Oligometastatic non-small cell lung cancer (NSCLC)

Lung Cancer 139 (2020) 216–218

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Editorial

Oligometastatic non-small cell lung cancer (NSCLC): Does number of metastasis matter?

Synchronous oligometastatic (sOM) status is perceived as a distinct disease from polymetastatic presentation, with a potential higher overall survival (OS) probability when treated with local radical treatment (LRT).

Recently, the long-term outcomes of the practice changing phase II randomized trial on sOM non-small cell lung cancer (NSCLC) were published [1]. Forty-nine patients with up to 3 metastases (primary tumor excluded) after first line systemic therapy were randomized to either LRT (i.e. radiotherapy or surgery) to all disease sites or maintenance systemic therapy (MT)/observation (O). This trial demonstrated that LRT improved OS, median 41.2 months (95 % CI, 18.9 months to not reached) in LRT and 17.0 months (95 % CI, 10.1–39.8 months) in MT/O ($p = 0.017$). These results supported the integration of LRT in sOM-NSCLC and its implementation in daily clinical practice.

However, despite some consensus about sOM status, a uniform definition does not exist as reported in a systematic review performed by the European Organization for the Research and Treatment of Cancer (EORTC)

Table 1
Article included in the systematic review [2] and current literature [3,4].

Articles	Number of patients	Maximal number metastases defined	Maximal number of metastases treated	Patients with ≤ 2 metastases treated (%)	Patients with ≥ 3 metastases included (%)
Downey R. 2002	23	1	1	100%	0%
Khan A. 2006	23	2	2	100%	0%
Inoue St et al. 2010	25	5	5	N.A.	N.A.
Cheruvu P. 2011	38	8	8	N.A	N.A
Collaud S. 2012	29	1	1	100%	0%
Congedo M. 2012	53	2	2	100%	0%
De Ruysscher D. 2012	40	5	3	97.4%	2.6%
Lopez Guerra J. 2012	78	4	4	91%	9%
Griffioen G. 2013	61	3	3	96.7%	3.3%
Nieder C.S. 2014	23	3	2	100%	0%
Parikh R. 2014	186	5	5	74%	26%
Sheu T. 2014	90	3	3	88%	12%
Plones T. 2015	56	5	4	99%	1%
Su Ss. 2015	198	3	3	56%*	44%*
Xanthopoulos E. et al. 2015	25	4	4	84%	16%
Fleckenstein J. 2016	39	5	5	90%	10%
Johnson K. 2016	37	5	N.A.	N.A.	N.A.
Sakai Ks.2016	18	5	N.A.	N.A.	N.A.
Su Ss. 2016	91	4	N.A.	N.A.	N.A.
Iyengar P. 2017	29	5	3	93%**	7%
Gomez D. 2019	49	3	3	98%	2%
Bauml JM. 2019 [3]	51	4	4	94%	6%
Arrieta O. 2019 [4]	37	5	N.A.	65%	35%

*56 % with single metastasis, 44 % ≥ 2 metastases; ** 14 patients received a LCT (randomized trial); N.A.: not available.

https://doi.org/10.1016/j.lungcan.2019.11.005
Received 4 November 2019

lung cancer group (LCG) [2]. Specifically, EORTC (in collaboration with European Society for radiotherapy and oncology – ESTRO) is promoting an ongoing trial (E^2-RADIatE–OligoCare) including sOM and oligorecurrent patients with the primary outcome to identify patient, tumour (NSCLC, breast, prostate and colon-rectal cancers) staging and treatment characteristics impacting in OS.

About the systematic review, the aim was to provide an overview of sOM-NSCLC definition from reported series and trials [2]. The maximum number of metastases ranged from 1 to 8 in 21 selected articles [2]. Additionally, the definition of sOM-NSCLC in prospective clinical trials is also heterogeneous and vary between 1 and 6 [2–5]. Further, 74–100% of 1211 included in the systematic review patients had ≤ 2 metastatic sites. Furthermore, total numbers of metastases detected and treated were not described in 5 (24 %) studies, restricting clinical interpretation on the role of LRT (Table 1). In the recent randomized *Gomez et al.* trial, inclusion criteria allowed up to three metastases but the majority of patients (65 %) had only 0–1 [1].

Not surprisingly, the field is moving towards allowing higher number of metastases in clinical trials, as technically LRT is feasible for an increasing number of sites.

Recently, the EORTC-LCG published a consensus about the maximal number of metastases allowed to define sOM-NSCLC. Authors evaluated sOM-NSCLC definitions in daily clinical practice in Europe, by a survey and discussion of ten real life cases [7,8]. In the survey, the maximum number of metastases considered as sOM-NSCLC was again variable and 42 % of responders identified 3 as the correct definition [7]. Then analyzing real life cases, sOM-NSCLC was conservative and linked to radical intent of treatment. Members of the consensus meeting concluded that the maximum number of metastases is depending on the possibility to offer a LRT strategy [6].

Finally, based on the systematic review, most studies did not specify the local nodal status (N-status), although it is known that advanced N-status is associated with lower OS [7]. In the Gomez et al. trial, besides LRT, only number of metastases and presence of a driver alteration were associated with improved OS [1]. N2/N3 disease was non-significant in OS, probably due to the limited number of enrolled patients. As even, in *Gomez et al.* not all patients benefited from LRT and a correct selection is advocated. The ongoing SARON trial (NCT02417662) could provide answers, as patients will be stratified according to mediastinal N-status (N 0-1 vs N2-3), histology (adeno- vs non-adenocarcinoma), brain metastases (present vs absent) and number of oligometastatic sites (1 vs 2 vs 3). Other factors such as circulating tumour DNA and molecular signatures should be evaluated in future trials [10,11].

In order to select sOM-NSCLC patients, accurate radiological and pathological staging (preferably including molecular characterization) is needed [9]. Therefore, as described in EORTC articles [2,5], ^{18}FDG-PET-CT, brain MRI-scan and a possible pathological proof of a metastasis are necessary. The promising data about immunotherapy and radiation combination are inspiring new sOM-NSCLC trials, investigating the association of these treatments [3]. Hence, a single definition and recommended staging work-up are crucial.

The EORTC LCG approach is based on a secure methodology, because expert team carried out the systematic review, while survey and clinical cases discussion contributed on basic scenario about sOM-NSCLC treatment in Europe. Finally, a consensus meeting was held. Based on findings coming from the previous 3 steps, proposals were discussed and definitions were consensually agreed between scientific societies involved in lung cancer treatment (surgeon, pneumologist, radiation and medical oncologist) [6]. The EORTC LCG consensus definition is a good starting point for future clinical trials selecting the correct patient for the fit oncological treatment [5].

Contributors

All Authors contributed equally.

Declaration of Competing Interest

None.

References

[1] D.R. Gomez, C. Tang, J. Zhang, G.R. Blumenschein Jr, M. Hernandez, J.J. Lee, 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. 37 (2019) 1558–1565.

[2] N. Giaj-Levra, M. Giaj-Levra, V. Durieux, S. Novello, B. Besse, B. Hasan, et al., Defining synchronous oligometastatic non-small cell lung cancer: a systematic review, J. Thorac. Oncol. (2019), https://doi.org/10.1016/j.jtho.2019.05.037 [Epub ahead of print].

[3] J.M. Bauml, R. Mick, C. Ciunci, C. Aggarwal, C. Davis, T. Evans, et al., Pembrolizumab after completion of locally ablative therapy for oligometastatic non-small cell lung Cancer: a phase 2 trial, JAMA Oncol. (2019), https://doi.org/10.1001/jamaoncol.2019.1449 [Epub ahead of print].

[4] O. Arrieta, F. Barrón, F. Maldonado, L. Cabrera, J.F. Corona-Cruz, M. Blake, 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 130 (2019) 67–75.

[5] J. Conibear, B. Chia, Y. Ngai, A.T. Bates, N. Counsell, R. Patel, et al., Study protocol for the SARON trial: a multicentre, randomised controlled phase III trial comparing the addition of stereotactic ablative radiotherapy and radical radiotherapy with standard chemotherapy alone for oligometastatic non-small cell lung cancer, BMJ Open 8 (2018) e020690.

[6] A.C. Dingemans, L.E.L. Hendriks, T. Berghmans, A. Levy, B. Hasan, C. Faivre-Finn, et al., Definition of syncronous oligo-metastatic non-small cell lung cancer - a consensus report, J. Thorac. Oncol. (2019), https://doi.org/10.1016/j.jtho.2019.07.025 [Epub ahead of print].

[7] A. Levy, L.E.L. Hendriks, T. Berghmans, C. Faivre-Finn, M. GiajLevra, N. GiajLevra, et al., EORTC Lung Cancer group survey on the definition of NSCLC synchronous oligometastatic disease, Eur. J. Cancer 122 (2019) 109–114.

[8] L.E.L. Hendriks, C. Dooms, T. Berghmans, S. Novello, A. Levy, D. De Ruysscher, et al., Defining oligometastatic non-small cell lung cancer: a simulated multidisciplinary expert opinion, Eur. J. Cancer 23 (123) (2019) 28–35.

[9] N.M. deSouza, Y. Liu, A. Chiti, D. Oprea-Lager, G. Gebhart, B.E. Van Beers, 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 91 (2018) 153–163.
[10] A.B. Ashworth, S. Senan, D.A. Palma, M. Riquet, Y.C. Ahn, U. Ricardi, et al., An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligo-metastatic non-small-cell lung cancer, Clin. Lung Cancer 15 (2014) 346–355.
[11] A. Uppal, S.C. Wightman, S. Mallon, G. Oshima, S.P. Pitroda, Q. Zhang, et al., 14q32-encoded microRNAs mediate an oligometastatic phenotype, Oncotarget 6 (2015) 3540–3552.

Niccolò Giaj-Levra[a,b,*]
[a] *Department of Advanced Radiation Oncology, IRCCS Sacro Cuore Don Calabria Hospital, Negrar di Valpolicella, Italy*
[b] *Young Investigators European Organization for Research and Treatment of Cancer Lung Cancer Group, Brussels, Belgium*
E-mail address: niccolo.giajlevra@sacrocuore.it.

Matteo Giaj Levra[a,b]
[a] *Young Investigators European Organization for Research and Treatment of Cancer Lung Cancer Group, Brussels, Belgium*
[b] *Respiratory Oncology Unit, Department of Thoracic and Vascular Disease, CHU Grenoble Alpes, Grenoble, France*

Thierry Berghmans
Department of Intensive Care and Oncological Emergencies and Thoracic Oncology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

Silvia Novello
Oncology Department, University of Turin, AOU San Luigi, Orbassano, Italy

Lizza E. Hendriks[a,b]
[a] *Young Investigators European Organization for Research and Treatment of Cancer Lung Cancer Group, Brussels, Belgium*
[b] *Department of Pulmonary Diseases, GROW-School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands*

Antonin Levy[a,b]
[a] *Young Investigators European Organization for Research and Treatment of Cancer Lung Cancer Group, Brussels, Belgium*
[b] *Department of Radiation Oncology, Gustave Roussy, Institut d'Oncologie Thoracique, INSERM U1030, Université Paris-Saclay, F-94805, Villejuif, France*

Benjamin Besse
Department of Cancer Medicine, Gustave Roussy, Institut d'Oncologie Thoracique, Gustave Roussy, Université Paris-Saclay, F-94805, Villejuif, France

Anne-Marie C. Dingemans[a,b]
[a] *Department of Pulmonary Diseases, GROW-School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands*
[b] *Department of Pulmonary Diseases, Erasmus Medical Center, Rotterdam, the Netherlands*

[*] Corresponding author at: Department of Advanced Radiation Oncology, IRCCS Sacro Cuore Don Calabria Hospital, Negrar di Valpolicella, Italy.