Future directions in multimodality therapy for NSCLC

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Patients with stage III non-small-cell lung cancer comprise a heterogeneous population; the role of surgical resection in this setting has been controversial. Albain and colleagues recently demonstrated that trimodality therapy with lobectomy had clinical benefit for patients with pathologic nodal N2 stage III NSCLC.

The role of surgical resection in stage III non-small-cell lung cancer (NSCLC) is controversial, as the population of patients with this disease is rather heterogeneous. Albain et al. reported the results of a phase III trial that compared definitive concurrent chemotherapy and radiation to trimodality therapy with concurrent chemotherapy and radiation followed by surgical resection in 396 patients with pathologic nodal stage 2 (pN2) IIIA NSCLC.[1] The study results suggest that such patients may have a survival benefit from trimodality therapy if a lobectomy can be performed. These findings contradict those reported by van Meerbeeck et al., who did not find a survival benefit for trimodality therapy in any patients with pN2 stage III NSCLC.[2]

The trial by Albain et al. was an international, multicentre study that required pathologic proof of N2 disease, confirmation by a thoracic surgeon that tumours were resectable and exclusion of N3 disease (stage IIIB). In the intent-to-treat analysis, patients who received trimodality therapy had a median overall survival of 23.6 months compared with 22.2 months in the definitive chemoradiation arm (P=0.24). At five years, the absolute difference in survival between the two groups was 7%, in favour of the surgery arm. Although overall survival was not significantly different between the groups, median progression-free survival was better in the trimodality arm (12.8 months vs 10.5 months, P=0.017). The local relapse rate was 10% in the surgery arm, compared with 22% in patients who did not receive surgery, with the greatest effect on relapse achieved at the primary tumour site (2% vs 14%, respectively). Distant

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relapse rates did not differ between the two groups. One of the suggested reasons for the lack of improvement in overall survival, despite the enhanced progression-free survival, was the increased mortality in the trimodality arm after pneumonectomy compared with the chemoradiation arm; 14 of the 16 deaths in the trimodality arm occurred after pneumonectomy, whereas a total of four deaths occurred in the definitive chemoradiation arm. In an exploratory subgroup analysis, patients who underwent lobectomy had a significant overall survival benefit compared with a matched cohort in the chemoradiation arm (33.6 months vs 21.7 months, P=0.002).

The findings of this study have implications for two important surgical issues. First, patients who underwent pneumonectomy (especially right-sided) had significantly worse outcomes than those who were not surgically treated; the exploratory subgroup analysis reported a median survival of 18.9 months for such individuals, compared with 29.4 months in a matched cohort of patients who received chemoradiation alone. One should note that some of these pneumonectomies could have been avoided, as 13 (45%) of the 29 patients whose disease was downstaged to pT0N0 after concurrent chemoradiation had undergone pneumonectomy. Operative mortality with pneumonectomy was 26%. Although these results were from an exploratory matched-pair analysis that was not preplanned, the data suggest that pneumonectomy should be avoided after combined chemoradiation. Other studies, however, have reported much lower operative mortality for pneumonectomy after induction therapy. The reason for this discrepancy among clinical trials is not clear.[3]

Secondly, the trial by Albain et al.[1] supported the use of trimodality therapy in patients with solitary N2 disease who were candidates for lobectomy; however, the benefit was less clear in patients with multistation N2 disease. The subgroup analysis showed improved survival with trimodality therapy only if one N2 nodal station was involved, rather than multistation N2 disease. However, patients whose disease was downstaged to N0 after neoadjuvant therapy had the highest median overall survival (34.4 months); 76 of 164 patients who underwent thoracotomy were downstaged to N0. This finding seems to be independent of the number of nodal N2 stations originally involved before the administration of neoadjuvant therapy and, therefore, supports the use of surgical resection in patients with multistation N2 disease if neoadjuvant therapy accomplishes adequate downstaging. The median survival for patients with residual nodal disease following resection was 26 months, which suggests that these patients may also benefit from surgery if operative mortality is low. Future advances in survival for patients with pN2 stage IIIA disease, therefore, will be dependent on improvements in systemic therapy and in appropriate selection of patients for trimodality therapy.

In addition to defining the role of surgery in patients with stage III NSCLC, this trial also influences the future management of locoregional disease by suggesting that patients with downstaged N2 disease have superior survival. A similar survival benefit in patients with downstaged disease has previously been reported in other neoadjuvant trials.[2,4,5] Use of advanced systemic therapies, therefore, may lead to improved survival outcomes in these patients. Personalised medicine, or the selection of patients for specific systemic therapies, has already been embraced in the metastatic NSCLC setting. This approach could now be incorporated into the management of patients with locoregionally advanced disease, as selection criteria for most trials do not categorise NSCLC beyond disease extent and stage.

In the future, systemic treatment will be optimised according to tumour histology and molecular profiles, with the potential goal of replacing chemotherapy with novel targeted agents to limit toxic effects while improving efficacy. Molecular selection has been incorporated into the management of metastatic NSCLC – the selection of patients with EGFR mutations who are sensitive to receptor tyrosine kinase inhibitors (TKIs) has resulted in improved survival.[6] However, a prior study[7] of unselected patients with stage III NSCLC who were treated with epidermal growth factor receptor (EGFR) TKIs and radiation did not demonstrate a survival benefit.

Whether subgroups of patients with specific EGFR mutations would benefit from EGFR TKI-based therapy, therefore, remains unclear. Recently, patients with NSCLCs that expressed the EML–ALK4 fusion protein were shown to benefit from ALK inhibitor treatment[8], and insulin-like growth factor receptor inhibitors seem to work effectively in patients with squamous-cell-carcinoma histology.[9]

Whether these targeted agents should be administered alone, with chemotherapy, or with radiation therapy as neoadjuvant or combined definitive treatment remains unknown at this time.

The issue of what sequence of administration of therapy is optimal in the trimodality setting remains controversial. The German Lung Cancer Cooperative Group conducted a multicentre phase III trial in 558 patients with NSCLC that compared neoadjuvant chemotherapy with postoperative radiation therapy versus neoadjuvant chemoradiation. This study reported

increased mediastinal downstaging with chemoradiation, albeit without a difference in overall survival between the two arms.[5] Surgery after chemoradiation is more technically challenging than it is after chemotherapy alone, and carries a two- to three-fold higher operative mortality.[2,5] Neoadjuvant chemotherapy followed by restaging and surgical resection in a patient whose disease was successfully downstaged followed by adjuvant radiotherapy to the mediastinum is already commonly utilised in clinical practice. In the era of molecularly targeted therapies, whether bimodality neoadjuvant treatment is preferable to radiotherapy after surgical resection remains to be determined. The sequencing of therapy administration should be explored but only in parallel with identifying predictive biomarkers and utilising the appropriate targeted agents for maximum benefit.

Selection of patients for aggressive trimodality therapy is currently based on clinical prognostic factors, which are not ideal for identifying individuals who would benefit from treatment. Advances in prognostic molecular modelling need to be developed further and incorporated into the clinical management of patients with NSCLC.

One example is the Lung Metagene genomic profiling analysis, which may identify distinct populations of patients with stage IA NSCLC who have a high risk of disease recurrence despite surgical resection.[10]

Other genomic-profiling platforms are under investigation. These prognostic technologies must be incorporated into multimodality trials and validated to optimise therapy and identify patients who might require an aggressive approach to treatment. One potential future scenario would be to reserve trimodality therapy for patients with pN2 stage III NSCLC who have a high likelihood of disease recurrence according to these prognostic models, in whom the high risk of local recurrence would, therefore, justify the potential added risks of surgical resection in trimodality therapy. Patients whose tumours have a favourable prognostic molecular signature would receive definitive concurrent chemoradiation.

Based on the results of the Albain et al. study,[1] we believe that surgical resection (lobectomy) after neoadjuvant chemoradiation in medically fit patients with pN2 stage III NSCLC can be considered as a therapeutic option. Many US cancer centres already incorporate surgery after either neoadjuvant chemotherapy or chemoradiation for patients with pN2 NSCLC. Incorporation of novel targeted agents and predictive biomarkers to personalise systemic therapy is ultimately likely to improve clinical outcomes. Moreover, prognostic molecular models, such as those that involve genomics, may aid tailoring of how aggressive the multimodality therapy should be for each individual patient. These new technologies have the potential to enable further optimisation and refinement of treatment for patients with stage III NSCLC.

Practice point

Surgical resection (lobectomy) after neoadjuvant combined chemoradiation can be considered as a therapeutic option in medically fit patients with pN2 stage III NSCLC.

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