Editorial Commentary

The heterogeneity in oligoprogression and stereotactic body radiation therapy

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Light from the sun, that is, "white light", has a uniform color and appears natural to the human eye, but when it is passed through a prism, a "spectrum" of different colors appears.

In 1995, Hermann and Weichselbaum proposed the "spectrum theory", which stated that cancer is continuous like the spectrum of light, ranging from a localized state with no metastasis to a state with multiple and extensive metastases; they named the intermediate metastatic state with few lesions as "oligometastasis" (1). Oligometastasis is a concept that appears to be uniform throughout, like white light, but encompasses a variety of states, and "Oligo-" diseases have since been proposed for a variety of clinical scenarios (2,3). Among these, oligoprogression is a relatively new concept that emerged around 2010.

Oligometastases and oligoprogression: their distinct nature

The concept of oligoprogression has been proposed with the development of highly effective systemic therapies such as molecularly targeted drugs that target driver gene mutations, translocations, and immune checkpoint inhibitors. Oligoprogression is distinct from genuine oligometastatic disease (OMD), as originally defined by Hellman and Weichselbaum (1,4). Oligoprogressive disease (OPD) arises within the context of polymetastatic disease (PMD).

Oligoprogression is a condition in which many lesions respond to systemic therapy and disappear; however, a small number of lesions become resistant and enlarge owing to the heterogeneity of metastatic sites (2).

This heterogeneity is attributed to the accumulation of somatic mutations in drug-resistant cells that survive systemic therapy. Genetic heterogeneity has been reported in many cancers (5). For example, in breast cancer, mutation loads have been shown to be higher in metastatic lesions compared to primary tumors within the same patient, with distinct driver mutations observed in metastatic sites. These genetic differences contribute to the metastatic potential and prognosis of breast cancer (6). The inherent genetic variability and evolutionary dynamics, therefore, underline the heterogeneity observed in OPD.

In such situations, clinicians face difficulties in deciding whether to continue the current systemic therapy or switch to a potentially less effective agent (7).

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Metastasis-directed therapy (MDT), a local therapy aimed at eradicating specific metastatic lesions, may prolong disease control and extend the duration of time for which patients can continue their current effective systemic therapy by eradicating drug-resistant clones in OPD (8,9). The advantages of stereotactic body radiation therapy (SBRT) as an MDT for oligoprogression are high local efficacy, minimal interruption of systemic therapy, the ability to treat patients on an outpatient basis, convenience in fewer fractions, and often minimal side effects.

SBRT curbs OPD

It is still unclear as to which patients with oligoprogression will benefit from SBRT. Oligoprogression has only been studied in retrospective or single-arm prospective trials; however, in 2023, the Consolidative Use of Radiotherapy to Block (CURB) trial, the first open-label, randomized, phase II trial investigating the efficacy of SBRT in patients with oligoprogression, was published (10).

The "CURB trial", published by Tsai *et al.*, is an influential study that demonstrates the importance of identifying oligoprogressive lesions for which SBRT is effective. The results of this study showed that the addition of SBRT in patients with OPD prolonged progression-free survival (PFS) compared to that in patients treated with standard therapy alone. Particularly, the addition of SBRT in patients with non-small cell lung cancer (NSCLC) extended the median PFS by more than 4 folds, indicating that SBRT is an effective local treatment for OPD. In contrast, no benefits were observed in patients with breast cancer.

The reason for the difference between the lung and breast cancer groups in the CURB trial remains unclear. However, key contributing factors may include greater tumor heterogeneity in breast cancer patients (e.g., differences in subtypes and drug sensitivity), a higher number of prior treatments, and more extensive pre-existing metastases. Therefore, regardless of the use of SBRT, it is possible that tumor biology and drug-resistant clones in breast cancer patients became more diverse, leading to further disease progression.

Is SBRT really ineffective for the oligoprogression of breast cancer?

In contrast to the results of the CURB trial, the AVATAR trial (11), a multicenter, prospective, single-arm, phase II trial presented at the 2023 American Society for Radiation Oncology (ASTRO) Annual Meeting, demonstrated the benefit of SBRT in patients with oligoprogressive breast cancer.

There is a common factor underlying the differences in the results between the AVATAR and CURB trials, as well as the differences in the treatment efficacy of SBRT for NSCLC and breast cancer, as demonstrated in the CURB trial.

The AVATAR trial included only hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer subtypes. In contrast, the CURB trial included all subtypes with a particularly high proportion (34%) of patients with triple-negative breast cancer (TNBC). Compared to those of HR-positive/HER2-negative and HER2-positive breast cancers, TNBC is a subtype with fewer systemic therapy options, lower effectiveness, a higher likelihood of early relapse, and greater difficulty in treatment. In other words, patients with breast cancer in the CURB trial included a higher number of subtypes with higher biological grades, which may have affected the treatment outcomes.

Regarding the number of prior systemic therapies, in the AVATAR trial, patients received only 1–2 lines of prior therapy [endocrine therapy alone or endocrine therapy + cyclin-dependent kinase (CDK) 4/6 inhibitors], whereas in the CURB trial, patients with breast cancer received more systemic therapies; the median number of therapies for the standard therapy and SBRT groups in the CURB trial was four and three, respectively (one *vs.* two in patients with NSCLC).

Additionally, the CURB trial included a smaller proportion of patients with *de novo* metastases (breast cancer, 17%; lung cancer, 53%), and many patients with breast cancer did not respond to multiple chemotherapy regimens.

Therefore, some patients with breast cancer in the CURB trial may have been close to PMD and were not ideal candidates for SBRT (12). In contrast, the introduction of SBRT at an early stage in OPD, before it progressed to PMD, appears to be associated with better outcomes.

Is metastasis count a valid prism?

No biomarker clearly distinguishes OMD from PMD, and the number of progressive lesions on imaging is commonly used as a criterion. In their consensus definition of OMD, the European Society for Radiotherapy and Oncology

(ESTRO) and the ASTRO set the maximum number of extracranial OMD at five. Currently, most studies consider 1–5 lesions as a criterion (4).

In contrast, studies on oligometastasis have reported that total tumor burden influences treatment outcomes (6,13). Although tumor volume is an important factor in the management and prognosis of metastatic disease, it has not been adequately addressed in many studies and consensus documents (6).

According to the latest National Comprehensive Cancer Network (NCCN) guidelines, the indication for the treatment of intracranial oligometastases is based on tumor burden rather than the number of metastases (14). Intracranial oligometastases have been studied before extracranial regions, demonstrating the efficacy of MDT. Therefore, the results of the MDT for cerebral OMD may be useful while considering MDT for OMD in other regions.

The role of stereotactic surgery (SRS) in fewer than four oligometastases has already been established because of its potential for long-term tumor control and reduced late toxicity (15). Although <4 metastases have been recommended for stereotactic irradiation, the results of a multicenter gamma knife study published in the JLGK0901 trial in 2014 reported no difference in survival or adverse events for 5–10 brain metastases compared to that for 2–4 brain metastases (16).

Based on the JLGK0901 trial, the concepts of "limited brain metastasis" and "extensive brain metastasis" were adopted in the 2018 NCCN guidelines. Limited brain metastasis is defined as a group of patients for whom SRS is equally effective and offers significant cognitive protection compared with whole-brain radiation therapy. Moreover, the definition of limited brain metastases in terms of the number of metastases or total intracranial disease volume is evolving and may depend on the specific clinical situation (14).

According to the JLGK0901 study inclusion criteria (≤10 tumors, largest tumor <10 mL in volume and <3 cm in longest diameter, total cumulative volume ≤15 mL and Karnofsky performance status score ≥70) (16), two metastases with diameters of 2.6 and 2.2 cm would result in a total volume of approximately 15 mL. Conversely, if there were 10 foci measuring <1 cm in diameter, the total tumor volume would be only approximately 5 mL, and irradiation would be possible on a volumetric basis; however, the treatment of >10 foci was not indicated in the JLGK0901 trial. Therefore, the definition of limited brain metastases varies depending on the patient's clinical situation.

Although extrapolating these findings to extracranial OPD, the tumor burden that can be safely treated with SBRT needs to be considered, even in extracranial areas. Additionally, it is important to clarify the optimal conditions for SBRT that can facilitate safe delivery according to metastatic lesions.

Optimal dose of SBRT: control and safety

SBRT has high rates of local control (70–90%) and safety against oligometastases (17). However, the appropriate dose fractionation of radiotherapy as an MDT for oligoprogression has not yet been established.

Although the results of several randomized controlled trials comparing irradiation doses have been reported, no consistent view has been reached (12,18,19). The ESTRO-ASTRO consensus document stated that although there are insufficient reports on the appropriate dose or biological equivalent dose (BED), a BED of 10 (BED_{10}), assuming an α/β ratio of 10, ≥100 Gy should be aimed for when possible until new data are available (4).

However, this BED_{10} ≥100 Gy is the standard SBRT curative dose reported by Onishi *et al.* for early-stage lung cancer and maybe a high SBRT dose when considering the treatment goal of OPD (20). A retrospective study by Nicosia *et al.* evaluated the efficacy of SBRT in 79 patients with oligoprogression (9). In this study, the median BED_{10} score was 78. A BED_{10} >70 resulted in a 90% control rate of local progression, whereas it was 74.2% when the BED_{10} was <70.

In the CURB study (10), the dose fractions used were 27–30 Gy/3 fractions [58 lesions (52%)] and 30–50 Gy/5 fractions [21 lesions (19%)], with BED_{10} values ranging from 51.3–60 and 48–100, respectively. A larger proportion of patients in the CURB study could have been treated with lower $BEDs_{10}$ than those mentioned above, which may have affected the efficacy of SBRT. In contrast, the CURB study protocol recommends doses of BED_{10} ≥70 for all lesions and states that lower doses of ≥50 Gy are acceptable at the discretion of the treating physician if there is concern for normal tissue toxicity.

Oligoprogression may require higher doses depending on the histology. Indeed, patients with oligoprogressive breast cancer require higher doses of SBRT to achieve local control outcomes comparable to those in patients with oligometastases (12). However, the role of SBRT in the clinical management of OPD is to prolong disease control

by eradicating treatment-resistant disease and extending the duration of current systemic therapy (21). Therefore, while using SBRT for OPD, treatment-related toxicity must be considered rather than trying to increase the treatment intensity as much as possible.

In the CURB study (10), most patients did not experience serious adverse events; however, grade 2 or higher adverse events occurred in 41% (21 patients) of the standard care group and 62% (34 patients) of the SBRT group. In addition, 16% (9 patients) of the SBRT group experienced grade 2 or higher SBRT-related toxicity, mostly including hematologic toxicity (lymphopenia and anemia) and one case of grade 3 radiation pneumonitis in the SBRT group.

The Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases (SABR-COMET) trial (22), one of the largest clinical trials to date, demonstrated that SBRT can extend overall survival (OS) in oligometastatic or oligoprogressive cancers of various primary tumors and that 4.5% of patients experience grade 5 radiation-related toxicity, even with strict dose limits and careful radiation planning. Although this incidence appears to be higher than that reported in other studies (23,24), SBRT can cause serious side effects depending on the tumor volume and location. The establishment of appropriate dose fractions and dose constraints that balance therapeutic efficacy and safety is required.

The BED is defined as $BED = nd \times [1 + d/(\alpha/\beta)]$ (n: number of fractions, d: dose per fraction). The α/β ratio represents the dose at which linear and quadratic cell killing are equal for a given tissue. The α/β of normal tissue is 3, whereas the α/β of tumors is generally considered to be 10. BED_{10} represents the BED of α/β 10.

A holistic perspective on OPD

There is no uniform definition for the site of metastases in OPD. One of the main concerns is that there is no clear rule for the inclusion of brain metastases in OPD. Because of the different nature of brain metastases compared to metastases at other sites and the fact that MDT has been actively performed for brain OMD in the past, the treatment of brain metastases in oligometastases has not been established.

For example, the ESTRO-ASTRO and ESTRO-European Organization for Research and Treatment of Cancer (EORTC) consensus systematic reviews excluded OMD only for brain metastases (2,4). Conversely, the SABR-COMET trial included brain metastases as an OMD (22).

The CURB trial targeted EXTRACRANIAL oligoprogression. In the CURB trial, patients with brain metastases prior to enrolment received standard brain radiation (either whole-brain radiotherapy or stereotactic radiotherapy) (10). In this study, 21 (19.8%) patients [breast cancer, 12 (25.5%); NSCLC, 9 (15.2%)] had brain metastases at enrollment. In the CURB study, brain metastases may have influenced the outcomes.

Historically, the prognosis of patients with brain metastases has been poor. However, with the recent development of third-generation tyrosine kinase inhibitors (e.g., osimertinib) and stereotactic radiotherapy, patients with brain metastases may have a favorable disease course. Up to 30% of patients with cancer develop brain metastases during the disease course (25). Additionally, patients with oligoprogression may experience intracranial and/or extracranial oligoprogression. Therefore, it is important to consider multidisciplinary management from a holistic perspective in the management of OPD.

Conclusions

The CURB trial demonstrated that SBRT for OPD can prolong PFS and potentially OS, shedding new light on future OPD research. However, the trial also highlighted that the heterogeneity of the study cohort, in terms of cancer biology and treatment status, may complicate the evaluation of the benefits of MDT for OPD. This highlights the need for future research to clearly define the status of OPD, further stratify risks for specific cancers and patient groups, and focus on studying more homogeneous patient populations.

Recently, reports of SBRT for oligoprogression have increased; however, there is still insufficient data to confirm the efficacy of SBRT in OPD. In the future, the optimal treatment strategy should be determined from a holistic perspective, defining oligoprogression and optimal treatment for each OPD condition (primary cancer type, histology, subtype, number of metastases, tumor burden, and metastatic site). The development of biomarkers to discriminate between PMD and OPD and the optimal conditions for SBRT are topics for further study.

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