Editorial Commentary

Oligometastatic disease: a need for consensus to cure the incurable in a multidisciplinary approach

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For the last decades, one of the most attractive approaches in oncology is the addition of local consolidative therapies [such us surgery and radiation therapy (RT)] to systemic treatment in the context of oligometastatic disease (OMD) (1). This enables treating advanced stage cancer with curative attempt, since cure would be unlikely when patients are treated with systemic therapy only.

Evidence of benefits of this strategy has been arising since the latest years of the previous century, initially from patients with colorectal cancer or sarcoma (2,3). From that point, further evidences have been incorporated to the clinical practice guidelines for several cancer types (colorectal cancer, soft tissue sarcomas, neuroendocrine tumors, etc.), which recommend combining systemic therapy with local treatments to all metastatic sites in case of OMD when feasible (4-6). However, others believe that a more indolent biology (rather than local treatments) could explain the more favorable results observed. It has also been questioned whether the oligometastatic state can be cured (7).

In non-small cell lung cancer (NSCLC), new modalities of RT such us stereotactic body RT (SBRT)/stereotactic ablative RT (SABR) as well as minimally invasive surgery approaches (such as video-assisted and robotic surgery) and sublobar resections have changed the landscape of local treatments, improving outcomes while reducing side effects (8-10). Recent clinical trials have provided evidence that adding local therapy to systemic therapy in OMD NSCLC may improve progression-free survival (PFS) (11-14) and even overall survival (OS) (11,13,14). Patients included were diagnosed with both oncogene-addicted disease (11,13,14) and non-oncogene-addicted disease (12-14).

In this context, the American Society for Radiation Oncology (ASTRO) and the European Society for Radiotherapy and Oncology (ESTRO) have developed a joint clinical practice guideline for the management of OMD in NSCLC (15). This clinical practice guideline provides recommendations about how to select patients for definitive local therapies according to patient and disease characteristics, how to choose the local treatment modality, how to sequence the different therapies, how to design the RT treatment and about when to consider local treatments at progressive disease (15).

Management of OMD in NSCLC presents some difficulties. First, OMD is a very heterogeneous scenario. Patients can present oligometastatic lesions at diagnosis or during systemic treatment at a limited number of sites (oligoprogression), or the persistence of a limited number of metastatic lesions (oligopersistent). Patients can also

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present growth of a limited number of metastatic deposits in patients off systemic therapy (oligorecurrence) (16). Moreover, there is a lack of evidence when treating patients with OMD NSCLC that do not completely fit in the inclusion criteria of clinical trials (different number or location of metastatic lesions, previous use of local treatments, or the use of local treatments different from RT), and there is absence of results from randomized clinical trial (RCT) since the widespread use of first-line immunotherapy (11-14). That is why, among the whole clinical practice guideline, some fundamental strategies are highlighted (15): the need for a multidisciplinary approach, enabling individualized consideration of each patient case and integration of all specialties' points of view; the pertinence of shared decision-making prioritizing patients preferences; the balancing between outcomes and toxicity, with special consideration about symptomatic lesions (local treatments in these cases also include a palliative approach); and the equity in the treatment application to avoid health disparities around the world.

Regarding selection of patients for definite approaches, the guideline acknowledges that, although OMD is believed to have a different biology than poly-metastatic disease, no biomarker has been described so far, so the definition of OMD relies completely in imaging technics. That is why all efforts are recommended to be made at the staging work-up, including pathological confirmation of the metastases when feasible. Special consideration deserves the presence of synchronous or metachronous second lung nodes, being difficult to differ between isolated metastasis and a second primary tumor; in this scenario, pathological confirmation becomes even more important. The guideline underlines the clear benefit in selecting patients with 1–2 metastatic lesions for definite therapy, even if central nervous system (CNS) is affected, although whether if the primary tumor should be considered within the number of lesions to define OMD is unknown (15). However, the benefit is less clear when locally treating 3–5 lesions, since most patients included in clinical trials presented less than three lesions (11-14). The presence of pleural, pericardial or peritoneal metastases is considered to be not suitable for definite treatment, although new focal therapies such us hyperthermic chemotherapy associated with surgery are arising and these may be reconsidered in a near future (17). Finally, the guideline recommends adding local therapy according to the number and location of metastatic lesions, irrespective of the presence of a driver mutation: this is based on the findings of a RCT of patients treated with first generation epidermal grow factor receptor tyrosine kinase inhibitors (EGFR TKI) (11). However, a new generation of targeted therapies with significantly improved outcomes has been developed (18,19) and local therapy should also be weighted in this context, especially in patients with higher number of lesions.

When considering which modality of local therapy choose to treat OMD, the guideline favors RT since the majority of patients included in clinical trials were treated with SBRT instead of surgery (11-14). Moreover, surgery often requires a recovery period that may imply a delay or interruption of other crucial therapies. However, surgery may be considered when SBRT exceeds the maximum dose of radiation in healthy tissues, when a lung lesion is large and/or central, when the patient presents inflammatory diseases that may imply a higher risk of toxicity or when pathological confirmation is needed (13,20-22). Specifically for pulmonary metastases, when surgery is considered, the guideline advices against extensive resections and recommends to avoid pneumonectomy and to consider for example sublobar resections when feasible (in terms of size and location), extrapolating data form recent clinical trials including patients with peripheral, small size primary lung cancer (9,10).

It is important to note that these recommendations are based in general principles of treatment in primary tumors, but there are no comparative studies between surgery and SBRT in oligometastatic lesions, so multidisciplinary discussion and shared decision-making with the patient are again crucial. Prospective validation of these decision-guiding principles may ensure to select the more appropriate local therapy in each particular subset of patients.

In terms of sequencing local and systemic therapies, the guideline recommends the administration of systemic therapy before any local consolidative therapy, except in the presence of a symptomatic lesion. This approach allows selecting patients which will not benefit from local therapy because of either a progressive disease or a complete response; and also due to the fact that most of the clinical trials were designed with at least 3 months of systemic therapy before local therapy (12-14). There is only one study with first generation EGFR TKI that planned local therapy before systemic therapy (11), and that is why this guideline does not support this sequence. As a result, individual consideration in a case-by-case basis may be even more appropriate in oncogene-addicted NSCLC due to the heterogeneity of these diseases and the previously

mentioned improvements with new generation targeted therapies (18,19). A different issue emerges considering patients without oncogene-addicted NSCLC due to the fact that immunotherapy has become the cornerstone of first-line therapy, and 3 months of treatment may not be enough time to evaluate the control of disease since there are different patterns of response such us pseudoprogression, with known lesions initially gaining size before displaying stabilization or improvement (23). It is important to underline that a disease progression after 3 months of systemic therapy may translate an aggressive biology of the disease, so upfront local consolidative therapy would not imply a curative strategy since the polymetastatic progression would also occur (and probably sooner) if systemic therapy is delayed to deliver local therapies first. Moreover, although local therapies may still be technically feasible when progression affects exclusively known metastatic sites during the first 3 months of upfront systemic therapy, second line systemic therapy may be more appropriate to pursue disease control before proceeding with local therapies.

Additionally, local consolidative therapy may not be necessary in patients with a complete response, due to the good prognosis of these patients, especially with novel systemic therapies (18,19,24,25). However, in case of progression after a complete response there is little evidence about if these progressions occur at initial or at new metastatic sites: if progression occurs at initial metastatic sites, consolidative local therapy may be beneficial.

Regarding the technical aspects of RT regimen, to ensure local control the guideline suggests adapting the total dose depending on whether systemic therapy is combined or not (11,12,14), underlining again the importance of multidisciplinary discussion of these cases. The guideline also recommends the use of the latest technology in both treatment planning, using advanced dose calculation algorithms, and treatment implementation, specially mitigating respiratory movements using four-dimensional (4D) computed tomography (CT), fluoroscopy or magnetic resonance (MR)-cine (26). While some of these technologies are often available in some regions, efforts should be made to ensure worldwide equity in the access of these and other upcoming breaking-edge technologies.

Finally, in the oligoprogressive disease setting, in addition to previous considerations it should be taking to account the time from previous definite therapies, the feasibility of administering one or more local therapies safely and the availability of further systemic therapy (15). Since there are more factors to consider and the evidence available is even more scarce, multidisciplinary discussion and shared decision-making are again mandatory to crack this "and more difficult still" scenario.

In conclusion, this guideline summarizes available evidence in the local consolidative treatment of OMD, provides evidence-based recommendations and points out the knowledge gaps that exist in the field. Joint collaborative initiatives between different international scientific societies, such us this document, are essential for this purpose. To reach consensus in OMD, further efforts should involve other specialties such us surgical oncology and medical oncology societies, as well as pathology and imaging representatives.

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