy followed by surgery and adjuvant radiation (chemotherapy arm) or induction chemotherapy followed by an accelerated course of chemoradiation and surgery (chemoradiation arm) (7). R0 resection rates seemed to be higher in chemoradiation group (69.0% *vs.* 54.5%), but the difference was not significant. Interestingly, complete pathological response rate was significantly higher in chemoradiation group (41% *vs.* 11%); however, this advantage did not translate into a survival benefit. Five-year survivals were 16% in chemotherapy group and 14% in chemoradiation group. In addition, there was no significant difference regarding local progression rates between the two arms (62% *vs.* 50%). Because the radiation was given after surgery in chemotherapy group, this study was actually designed to compare thoracic radiotherapy in neoadjuvant and adjuvant settings. Another trial reported by Pless *et al.* in 2015 included 232 patients with stage IIIA diseases who were subsequently randomized into induction chemotherapy followed by surgery or same induction followed by sequential radiotherapy (44 Gy) and surgery (8). There was no significant difference between the two arms in terms of R0 resection rate, complete pathological response rate, 5-year survival and local progression rate. Similar results were also obtained by another two recent clinical trials (9,10). These studies delivered a message that adding radiation into neoadjuvant setting did not provide any survival benefit, although it did produce better complete pathological response rate and downstaging. Therefore, there was no recommendation for preoperative chemoradiation at this stage apart from Pancoast's tumor without mediational lymphadenopathy (11,12).

This latest pooled study of RTOG 0229 and 0839 trials had a new insight into the safety and feasibility of neoadjuvant therapy with concurrent chemotherapy and full-dose thoracic radiation. The study enrolled 118 patients with resectable IIIA-N2 NSCLC. Induction therapy consisted of weekly carboplatin [area under the curve (AUC) =2.0] and paclitaxel (50 mg/m^2) and concurrent radiotherapy 60.0 Gy in 30 fractions [0839]/61.2 Gy in 34 fractions [0229]. The results showed 91 patients received anatomic resection, including 81 lobectomy, 6 pneumonectomy, 3 bilobectomy and 1 sleeve lobectomy. R0 resection was achieved in 74 patients. Minimally invasive approach was attempted in 12 cases, but 2 of them were converted to thoracotomy. According to this part of data, radical resection after concurrent full-dose chemoradiation seemed to be technically feasible with complete resection rate up to 81%. Even thoracoscopic approach was reasonably manageable in selective cases with a low conversion rate. However, the major concerns were still those surgery-related ≥ grade 3 adverse events (AEs). It was reported that total rate of surgery-related AEs was 24%, pulmonary AEs happened in 17 cases (19%) and 30-day postoperative death 4 cases (4%). Not surprisingly, patients who received more extensive resections than a lobectomy had higher rates of ≥ grade 3 AEs (50% *vs.* 21%, P=0.06), ≥ grade 3 pulmonary AEs (50% *vs.* 15%, P=0.02), and mortality (30% *vs.* 1%, P=0.004). From surgical point of view, such a high morbidity and mortality rate is unbearable for thoracic surgeons. Although there was no direct head-to-head comparison in the literature, the usual morbidity and mortality data related to pulmonary resections in a thoracic center of excellence should be significantly lower than the above. It is fairly clear from the previous studies that the success of surgery for stage IIIA-N2 NSCLC heavily relied on surgery-related mortality control. The survival benefit from radical resection would be compromised by poor postoperative complication control. Moreover, concurrent full dose neoadjuvant chemoradiation might theoretically

offer better locoregional control from oncobiological point of view, unfortunately this advantage did not translate into long-term survival outcome. It is not unreasonable to suspect that the potential value of such an intensive regimen might have been neutralized by a high surgery-related mortality rate which was attributed by therapeutic toxicity, but more studies should be performed before a conclusion could be drawn. Considering there is so far no evidence to prove neoadjuvant chemoradiation could improve patients' survival than chemotherapy alone, we believe it would be unwise to add on radiation of any sort in preoperative setting.

In conclusion, although curative surgery is not universally suitable for every patient, we believe it is still an essential component of the multimodality management for stage IIIA-N2 NSCLCs. The recommended surgical strategy in current National Comprehensive Cancer Network (NCCN) guideline is neoadjuvant therapy followed by radical anatomic resection, which is considered to be an equivalent alternative to definitive chemoradiation in selected individuals. Given that adding on radiotherapy in neoadjuvant setting may not improve the survival outcome but increase the postoperative risks, induction chemotherapy alone would be a better option and should be recommended in clinical practice.

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Footnote

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

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