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Oligometastatic Disease and Metastasis-Directed Radiotherapy: A Partnership for an Innovative Palliative Approach

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1. Introduction

"Oligometastatic" disease (OMD) has been proposed as an intermediate state between localised and widespread systemic disease [1]. In OMD patients with different tumor types/histologies, early published studies show improved clinical outcome when radical local therapy as surgery or metastasis-directed radiotherapy (MDRT) are administered [2-6]. Unfortunately, neither OMD specific biomarkers nor prospectively validated prognostic scoring systems yet exist so it remains impossible to identify patients with truly limited metastatic capacity, who might really benefit from such a radical approach [7]. The current definition of oligometastatic status is based solely on the number of metastases (less than 3-5) on high resolution imaging findings. Therefore, a PET/CT, contrast-enhanced chest/abdominal and pelvis CT scans, and/or MRI of brain or spine are necessary for case by case diagnostic evaluation [2-6].

The MDRT is generally administered with 3 to 5 fractions of high-dose stereotactic body radiotherapy (SBRT) or with high single dose brain radiosurgery (SRS). Both SBRT and SRS allow to administer a so called ablative external beam doses to the tumor sparing the surrounding healthy tissues by a rapid fall of dose outside the target. The "ablative effect" associated to the high-dose of radiation delivered (at least 8Gy) overcome the possible intrinsic few tumor cell radio sensitivity because ablates tumor directly and induces indirect effects, including vascular endothelial injury and immune activation [8]. This approach is performed with the help of high resolution image-guided procedures which can either visualize and locate the target itself and anatomical structures that are closely correlated to the target. There are various

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possible modalities to give this special radiotherapy technique with the majority of the available modern radiotherapy machines [5, 9].

2. ESTRO-ASTRO Consensus Document

Oligometastatic disease is a broad status that might consist of patients with very different prognoses and treatment options. For example, a patient with oligometastatic lung carcinoma at diagnosis, and a patient with an initial, polymetastatic lung carcinoma and residual oligometastatic disease after first-line systemic therapy, both fall under the same definition of OMD, although being very different from a clinical perspective [10]. To account for the different time points in the history of oligometastatic patients, a consensus document on OMD and MDRT has been proposed by an international panel of the European and American Associations of Radiation Oncology (ESTRO-ASTRO) experts. Studies published on the topic were reviewed and discussed according to Delphi process [11, 12]. Sixteen statements were analysed. We report topics which can result more useful for all physicians interested in cancer care leaving out the topics of strictly specialized relevance.

There was a total agreement between experts on the concept that MDRT of OMD is independent of primary tumor type, histology and metastatic site. Diagnostic imaging (such as CT scan, MRI, PET/CT) should be performed using whichever modalities are most adequate to image sites of common metastases and to detect small lesions for that histology [11].

The maximal number of metastases, the maximal lesion size and number of involved organs to consider a patient oligometastatic are yet unknown. However, the consensus agreed that 5 lesions, a maximum cut-off size of 5 cm and single/limited number of organs should be considered an upper bound off-protocol. It is important to note that the number of OMD can exceed 5 in case of brain disease and SRS can be successfully administered also when 6-10 metastases are present to give an ablative dose and avoid patient possible cognitive deficits associated with whole brain irradiation [13-15]. This topic was not careful analysed in this consensus but the suggestion to consider both SBRT and SRS in future trials was provided [11].

Regarding definition of OMD with respect to the interval between primary cancer diagnosis and development of OMD, the panel suggested following classification. “Synchronous” OMD arises at the time of initial diagnosis, that is, primary tumor and limited number of metastases are detected simultaneously. “Metachronous” OMD or “oligorecurrence” occur during the course of disease at least 3 months after the initial diagnosis, in other words, metastases detected while the primary tumor is controlled and that can be treated with directed local therapy. A metachronous OMD can be an “oligoprogression” if few lesions progress on a background of widespread but stable metastatic disease, or an “oligopersistence” when there is persistent disease after systemic therapy (“induced” OMD after systemic therapy) [11].

Overall survival (OS), disease-free survival (DFS) or progression-free survival (PFS), local control (LC), toxicity, quality of life (QoL), patient-reported outcome measures, cost, delay or deferral of systemic therapy and ability to stay on the same line of systemic therapy are all considered important endpoints [11]. In the literature, efficacy of treatment for OMD is measured by various parameters, OS, PFS, LC and toxicity being most frequent. In particular, MDRT in oligometastatic patients resulted well tolerated, no time consuming and generally not associated to relevant iatrogenic toxicity. Unfortunately, QoL is infrequently considered in published studies [2-6, 9, 10, 13-15].

In addition to the above classification of OMD, another consensus recommendation has been recently published by EORTC (European Organization of Research and Therapy in Cancer) jointly with ESTRO [16]. Basically, there are no differences between the classifications and recommendations of the two panels except for the time interval necessary to define metachronous OMD, which was at least 3 months after the initial diagnosis of disease for ESTRO-ASTRO and 6 months for EORTC-ESTRO consensus proposals. Another notion clearly reported by EORTC-ESTRO consensus recommendation was the existence of "repeat" OMD, namely, diagnosis of a new and growing or re-growing oligometastasis which can be treated more than one time with metastasis-directed therapy [11, 16-19].

3. Conclusion

The new clinical evidence of OMD condition, together with the possibility that MDRT improves patient clinical outcome, is an appealing issue in part already verified in many trials. The need for other prospective trials to gain a more solid evidence was shared in ESTRO-ASTRO consensus document and EORTC-ESTRO consensus recommendation which concluded that the prognostic value of reported statements will be assessed in the ongoing OligoCare prospective cohort trial (*NCT03818503, ClinicalTrials.gov*).

As in the Virgilio's poetry verse (*fama vires acquirit eundo*) regarding the fame which grows the more it walks (i.e., it spreads), also the partnership between OMD and MDRT can grow over time as an innovative approach for cancer patient palliation.

4. Declarations

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- Conceptualization: Ernesto Maranzano
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