Unsuspected N2-positive non-small cell lung cancer after complete resection: is there a place for multimodal adjuvant therapy?

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Unsuspected N2 disease after surgical resection is found in a substantial proportion of patients with locally advanced non-small cell lung cancer (NSCLC) despite adequate preoperative mediastinal staging. This situation is challenging for clinicians, as optimal adjuvant strategies remain controversial and such patients are at risk of local recurrence and distant metastasis (1,2).

The recent article by Sun *et al.* published in *Journal of Thoracic Oncology* online, 26th September 2017, discusses the role of adjuvant treatment in completely resected unsuspected N2-positive NSCLC (3). This was a randomized phase II trial comparing concurrent chemoradiotherapy (CRT) with chemotherapy (CT) in 101 NSCLC patients, preoperatively staged N0-N1 and diagnosed with pathologic N2 disease after surgery with negative margins. In this trial, postoperative concurrent CRT failed to demonstrate a benefit over CT alone in terms of both median disease-free survival (DFS) {24.7 months for the concurrent CRT arm and 21.9 months for the CT arm [hazard ratio (HR) 0.94, 95% confidence interval (CI), 0.58–1.52, P=0.40]} and overall survival (OS) [74.3 months for the concurrent CRT arm and 83.5 months for the CT arm (HR 1.33, 95% CI, 0.71–2.49, P=0.38)]. Preoperative mediastinoscopy and/or endobronchial ultrasound was performed in 42 patients (41.6%). Interestingly, 17 patients (16.8%) did not undergo any invasive mediastinal staging procedure before surgery despite this being indicated. Also noteworthy was the low compliance rate in the concurrent CRT arm, suggesting that sequencing treatment modalities may be a reasonable option in this particular scenario.

The efficacy results from Sun *et al.* study contrast with those from another single institution randomized trial comparing concurrent CRT with CT alone in pathologic N2 NSCLC, demonstrating superior DFS and OS for concurrent CRT (4). This trial, however, was stopped early due to slow accrual.

Adjuvant platinum-based CT for completely resected NSCLC with nodal involvement improves OS and is currently considered the standard of care (5-8). In contrast, the use of postoperative radiotherapy (PORT) after successful R0 resection is still under debate. An early meta-analysis showed a detrimental effect of PORT on OS in patients with completely resected NSCLC, especially in N0-N1 tumors compared with N2 (9). Subsequent studies have demonstrated that PORT provides clinical benefit in N2-positive disease (10-14), and current guidelines support its use following individual risk assessment (7,8). A retrospective study in 334 patients with surgically removed pathologic N2 NSCLC identified a series of clinicopathologic variables, such as histology, T stage, number of N2 stations, extra-capsular extension and type

of surgery, for predicting patient outcome after receiving PORT (15). Randomized prospective data are needed in order to validate any risk score model predictive for efficacy in this situation. The ongoing phase III Lung ART trial comparing observation with conformal PORT may shed light on the benefit of PORT using modern techniques in operated NSCLC patients with histologically proven (previously suspected or otherwise) N2 disease. In this study, patients may receive CT either before or after surgery, but not during PORT (ClinicalTrials.gov identifier: NCT00410683) (16).

The use of CRT, although considered the definitive standard of care as for unresectable clinical N2 locally advanced NSCLC (7,17,18), is also somewhat controversial in the adjuvant setting for patients with completely resected pathologic N2 disease. The RTOG 9501 trial randomized these patients either to PORT alone or to concurrent CRT, demonstrating no survival benefit for the latter (19). Compared with these results, however, a multicenter retrospective analysis and two phase II non-randomized studies have reported favorable outcomes with the addition of CT to PORT in resected NSCLC (20-22). Sequencing CT and PORT in NSCLC patients with pathologic N2 disease after complete resection has been associated with superior OS compared with concurrent CRT in a recent retrospective analysis of nonrandomized data (23). Sequential adjuvant therapy is now becoming common practice for these patients, with less treatment-related toxicity. This is of vital importance, since we are referring to a specific population with preexisting comorbidities and surgical morbidity that confer a significant vulnerability to the demonstrated higher toxicity of concurrent CRT. Current guidelines recommend sequencing CT and PORT where both strategies are administered after complete resection in N2-positive NSCLC (7).

It seems quite clear that, when adequate preoperative mediastinal staging is carried out, patients with N2 involvement discovered during or after complete resection for NSCLC harbor microscopic rather than gross disease. Given the risk of recurrence, adjuvant CT improves OS in these patients but is still insufficient to provide optimal outcomes, and the addition of PORT, especially when delivered concurrently with CT, is associated with increased side effects and is not supported by reliable evidence at the present time.

As previously mentioned, improvement may be obtained through better individual risk stratification, conformal radiation delivery, sparing vasculature and cardiac function, and sequential use of PORT and CT.

Tailoring systemic adjuvant therapy might also be another approach to consider. The phase III prospective randomized SCAT trial tested selected adjuvant CT for completely resected pathologic N1-N2 NSCLC according to BRCA1 expression levels (24). In this trial, sequential PORT was planned for N2 disease. Although no significant differences in OS were observed within the experimental arms, CT with single agent taxane showed no inferiority compared with cisplatin doublets in patients with high levels of BRCA1. Also, in the era of immunotherapy, where the use of durvalumab (MEDI4736) for unresectable locally advanced NSCLC after previous treatment with CRT has already demonstrated superior DFS compared with placebo (25), the incorporation of immune checkpoint inhibitors in the adjuvant setting in NSCLC is being studied. The LINC (BR.31) is an ongoing phase III trial evaluating durvalumab compared with placebo after complete resection (and possibly adjuvant CT) in NSCLC (ClinicalTrials.gov identifier: NCT02273375). Other ongoing phase III trials of immune checkpoint inhibitors in the adjuvant setting for NSCLC patients after resection include the PEARLS and ANVIL trials (ClinicalTrials.gov identifiers: NCT02504372 and NCT02595944, respectively). A phase II trial investigating the safety and efficacy of adjuvant (and neoadjuvant) atezolizumab in resectable NSCLC is also currently recruiting patients (ClinicalTrials.gov identifier: NCT02927301). According to current knowledge, there is no role for targeted drugs in the adjuvant setting for NSCLC, and data from currently ongoing trials is required before their implementation in clinical practice.

In summary, the article by Sun *et al.* reinforces the idea that adjuvant concurrent CRT is not the preferred option for completely resected unsuspected N2-positive NSCLC. The authors are to be congratulated for conducting a randomized trial in such challenging disease setting. Optimal approaches for multimodal adjuvant therapy after complete resection of lymph node-involved NSCLC remain to be defined in the near future, and patient enrollment into clinical trials in this setting should be a priority.

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