Oligometastatic non-small cell lung cancer (NSCLC)

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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

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

*56% with single metastasis, 44% ≥ 2 metastases; ** 14 patients received a LCT (randomized trial); N.A.: not available.
lung cancer group (LCG) [2]. Specifically, EORTC (in collaboration with European Society for radiotherapy and oncology – ESTRO) is promoting an ongoing trial (E²-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], 18FDG-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].

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All Authors contributed equally.

Declaration of Competing Interest

None.

References


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