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EDITORIAL

Beyond Oligometastases

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It has been 25 years since the oligometastatic hypothesis was formally defined and nearly a century since the first published report of an oligometastatic patient being treated with curative intent.[1,2] Despite the passage of time, there remains substantial debate regarding whether the oligometastatic state exists and whether patients benefit from aggressive local treatment to metastases.[3] Some authors argue that the oligometastatic state is a separate disease entity (variously defined with upper limits of 1, 3, 5, or 10 metastases) and that such patients are amenable to curative treatment strategies. Opposing arguments hold that these patients with only a few metastases represent only the tail end of a distribution of patients with widespread metastatic disease and that aggressive treatments expose patients to potential toxicities with little chance of benefit.[4]

We have now entered the era of phase 3 trials testing the oligometastatic hypothesis. These trials are supported by data from phase 2 randomized trials suggesting that patients treated with ablative therapies (eg, surgery, stereotactic ablative radiation [SABR], or radiofrequency ablation) benefit with improved progression-free survival or overall survival.[5-9] These new phase 3 trials are attempting to demonstrate overall survival benefits with ablative therapies in patients with a defined number of metastases (eg, 1-3, 4-10). Their findings will be critical to the field of oncology: By proving or disproving the oligometastatic theory, we will either usher in a new era of escalated treatment for patients previously considered palliative (ie, if trials are positive) or prove that these approaches were adopted into practice too quickly (if the trials are negative).

This focus on the number of metastases is based on the presumption that ablative therapies will only be beneficial if the number of metastatic lesions is low. But what if "oligo" does not matter? Could ablative therapies be beneficial, in terms of important clinical outcomes, regardless of the number of metastases, even in a patient with 20 or 30 lesions?

Before considering this question, we must first consider what types of ablative therapies would be possible with large numbers of metastases. In most situations, surgery would not be feasible. Widespread surgery to resect large parts of several visceral organs and bones is expected to be toxic and lead to substantial morbidity. Percutaneous approaches, such as radiofrequency ablation, microwave ablation, and cryotherapy, are useful for anatomically favorable locations,[5,10,11] but not all sites of the body (eg, brain or locations near major vessels) are treatable. SABR is the best candidate for such a widespread approach because all body sites can be treated if the doses are appropriately reduced and attention to total body and bone marrow dose is integrated into planning considerations. As an example, in the ongoing phase 3 SABR-COMET-10 trial,[12] patients with 4 to 10 oligometastases undergo radiation preplanning before randomization to ensure that SABR can be delivered safely. All patients thus far (n = 18) who have undergone preplanning have passed and been enrolled, even patients with up to 10 lung lesions (the lesions must be small); an example is shown in Figure 1. It is likely that if lesions are small, it would also be possible to devise radiation plans that meet our parameters of normal tissue tolerance to treat liver, brain, or bone lesions in this same patient.

Under the assumption that SABR would usually be the best choice of modality to treat polymetastatic disease, we

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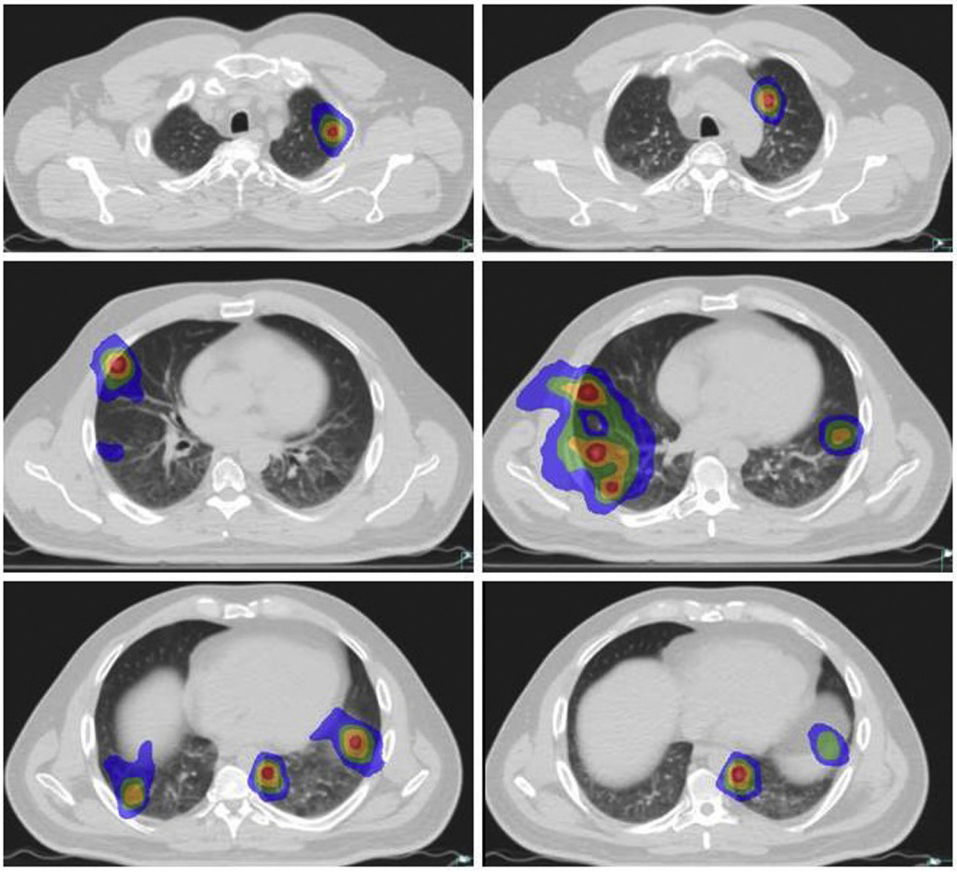

Fig. 1. Axial slices of a radiation plan for stereotactic radiation therapy treatment of numerous lung metastases in the same patient, as part of a clinical trial. The prescribed dose was 24 Gy in a single fraction to all lesions (blue colorwash indicates regions receiving ≥15 Gy, green ≥20 Gy, orange ≥24 Gy, and red ≥28 Gy). Doses to all normal tissues were within published safe tolerance doses. If metastases were present in other organs in this patient, design of stereotactic ablative radiation plans targeting those lesions, while meeting published normal tissue constraints, would be feasible. (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2019.12.023.)

will now revisit the question of whether "oligo" matters, or more specifically, whether it could be worthwhile to deliver SABR to large numbers of metastases. As an analogy, consider a theoretical drug that is useful in patients with metastatic disease. This drug has the effect of stopping the growth of all visible lesions for 1 year, with only modest toxicity; at 1 year, however, the cancer resumes growth at the previous rate, and the patient still ultimately dies of cancer, 1 year later than would have occurred without the drug. This would be a substantial survival improvement, more than many approved drugs, and would be a blockbuster drug; indeed, most Food and Drug Administration–approved cancer therapies gain approval based on a lower bar than this, using surrogate endpoints rather than overall survival.

Could SABR achieve the same toxicity and benefit profile as this theoretical drug? Could 20 or 30 sites of disease be safely treated, albeit with lower doses of SABR, to achieve a definite but temporary delay in cancer growth and lead to an improvement in overall survival? The goal of using SABR for all lesions would not be cure, or even permanent eradication of metastases, but merely a temporary growth arrest, an approach we would call Ablative Radiation Therapy to Restrain Everything Safely Treatable (ARREST).

How could ARREST of widely metastatic tumors be achieved? It would include 4 major tenets:

1. Minimization of toxicity. Treating large areas of the body with radiation is not a new concept and has precedent in the palliative setting. The use of hemibody radiation for palliation of painful bone metastases has been demonstrated to be safe and effective. Advances in supportive agents such as 5-HT antagonists can mitigate the systemic effects of large-volume irradiation noted in older trials.[13,14] Advances in radiation planning and targeting techniques have vastly improved the ability to deliver high doses of radiation with minimal toxicity. Most randomized trials of SABR for oligometastases

have demonstrated low overall toxicity rates, with grade 2 or higher toxicities comparable to the control arms or slightly higher.[7-9,12] Of note, one of these trials, SABR-COMET,[6] did report 3 deaths (4.5%) that were possibly treatment-related, warranting caution. Yet, toxicity can be lowered further by using modest doses of SABR, and when tumors abut important structures, target coverage can be compromised to maintain low doses to normal structures. As an example, in the SABR-COMET trial, doses of 54 to 60 Gy in 3 to 8 fractions were recommended for lung metastases.[6] In SABR-COMET-10, these have been reduced to doses of 20 to 35 Gy in 1 to 5 fractions.[12] This approach makes radiation planning much easier and is expected to minimize toxicity risks, at a cost of decreased long-term local control. With the ARREST approach, the goal would not be to eradicate metastases with large ablative doses approaching 60 Gy, but rather to provide a growth delay of several months with more modest doses. As a first step, the ARREST approach should be evaluated along the same lines as an investigational new drug with initial phase 1 trials to establish safety.

2. Leveraging technology for cost-effective solutions. In many jurisdictions, the cost of SABR increases substantially as additional targets are treated. A cost-effectiveness substudy of the SABR-COMET trial found SABR to be cost effective; in a hypothetical situation assessing cost-effectiveness in up to 10 lesions, however, as the number of lesions increases to 10, the benefit of SABR also needs to increase to maintain cost effectiveness.[15] An easier way to maintain cost effectiveness would be to change funding models for treatment of polymetastatic disease, recognizing the efficiencies inherent in radiation planning when adding extra lesions to a plan. Technologic proof of principle for treating extended volumes and multiple metastases safely with advanced technologies has been demonstrated.[16,17] Coupling of robust, automated lesion detection and segmentation with efficient large-field rotational delivery techniques is likely to improve the cost effectiveness of SABR in the coming years. Technical issues such as minimizing planning complexity and treatment time may be best addressed by choosing platforms that can treat multiple lesions in 1 session quickly, rather than more complex techniques that may achieve slightly better dose distributions at the cost of extended time requirements for planning and treatment delivery.

3. Minimize interference with systemic therapy and potentially improve systemic therapy efficacy. SABR would not be expected to address micrometastatic disease, and therefore many patients who are candidates for ARREST would likely benefit from systemic therapy. SABR delivery should not interfere with proven systemic therapies and thus must be delivered quickly. In the SABR-COMET-10 trial, all sites must be treated within 2 weeks to minimize interruptions in systemic therapy. With the use of single fractions of radiation to treat each lesion and treatment of multiple lesions per day, only short interruptions are achievable even with more than 10 metastases, and radiation could potentially be delivered between cycles of systemic therapy if shown to be safe. An ARREST approach could even potentiate systemic therapy: The Norton-Simon hypothesis holds that as overall tumor burden in the body increases, the effectiveness of systemic therapy decreases. Therefore, reducing overall tumor burden could indeed augment the effect of systemic therapy itself.[18]

4. Randomized trials. Carefully designed randomized trials are necessary before any such patients are treated off-trial. These trials should be easier to conduct than trials in oligometastatic patients for 3 reasons: (1) The situation of polymetastatic disease is much more common than oligometastatic disease; (2) it would be unlikely that any radiation oncologists would treat off-trial, a practice that has hampered accrual to oligometastases trials[19]; and (3) sample sizes may be much smaller than those required in oligometastatic tumors because polymetastatic patients would be expected to have shorter survival, which drives down the sample size required to find a given effect size. Inherent in such trials would be the need to incorporate robust patient-reported outcomes, quality-of-life measures, and toxicity stopping rules to ensure the goals of ARREST are achieved while minimizing risks to our patients.

Using SABR or other ablative therapies to treat widely metastatic disease is an idea that has historically been anathema to oncologists, because the treatment would be considered futile when the vast majority of patients progress within months after treatment. Yet the paradigm of delivering treatments with appreciable risks of serious side effects, knowing that progression is inevitable, is central to medical oncology practice. With modern radiation oncology technologies, using SABR to treat widely metastatic disease would be a radical departure from the traditions of oncology. However, a paradigm of using ARREST to delay tumor progression, albeit temporarily, at multiple tumor sites could be consistent with principles accepted in medical oncology and could redefine the treatment of metastatic disease.

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