Editorial

Ablative therapy in oligometastatic non-small cell lung cancer—an editorial on recent evidence

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Lung cancer is the leading cause of cancer-related mortality, and will account for 26% of all cancer deaths in 2017 (1). With approximately 40% of all patients diagnosed with non-small cell lung cancer (NSCLC) presenting with stage IV disease (2), the optimal management of metastatic disease is an important question. In patients with oligometastatic NSCLC, often defined as 1 to 3 or 1 to 5 sites of metastatic spread, there is significant controversy in treatment approach (3).

Historically, the management of metastatic NSCLC entailed cisplatin-based palliative chemotherapy and lead to a median overall survival of approximately 8 months (4). Local treatments including radiotherapy were reserved for the palliation of focal symptoms. Over the last several years, significant improvements in outcomes have been achieved with systemic agents in certain patient groups, such as those with anaplastic lymphoma kinase (*ALK*) gene rearrangements, epidermal growth factor receptor (EGFR) mutations, and overexpression of programmed death ligand 1 (PD-L1) (5-8).

In the oligometastatic setting, there has been a move to reconsider the role of local therapies. Initially proposed by Hellman and Weichselbaum in 1995 (9), it has been postulated that by ablating limited metastases, there may be an opportunity to achieve long-term survival (10), particularly in NSCLC where the majority of failures after systemic therapy are at known sites of disease (11). An individual patient meta-analysis of patients with oligometastatic NSCLC published by Ashworth *et al.* showed that patients who underwent ablative therapy to metastatic sites could achieve favourable survival rates, with better survival in those with metachronous disease and N0 disease at presentation (10).

The first randomized trial of local ablative therapy to all sites of disease in patients with oligometastatic NSCLC was published by Gomez *et al.* in 2016 (12). In this randomized multicenter phase II study, 49 patients with 3 or fewer metastases were treated with 4 cycles of platinum doublet chemotherapy or 3 months of EGFR or ALK inhibition depending on mutation status. Patients without progressive disease were then randomized to receive maintenance systemic therapy/observation with or without local consolidative therapy (LCT) with surgery or radiation. Though a sample size of 94 patients were required to meet the authors' stated 10% type I error and 90% power to detect a difference in progression free survival (PFS) of 3 months, the study was stopped early by the Data Safety Monitoring Committee due to a substantial difference in PFS in favour of LCT. Out of 74 enrolled patients, 49 were eligible for randomization at that time.

The median follow-up time was 12.4 months. PFS was significantly longer in the LCT group compared to the maintenance group (11.9 versus 3.9 months), with a hazard ratio of 0.35 (90% CI: 0.18–0.66, P=0.005).

Table 1 Differences in trial design and patient factors between two randomized phase II trials in oligometastatic NSCLC

Trial design factor	Gomez *et al.* (12)	Iyengar *et al.* (14)
Number of patients (accrued/planned)	49/94	29/36
EGFR or ALK mutations	Eligible	Ineligible
First line systemic therapy	Chemotherapy, EGFR inhibitor or ALK inhibitor	Chemotherapy
Number of metastatic sites	≤3 (including brain)	≤6 (not including brain)
Number of patients with brain metastases	13 (13.8%)	11 (30.5%)
Treatment of metastatic sites	Surgery and/or radiotherapy	Radiotherapy

NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

Subsequent analysis also showed that time to appearance of a new lesion was longer in those receiving LCT (11.9 *vs.* 5.7 months), perhaps suggesting that local therapy to sites of known disease may prevent or delay further seeding of new metastatic sites. The idea of metastatic sites seeding additional metastases has been observed in other cancers, such as in prostate cancer where this pattern of spread has been confirmed via genetic analysis (13). Overall survival data was immature and not reported. Significant missing data in quality of life measurements limited possible statistical comparisons, and therefore these results were not reported.

More recently, Iyengar *et al.* published a randomized phase II trial on the use of consolidative radiotherapy for oligometastatic NSCLC (14). In this trial, patients with up to 6 extracranial sites of metastases from NSCLC were treated with 4 to 6 cycles of platinum-based chemotherapy, and were then randomized to either stereotactic body radiotherapy (SBRT) followed by maintenance chemotherapy or maintenance chemotherapy alone. Due to the results from the trial by Gomez *et al.*, the Data Safety Monitoring Committee recommended an unplanned interim analysis at a point where 29 out of 36 patients had been enrolled. As a result, the trial was closed early due to a large difference in PFS favouring the SBRT arm. Median follow-up was 9.6 months. PFS was significantly longer in the SBRT arm compared to the maintenance alone arm (9.7 *vs.* 3.5 months), with a hazard ratio of 0.30, 95% CI: 0.113–0.815, P=0.01. No grade 4–5 toxicities were observed in the SBRT arm, and 1 grade 4 hematologic toxicity was seen in the maintenance chemotherapy alone arm. Median survival was not reached in the SBRT arm, and was 17 months in the maintenance alone arm. No differences in PFS or survival were seen comparing those with brain metastases to those without.

Some important clinical differences between these two phase II trials are summarized in *Table 1*. Statistically, the study by Iyengar *et al.* was designed with a lower power (80%), and to detect a larger difference in PFS (6 months), which is reflected in the lower number of patients planned for accrual. Additionally, the clinical eligibility criteria of patients on the trial by Gomez included features which are associated with more favorable prognosis, with patients eligible for enrollment having less metastatic burden, and potentially more favourable disease biology owing to EGFR/ALK mutations.

Taken together, these two prospective, randomized phase II trials represent important milestones in determining the efficacy of local ablative therapy to sites of oligometastatic disease in stage IV NSCLC. An observed improvement in PFS without significant increase in toxicity provides a good rationale for proceeding with additional studies investigating the effect of this approach on arguably more important outcomes such as overall survival and patient quality of life. One such study is NRG-LU002 (15), which is a phase II/III trial randomizing 300 patients to maintenance chemotherapy or SBRT to all sites of disease followed by maintenance chemotherapy. Eligible patients include those with oligometastatic NSCLC post-induction chemotherapy with 3 or fewer extracranial metastases. The phase III component is powered for overall survival, and quality of life is also being investigated as a secondary outcome.

Given the retrospective and randomized prospective data supporting the ablative treatment of oligometastatic disease in NSCLC, we believe eligible patients should be offered treatment on clinical trials if available. Off-trial, the management of carefully selected patients should be discussed in a multidisciplinary setting. Patients must be thoroughly consented before treatment as to potential

toxicities, as well as the uncertain benefit of this approach for either disease specific mortality or overall survival. The improvement in local control and progression free survival seen in past trials, as well as the potential to prolong the time to development of new metastases as seen by Gomez *et al.* (12), provide intriguing ideas on which to build future studies.

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Footnote

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

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7-30.
2. Morgensztern D, Ng SH, Gao F, et al. Trends in stage distribution for patients with non-small cell lung cancer: a National Cancer Database survey. J Thorac Oncol 2010;5:29-33.
3. Kennedy TA, Corkum MT, Louie AV. Stereotactic radiotherapy in oligometastatic cancer. Chin Clin Oncol 2017;6:S16.
4. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-8.
5. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
6. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385-94.
7. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-42.
8. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-8.
9. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol 1995;13:8-10.
10. Ashworth AB, Senan S, Palma DA, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. Clin Lung Cancer 2014;15:346-55.
11. Rusthoven KE, Hammerman SF, Kavanagh BD, et al. Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? A patterns-of-failure analysis. Acta Oncol 2009;48:578-83.
12. Gomez DR, Blumenschein GR Jr, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol 2016;17:1672-82.
13. Gundem G, Van Loo P, Kremeyer B, et al. The evolutionary history of lethal metastatic prostate cancer. Nature 2015;520:353-7.
14. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. JAMA Oncol 2018;4:e173501.
15. Maintenance Systemic Therapy Versus Consolidative Stereotactic Body Radiation Therapy (SBRT) Plus Maintenance Systemic Therapy for Limited Metastatic Non-Small Cell Lung Cancer (NSCLC): A Randomized Phase II/III Trial: clinicaltrials.gov; Available online: https://clinicaltrials.gov/ct2/show/NCT03137771

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