Editorial Commentary

What is synchronous oligometastatic non-small cell lung cancer?

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Provenance: This is an invited article commissioned by the Section Editor, Xiaozheng Kang, MD (Department of Thoracic Surgery, Beijing Cancer Hospital, Peking University, Beijing, China).

Comment on: Dingemans AC, Hendriks LEL, Berghmans T, *et al*. Definition of synchronous oligometastatic non-small cell lung cancer-a consensus report. J Thorac Oncol 2019;14:2109-19.

Submitted Nov 05, 2019. Accepted for publication Dec 09, 2019.
doi: 10.21037/jtd.2019.12.44
View this article at: http://dx.doi.org/10.21037/jtd.2019.12.44

Lung cancer accounts for one-quarter of all cancer deaths and remains as the dominant contributor to cancer mortality despite steady, continuous decline in incidence (1). Management of non-small cell lung cancer (NSCLC), which accounts for approximately 85% of lung cancer, is therefore one of the most actively investigated fields to improve patient outcomes. As oligometastatic disease represents a status with limited metastatic burden with limited biologic potential for diffuse dissemination, local radical therapy to the metastatic site while controlling the primary disease is thought to offer a potential for prolonged disease control, survival and even cure. For oligometastatic NSCLC, two randomized phase II trials have shown progression-free survival benefit with local radical therapy, one of which also demonstrated an overall survival benefit (median survival of 41.2 *vs.* 17.0 months) in their updated report (2-4). There was also a retrospective study assessing 34,887 patients that showed an overall survival benefit with the addition of local treatment of metastases (5). As such, this strategy has gained tremendous interest, with the most studied approaches being surgical resection, stereotactic ablative radiotherapy (SABR), and thermal ablation. Although the concept of oligometastasis has been actively discussed for over two decades, identifying the patients that would benefit most from local treatment of oligometastases continues to pose a challenge across all primary diseases including NSCLC.

One of the difficulties around patient selection results from lack of a consistent definition of oligometastases within reported studies, which in turn is associated with several issues. The word oligo, by definition, indicates a few or limited number, but deciding on a maximum number can be arbitrary. Secondly, the time point at which the diagnosis of oligometastases is made has been variable. Although the time interval between the diagnosis or treatment of the primary tumor and the occurrence of metastases is a major prognostic factor and important in determining synchronous (metastasis present at the time of diagnosis of primary tumor) versus metachronous (metastasis detected separately after an interval of time) oligometastases, it is often difficult to determine with confidence, due to the variable frequency and type of imaging employed for initial staging and re-staging. Finally, there has been uncertainty regarding the most appropriate staging investigations, as well as the need for comprehensive pathologic confirmation of malignancy.

It is in this context that the European Organisation of Research and Treatment of Cancer (EORTC) Lung Cancer Group explored several controversial topics related to harmonizing definitions in synchronous oligometastatic non-small cell lung cancer (sOM-NSCLC) patients (6). They utilized a rigorous multistep process starting with a

systematic review of 21 papers based on 1,215 patients, in parallel with a survey of 423 physicians based on 10 real-life cases, followed by a meeting where consensus statements were proposed after reviewing the results of the systematic review, survey and group discussions.

The consensus report highlights that oligometastasis represents the stage where modification of the disease course is feasible, thus the definition of synchronous oligometastases would be relevant only when a radical treatment is technically feasible with acceptable toxicity, with all sites being amenable to local treatment. The specifics of the definition, the authors acknowledge, may be subject to criticism as there is limited prospective evidence. Nonetheless, they conclude that up to 5 lesions from 3 organs, with the exclusion of serosal surfaces and bone marrow, are acceptable. They define mediastinal disease as regional disease and that only M1a per TNM staging would be considered as sOM-NSCLC, while acknowledging that the overall treatment intent and modality may differ significantly depending on the location and burden. Mandatory staging investigations proposed by this consensus report includes positron emission tomography-computerized tomography (PET-CT), brain imaging [magnetic resonance imaging (MRI) preferred over CT], and pathologic confirmation of at least one metastasis (unless risks outweigh benefits). Mediastinal staging is proposed as an optional staging investigation, but required if it influences treatment strategy. For solitary liver metastasis and solitary pleural metastasis, MRI liver and thoracoscopy with biopsy of ipsilateral pleura, respectively, were advised to rule out additional metastasis.

One of the important accomplishments of this multidisciplinary collaborative work was defining the aim of treatment of oligometastatic disease. It indicates that the definition of sOM-NSCLC is relevant when all sites are technically amenable to local radical treatment in order to modify disease course for long-term disease control. The distinction of "long-term disease control" versus "potential cure" is important to compare and interpret studies to date and may affect the direction of future studies. For example, surgical studies that have aimed for cure have excluded patients with N2 regional disease since it has been established as a negative prognostic factor, and the American College of Chest Physicians recommended to limit curative intent treatments to those without N2 disease (7,8). For future trials that aim to assess long-term control, these patients with mediastinal disease may well be included, especially since that N staging is irrelevant to define sOM-NSCLC per both the 8th edition American Joint Committee on Cancer staging manual and this consensus report, and control of local disease could become more important in N2 disease with the improving systemic therapies (9).

The multidisciplinary group was not able to reach consensus on the acceptable number of metastases for the definition of oligometastases despite the multi-step design of the study. Different maximum numbers were suggested from different parts of this study: up to 3 per multidisciplinary survey, 4 per the real-life cases as this part of study was based on cases involving up to 4 metastases, and 5 based on the systematic review (10,11). It was noted that the majority of patients enrolled in the individual trials that were included in the systematic review had 1 or 2 metastatic lesions, even though up to 5 lesions were allowed. Nonetheless, a maximum of 5 metastases is proposed as the definition of sOM-NSCLC as this was supported by published data that aimed to assess the benefit of local consolidative therapy in NSCLC oligometastatic, including the earliest phase II trial (12). Of note, the two randomized phase II trials to date by Gomez *et al.* and Iyengar *et al.* included patients with up to 3 metastases (including brain) and up to 6 sites of extracranial disease (including primary), respectively, and PET-CT was not required (2-4). In light of both this work and a recent EORTC guideline recommending mandatory addition of brain imaging and PET-CT as part of imaging investigations and particularly recommending MRI brain (13), allowing up to 5 metastases may in fact capture the similar patient population as those previously included in earlier trials. This would also allow more patients to be eligible for metastasis-directed therapies as technical feasibility improves over time.

Complete (100%) consensus on imaging investigations for staging, unlike on the definition of sOM-NSCLC, indicates the improved availability of PET/CT and brain imaging options and their importance in proper staging for sOM-NSCLC. An additional consideration, for both better diagnosis and treatment planning, would be to use of thin slices for the MRI brain for brain metastasis and to obtain MRI whole spine for known spine oligometastasis. Mandating pathologic confirmation of at least one metastasis, unless the risk outweighs the benefit, would reduce the chance of incorrect diagnosis leading to inappropriate treatments, such as an ablative therapy for a benign entity or an insufficient treatment approach for a synchronous primary cancer.

Consensus reports and guidelines help standardize the

definition, diagnosis, investigations and assessment. They also guide future studies allowing easier data interpretation and comparison. On the other hand, when based on a small group of trials available to date, they may facilitate propagation of suboptimal patient selection via either insufficient or excessive inclusion of patient population thereby undermining the statistical power of study results. Consensus guidelines are also subject to change with emergence of new prospective data, improvement in technical feasibility, and discovery of novel biomarkers. For example, given the prognostic importance of driver mutations for metastatic NSCLC, it is possible that patients with epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) positivity may significantly benefit from metastasis-directed therapies for greater number of metastases compared to those without those driver mutations.

Looking forward, there is a growing interest in defining oligometastasis in patients with metachronous disease. Also known as oligorecurrence, metachronous metastasis describes a state where one or a few metastatic sites show progression while the primary and other metastatic sites remain controlled on systemic therapy. Oligoremnant (or oligoresidual) disease refers to an induced oligometastatic state where a former polymetastatic disease responded to initial treatments. With greater utilization of newer, effective systemic options for metastatic NSCLC, we will encounter these entities more frequently. Similar to sOM-NSCLC, we will need a consensus definition and recommendations for staging and treatment for both the primary and metastatic sites. Finally, we agree with the authors that development of a risk stratification system will help us manage patients with oligometastases effectively and consistently. In addition to the established prognostic factors such as age, performance status, histology and availability of targeted therapy, improvement of risk stratification would depend on continued efforts assessing the prognostic values of the total number of metastasis and involved organs, tumor size and volume, and newer genomic and molecular markers.

Acknowledgments

None

Footnote

Conflict of Interest: Shankar Siva reports grants from Varian Industries outside the submitted work. Alexander V. Louie reports personal fees from Varian Medical Systems Inc. outside the submitted work. The Department of Radiation Oncology at VU University Medical Center has a research collaboration with Varian Medical Systems. Simon S. Lo reports research support from Elekta AB in Elekta Gamma Knife ICON Expert Group outside of submitted work. The other authors have 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. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
2. 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.
3. 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.
4. 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.
5. Uhlig J, Case MD, Blasberg JD, et al. Comparison of survival rates after a combination of local treatment and systemic therapy vs systemic therapy alone for treatment of stage IV non-small cell lung cancer. JAMA Netw Open 2019;2:e199702.
6. Dingemans AC, Hendriks LEL, Berghmans T, et al. Definition of synchronous oligometastatic non-small cell lung cancer-a consensus report. J Thorac Oncol 2019;14:2109-19.
7. Johnson KK, Rosen JE, Salazar MC, et al. Outcomes of a highly selective surgical approach to oligometastatic lung cancer. Ann Thorac Surg 2016;102:1166-71.
8. Kozower BD, Larner JM, Detterbeck FC, et al. Special treatment issues in non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College

of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e369S-9S.
9. Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. J Thorac Oncol 2016;11:39-51.
10. Hendriks L, Dooms C, Berghmans T, et al. MA25.03 Defining oligometastatic non-small cell lung cancer (NSCLC): an evolving multidisciplinary expert opinion. J Thorac Oncol 2018;13:S446-7.
11. Giaj-Levra N, Giaj-Levra M, Durieux V, et al. Defining synchronous oligometastatic non-small cell lung cancer: a systematic review. J Thorac Oncol 2019;14:2053-61.
12. De Ruysscher D, Wanders R, van Baardwijk A, et al. Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (Nct01282450). J Thorac Oncol 2012;7:1547-55.
13. deSouza NM, Liu Y, Chiti A, et al. Strategies and technical challenges for imaging oligometastatic disease: recommendations from the European Organisation for Research and Treatment of Cancer imaging group. Eur J Cancer 2018;91:153-63.

Cite this article as: Cho CJ, Vellayappan BA, Dunne EM, Siva S, Liu M, Louie AV, Hanna GG, Lo SS. What is synchronous oligometastatic non-small cell lung cancer? J Thorac Dis 2019;11(12):5666-5669. doi: 10.21037/jtd.2019.12.44

