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Editorial

Oligometastasis: More Lessons to Be Learned

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The first use the term "oligometastasis' in the literature was done by Hellman and Weichselbaum, who also built its concept as "the status between localized and widely metastatic" [1]. Though not all previous trials that evaluated the role of local aggressive treatment (LAT) in oligometastatic settings were affirmative, it cannot be denied that LAT has a strong tendency of improving clinical outcomes, which was elucidated through the effort of Oligometastasis Working Group of Korea Cancer Association [2]. As the meaning of the prefix "oligo-", with Latin origin, contains "few, small, or little" in number, the definition of oligometastasis has mostly been based on the metastatic lesion number, and most clinical trials, in fact, have adopted the number-based definition. The metastatic state, however, is more of a spectrum from none to numerous, and an exact cut-off number defining the oligometastatic status [3].

In this issue, Tan and Palma [4] summarized "10 lessons learned from clinical trials on oligometastasis", and suggested that, instead of the metastatic lesion number per se, the possibility of benefit to the patients by applying LAT should be more importantly considered. Since there should have existed a few practical limitations in counting the actual metastatic lesion number even with the most up-to-date diagnostic imaging studies. There has been no single perfect imaging modality, and all have varying ranges of false-negative and false-positive rates in almost all real-world clinical situations. The usually proposed numbers, therefore, are not the absolute criteria with "all or none" magic, but could usually serve as the useful guidance to the clinicians who encounter some important decision points. One of the extreme example has been elucidated in the National Comprehensive Cancer Network guideline for the management of metastatic brain tumors [5], in which the "limited metastasis" has been defined mainly based on the applicability of radiosurgery instead of whole-brain radiation therapy, while notwithstanding the number of metastatic lesions detected. In addition, shortly following the acceptance of Tan and Palma's review article on our journal, a substudy of the SABR-COMET-10 trial [6], ongoing randomized phase 3 trial that intends to assess the stereotactic ablative radiation therapy (SABR) effect in the patients having 4 to 10 metastatic lesions, was published. These authors have already started recruiting the patients with larger lesion number than the previously reports, which limitedly recruited those with 3 or 5 lesions [7-9], and found that the planning outcomes of the first 60 patients were within minimal compromise of dose constraints. This could serve another endorsement to the Tan and Palma's speculation. The simple counting the metastatic lesion number may not have as great critical significance when compared with the past era. This trend of broader criteria of oligometastasis may have been possible in close relation with the wide availability of highly reliable, safe, and effective LAT modalities as well as systemic therapy regimens. We need to move forward from the number-based to more practical and clinically relevant definition of oligometastasis in order to give improved outcomes to more candidates of LAT. Other factors than the metastatic lesion number to be considered in this refinement effort may include the tumor size [10,11]. 3-Dimensional tumor volume [12], and the velocity of tumor progression [13], respectively. Moreover, there may also be some unique underlying biologic features in the oligometastatic patients, which need our continuous investigation efforts [3].

Among several LAT modalities in treating the oligometastatic patients, SABR has the most accumulated evidence. In long-term analysis of SABR-COMET trial [14], SABR has proven as a curative option leading to durable overall and progression-free survival benefits without excess major toxicity risk to a subgroup of oligometastatic patients. There are, however, several unsolved issues regarding the SABR use. First, the optimal timing of SABR application along with systemic treatment course has not been established. Some trials applied SABR following systemic treatment, while another delivered SABR prior to systemic

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treatment [7,8,15]. This treatment sequence may need to be tailored based on the clinical situation and the available systemic regimens. For example, reducing tumor burden by SABR before applying immune checkpoint inhibitors may be beneficial [10,11]. On the contrary, reducing the tumor burden with systemic regimen may be desirable to reduce the radiation target volume as in the epidermal growth factor receptor mutant non–small cell lung cancer, where high response rate may be expected [16]. Second, the safety of SABR may need to be better understood by the radiation oncology and medical oncology societies. As stated in Tan and Palma's review article, grade 3 or higher toxicities related to SABR have been reported in less than 3% of the patients in most trials. In order to achieve such low rates of toxicities, however, the radiation oncology society should pay the highest attention and make continuous efforts on standardizing SABR protocols outside clinical trials such as the United Kingdom SABR consortium [17]. Also needed by the radiation oncology society is the enthusiastic and intimate communication and collaboration with respects to the effectiveness, safety, optimal indications, and optimal sequencing of SABR in relation to systemic therapy regimens with their medical oncology partners. In fact, LAT has not been widely agreed on, adopted, and incorporated into our routine clinical practices, as many medical oncology partners have been encouraged by the favorably improved response rates with the recently developed new drug regimens, while they still are skeptical on the toxicity risk by applying LAT [18]. Third, the dose-fractionation schedule based on the sites for SABR need to be optimally established and popularized. Some trials, especially those that used immune checkpoint inhibitors, allowed irradiation of not all sites expecting the abscopal effect [19,20]. Unfortunately, most trials, however, failed to observe the abscopal effect, while other trials that delivered SABR to all metastatic sites demonstrated clinical benefit [7,15]. Treating all lesions sometimes are frequent feared by many radiation oncologists because of the increased radiation toxicity risk, especially in case when the patients have more than five metastatic lesions. The feasibility of treating more than four to 10 lesions with SABR is being tested in a few trials whose results are awaited [6,21].

As Tan and Palma described, SABR is cost-effective in the oligometastatic setting [4]. However, the current reimbursement policy by the Korean National Health Insurance Service could be another hurdle, which recognizes the SABR application to five or less metastatic lesions while limiting SABR to single lesion per single organ. Considering the proven benefit and safety of SABR when applied to the patients having five or more metastatic lesions, this insurance policy that is based only on the lesion number needs to be modified. Instead, the lesion number to be treated should be based on the balance between the expected benefit at no excess toxicity risk. For this issue to be realized, incorporation of the dose constraints guidelines proposed by High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic in SABR planning [22] need to be referenced both by the providers and the insurance policy executers, hopefully through the central review process.

The benefit of LAT, especially SABR, has been demonstrated from multiple trials. However, the benefit patterns were different across different tumor histologic types. Moreover, the prognoses of oligometastasic patients are not the same according to the subtype of oligometastasis classified by the European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer [23-25], and therefore, the LAT's benefit may not be the same accordingly. Most of the recent clinical trials, however, have been in the basket-trial design mainly due to the difficulty in patients' accrual, and the histology-/subtype-specific benefit of SABR might not be properly evaluated. More innovative trial design with better definition of oligometastasis are highly desirable to further prove the proper role of LAT and to move this unique subset of patients one step forward to the state of real cure.

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