Radical local therapy in combination with standard treatment for oligometastatic stage IV non-small-cell lung cancer

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Recently, Gomez and colleagues reported the results of a randomized phase II study that aimed to assess progression-free survival (PFS) between aggressive local consolidation therapy versus maintenance therapy or observation in stage IV non-small cell lung cancer (NSCLC) patients with three or fewer metastases remaining after first-line systemic therapy (1). Although systemic therapy, including cytotoxic chemotherapy, and molecular targeted therapy are standard of care for stage IV NSCLC patients and improve overall survival (OS) and quality of life (QOL), stage IV NSCLC patients are generally considered to be incurable and mostly treated with a palliative intent. However, some patients once considered incurable sometimes seem to be potentially curable. One such example is patients with oligometastatic disease. Previous retrospective studies have suggested that a limited number of metastases was a positive prognostic factor in patients with metastatic NSCLC (2) and, in addition, aggressive local therapy has demonstrated survival benefits in patients with oligometastases compared with patients who have not received local therapy (3-5). Furthermore, several prospective studies have also shown clinical benefits of aggressive local therapy in patients with oligometastatic NSCLC. A prospective, single-arm phase II trial of surgery or radiotherapy in combination with systemic chemotherapy in 40 patients with one to five metastases was conducted by De Ruysscher *et al.* In this trial, median OS was 13.5 months and median PFS was 12.1 months (6). In another phase II study conducted by Iyengar *et al.*, 24 stage IV NSCLC patients with no more than six sites of extra-cranial disease who failed early systemic chemotherapy were treated with radiotherapy and concurrent erlotinib until disease progression. In this trial, the median PFS was 14.7 months and median OS was 20.4 months (7). These growing evidences have been recognized in the European Society For Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines, which recommend consideration of radical local treatment as an option for selected patients with oligometastatic disease (8,9).

Although these studies hypothesized that patients with oligometastases may be potentially curable when all detectable lesions can be radically treated with local treatment, such as surgery or radiotherapy, the definition of oligometastases varies between the studies (10-12). In addition, almost all the studies were in a non-randomized setting with a small sample size. The only randomized III trial to date was for NSCLC patients with oligometastases limited to brain metastases, demonstrating no clinical benefits of aggressive local therapy (13). Therefore, prospective randomized data supporting improved PFS or OS are lacking.

Here, with regard to Gomez's study (1), there were characteristic points compared with previous studies. First, oligometastases was defined as less than three lesions and

limited to the patients without progression after upfront systemic chemotherapy. This definition was not applied in previous studies, and this clinical scenario was applicable to the patients with curable intent. Second, this was the first randomized trial comparing the standard of care treatment group, that is, maintenance therapy or observation after first-line chemotherapy. Consequently, this trial demonstrated that local consolidative therapy improved PFS in patients with oligometastatic NSCLC who received induction systemic chemotherapy. The median PFS was 11.9 months (90% CI, 5.72–20.90) in the local consolidative therapy group, compared to 3.9 months (90% CI, 2.30–6.64) in the standard therapy group [HR 0.35 (90% CI, 0.18–0.66); P=0.0054]. Interestingly, time to the appearance of a new lesion was longer among patients in the local consolidative therapy group than among patients in the maintenance treatment group [11.9 months (90% CI, 5.7-not evaluable) *vs.* 5.7 months (95% CI, 3.1–7.0); P=0.0497]. Local consolidative therapy may also be able to increase the time to appearance of new sites of disease.

However, there are some limitations to Gomez's study. This study was initially planned for 94 patients; however, because of the benefits observed in the study group, the trial was stopped early. Thus, the study does not have the power to detect OS benefits, and crossover between both groups may have decreased these effects. Additionally, although the characteristics of both groups were well-balanced in this study, there were two ALK positive patients in the local consolidative therapy group compared with no ALK positive patients in the control group. It is evident that ALK-positive patients have significantly longer PFS by receiving ALK-inhibitors compared with cytotoxic chemotherapy (14), thus this imbalance would have influenced the improved PFS in the local consolidative therapy group.

Nonetheless, these results showed that NSCLC stage IV patients with oligometastases, defined as three or fewer lesions, may benefit from aggressive local therapy after standard chemotherapy. If validated in larger studies, the findings would report on both OS and QOL, and could represent a dramatic shift in clinical care for NSCLC patients. Although there were no considerations about immunotherapy in this study because immunotherapy was not standard therapy for stage IV NSCLC when this study was conducted, immunotherapy is markedly changing treatment strategies for NSCLC; therefore, we hope that further studies will be designed to include immunotherapy and make future findings more applicable to the treatment options available to patients.

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Footnote

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

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