Editorial Commentary

Radical consolidative treatments a hope for patients with oligometastatic non-small cell lung cancer

Marcelo F. Jimenez, Maria T. Gomez-Hernandez

Service of Thoracic Surgery, Salamanca University Hospital, IBSAL, Salamanca, Spain

Correspondence to: Dr. Marcelo F. Jimenez. Service of Thoracic Surgery, Salamanca University Hospital, 37007 Salamanca, Spain. Email: mfjl@usal.es.

Provenance: This is an invited article commissioned by the Section Editor Laura Chiara Guglielmetti (Cantonal Hospital Winterthur, Kantonsspital Winterthur, Switzerland).

Comment on: Arrieta O, Barrón F, Maldonado F, *et al.* Radical consolidative treatment provides a clinical benefit and long-term survival in patients with synchronous oligometastatic non-small cell lung cancer: a phase II study. Lung Cancer 2019;130:67-75.

Submitted Jun 02, 2019. Accepted for publication Jul 09, 2019.
doi: 10.21037/jtd.2019.07.22
View this article at: http://dx.doi.org/10.21037/jtd.2019.07.22

Lung carcinoma is the second most common cancer diagnosis by gender, behind breast cancer for women and prostate cancer for men and ranks as the first cause of tumor-related death worldwide in both sexes. Moreover, lung cancer is not often diagnosed until advanced stage disease is present. According to literature, 84% of all lung cancer cases are non-small cell lung cancer (NSCLC) (1) and within this type the proportion of patients with distant metastasis at diagnosis ranges from 46.8% to 61.2% (2). Stage IV NSCLC has limited therapeutic options and prognosis is poor with a median survival up to 12 months (3); these patients are generally not indicated for radical local treatment with curable intent and the standard treatment choice is palliative systemic management including cytotoxic chemotherapy and targeted therapy. However, stage IV NSCLC is a heterogeneous entity which includes subgroups of patients with different biological behavior and prognosis.

In 1995, Hellman and Weichselbaum proposed the term "oligometastasis" (4), which refers to restricted tumour metastatic capacity and can be considered an intermediate state between limited primary cancer and systematic disease in which local therapy for eradication of metastatic lesions can result in satisfactory survival (5). In clinical practice, both synchronous and metachronous oligometastasis in NSCLC patients have occasionally been resected if the primary tumour is resectable or controllable and other nodal or distant metastasis are ruled out. Considering extrathoracic metastases, patients with singe extrathoracic metastasis have better prognosis than those with several metastases. In the light of this data, the 8th staging system of lung cancer re-categorized the metastatic status and clearly differentiated between: M1b (single extrathoracic metastasis in a single organ) and M1c (multiple extrathoracic metastases in a single or multiple organs) (6). The differentiation between M1b and M1c can help to better define oligometastasis and to identify a subgroup of patients that could benefit from a local aggressive treatment in addition to systemic treatment.

Most publications concerning management of oligometastatic disease in NSCLC are retrospective studies which have showed that oligometastatic cancers are less biologically aggressive (7,8) and some phase II studies (9,10) have demonstrated that radical consolidative treatment (RCT) following systemic therapy can improve progression-free survival (PFS). These findings advocated potential curative intent with local ablative treatments for consolidation in patients with oligometastatic disease. However, due to the lack of prospective randomised studies and the heterogeneity of patients included in the different trials because of the absence of a clear definition of the term oligometastasis, it remains unclear whether the RCT could potentially improve overall survival (OS) and PFS in synchronous oligometastatic NSCLC.

The article by Arrieta and colleagues (11) published in April 2019 in Lung Cancer tries to resolve this debated question. To do that, they have carefully designed and conducted a prospective, open-label, single-arm phase

II study to evaluate the efficacy and safety of RCT in patients with oligometastatic NSCLC. The study enrolled a total of 43 patients diagnosed with stage IV NSCLC who had ≤5 synchronous metastases in any-site, assessed by positron emission tomography–computed tomography (PET-CT). The treatment protocol of the study consisted of four initial cycles of systemic treatment. After that, six patients with complete response or progression of the disease were excluded of the trial and the remaining 37 cases with stable disease or partial response were discussed in a multidisciplinary cancer team meeting and the primary tumour and the metastasis sites were treated with radical curative intention. RCT included surgery, radiotherapy, chemoradiotherapy, stereotactic body radiotherapy and radiofrequency ablation therapy. The response to RCT was assessed with PET-CT. As primary end-point the authors investigated OS and PFS, safety, best response on PET/CT and patterns of failure were analyzed as secondary outcomes. After completing the treatment, 51.4% of patients achieved complete response assessed with PET/CT. The median follow-up was 32.5 months. The median OS for the entire population was not reached, nonetheless patients with metabolic complete response on PET/CT had a longer OS than those who did not achieve complete response (not reached *vs.* 27.4 months), although this difference was not statically significant. The median PFS for the entire population was 23.5 months; for patients with complete response, PFS was not reached; however, PFS was 14.3 months for patients with non-complete response; in this case differences were statically significant. Regarding safety, although 70.3% of patients experienced any adverse event related with RCT, most were grade 1 and 2, and no deaths related to treatment were observed.

Arrieta *et al.* (11) conclude that patients with synchronous oligometastatic disease who achieved a complete response after RCT on PET/CT have significant longer OS and PFS, rendering metabolic response assessed by PET/CT an important potential prognostic factor. Its main clinical message is that patients who received first-line systemic therapy and whose primary and metastases sites were treated with RCT have a high response rate and favorable OS.

This phase II study presents a homogenous population which included patients who met the criteria for synchronous oligometastatic disease (≤5 metastatic sites detected up to one month after the diagnosis of the primary tumour). Despite of the discrepancies in the definition of "oligometastasis", inclusion criteria and trial design, results are comparable and consistent with those of other similar clinical trials (12) and offer similar conclusions: RCT improves clinical outcomes in oligometastatic NSCLC patients.

In May 2019, the long-term results of a multi-institutional, phase II, randomized clinical trial by Gomez *et al.* (13) demonstrated significantly improvement of OS and PFS with aggressive consolidative treatment in patients with oligometastatic NSCLC. With an updated median follow-up of 38.8 months, they found that local consolidative therapy prolonged OS (41.2 *vs.* 17 months) and PFS (14.2 *vs.* 4.4 months) compared to maintenance therapy or observation in patients with oligometastatic NSCLC (up to three metastasis) who did not progress after front-line systemic treatment. Although PFS was shorter than that observed in Arrieta's study, survival after progression reached 37.6 months in the local consolidative treatment arm. The trial was early closed after 49 patients were randomly assigned because of a significant PFS benefit in the local consolidative treatment arm.

In relation with the high incidence of epidermal growth factor receptor (EGFR) mutation in Latin American patients and management of oligometastatic stage IV EGFR-mutant NSCLC disease, Xu *et al.* (14) investigated whether local consolidative therapy could improve the survival after treatment with first-line EGFR-tyrosine kinase inhibitor (TKI) therapy. The authors found that local ablative consolidative therapy to all metastatic sites significantly improved PFS and OS compared with local treatment to partial sites or observation alone.

Although more evidence is needed, the current evidence regarding the advantages of locally ablative therapies of oligometastatic disease has led to the introduction of this multimodality approach in some clinical practice guidelines (15,16). In this way, the European Society for Medical Oncology (15) states that patients with synchronous oligometastasis may benefit from RCT, however the level of evidence for this recommendation is merely IIIB. However, the level of evidence for the same recommendation stated by the updated NCCN guidelines (16) is IIA. Both guidelines encouraged to assess these patients in a multidisciplinary tumour board and to include them in clinical trials.

On the other hand, the use of PET/CT to assess therapeutic response in cancer patients has been widely investigated. So, in relation with NSCLC, in 2016, Shang *et al.* (17) compared the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, the European Organization for Research and Treatment of Cancer (EORTC) criteria and the Positron Emission Tomography Response Criteria

in Solid Tumors (PERCIST) 1.0 for response evaluation in patients with advanced NSCLC treated with chemotherapy. The authors concluded that EORTC criteria and PERCIST 1.0 have better sensibility and accuracy than RECIST 1.1 for the evaluation of an early therapeutic response to systemic therapy. Moreover, PERCIST 1.0 is preferred due to its detailed and well-defined criteria and its better correlation with patient outcomes. So that, PET/CT can be considered an ideal tool to evaluate treatment response and the effectiveness of new anti-tumoral therapies in patients with metastatic NSCLC.

All these findings have important implications for management of oligometastatic NSCLC disease in clinical practice and for the design of future randomized controlled trials. Further studies are needed to optimize treatment regimens of RCT, to identify clinical or molecular predictors for the selection of patients who will benefit more from RCT and to standardise assessment of response to treatment after therapy. Moreover, last generation targeted therapy agents should be included in these trials as part of the systemic therapy and their efficacy should be evaluated since they may improve outcomes in patients with positive molecular test.

Acknowledgments

None.

Footnote

Conflicts of Interest: MF Jimenez: Medtronic, Baxter and BD -Honoraria, Advisor. Another author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. Walters S, Maringe C, Coleman MP, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. Thorax 2013;68:551-64.
3. Kubota K, Kawahara M, Ogawara M, et al. Vinorelbine plus gemcitabine followed by docetaxel versus carboplatin plus paclitaxel in patients with advanced non-small-cell lung cancer: a randomised, open-label, phase III study. Lancet Oncol 2008;9:1135-42.
4. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol 1995;13:8-10.
5. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol 2011;8:378-82.
6. Eberhardt WE, Mitchell A, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the M descriptors in the forthcoming eighth edition of the TNM classification of lung cancer. J Thorac Oncol 2015;10:1515-22.
7. Hishida T, Nagai K, Yoshida J, et al. Is surgical resection indicated for a solitary non-small cell lung cancer recurrence? J Thorac Cardiovasc Surg 2006;131:838-42.
8. Yano T, Okamoto T, Haro A, et al. Local treatment of oligometastatic recurrence in patients with resected non-small cell lung cancer. Lung Cancer 2013;82:431-5.
9. Albain KS, Crowley JJ, LeBlanc M, et al. Survival determinants in extensive-stage non-small-cell lung cancer: the Southwest Oncology Group experience. J Clin Oncol 1991;9:1618-26.
10. Li D, Zhu X, Wang H, et al. Should aggressive thoracic therapy be performed in patients with synchronous oligometastatic nonsmall cell lung cancer? A meta-analysis. J Thorac Dis 2017;9:310-7.
11. Arrieta O, Barrón F, Maldonado F, et al. Radical consolidative treatment provides a clinical benefit and long-term survival in patients with synchronous oligometastatic non-small cell lung cancer: a phase II study. Lung Cancer 2019;130:67-75.
12. 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.
13. Gomez DR, Tang C, Zhang J, et al. Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: Long-term results of a multi-institutional, phase II, randomized study. J Clin Oncol 2019;37:1558-65.
14. Xu Q, Zhou F, Liu H, et al. Consolidative local ablative therapy improves the survival of patients with synchronous oligometastatic NSCLC harboring EGFR activating mutation treated with first-line EGFR-TKIs. J Thorac Oncol 2018;13:1383-92.
15. Planchard D, Popat S, Kerr K, et al., on behalf of ESMO Guidelines Committee. Metastatic nonsmall cell lung

cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann Oncol 2018;29:iv192-237.
16. National Comprehensive Cancer Network. Non-small lung cancer (version 4.2019). Available online: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed May 20, 2019.
17. Shang J, Ling X, Zhang L, et al. Comparison of RECIST, EORTC criteria and PERCIST for evaluation of early response to chemotherapy in patients with non-small-cell lung cancer. Eur J Nucl Med Mol Imaging 2016;43:1945-53.

Cite this article as: Jimenez MF, Gomez-Hernandez MT. Radical consolidative treatments a hope for patients with oligometastatic non-small cell lung cancer. J Thorac Dis 2019;11(Suppl 15):S1986-S1989. doi: 10.21037/jtd.2019.07.22

