

Editor’s Note

Successfully executing radiotherapy-based prospective clinical trials is challenging in a rapidly evolving clinical environment where commercially available technological advances may outpace high-level evidence of effectiveness. This is especially the case with the increasing use of stereotactic body radiation therapy (SBRT) in patients with metastatic solid tumors. Furthermore, the literature has a plethora of SBRT-based studies, often using different definitions of oligometastatic disease, diverse treatment planning systems, and variation in primary end points. This variety speaks to clinicians’ valuing well-designed, prospectively gathered evidence of efficacy to ultimately help define best practices. However, it is often not fully appreciated that there is no optimal design to assess technologies like SBRT. Nevertheless, the NRG Oncology consortium is to be congratulated on attempting to study the role of SBRT in a prospective fashion for patients with oligometastatic disease.

Chmura et al1 report on one of the initial multi-institutional prospective trials of SBRT for oligometastatic disease in patients with solid tumors (including common types such as lung, breast, and prostate). Under the framework of the National Clinical Trials Network, the NRG-BR001 oncology trial used a novel early phase design as an attempt to further define the safety of SBRT for patients with 2 to 4 metastases. Targets could have been located in up to 7 different anatomic sites, including bone, soft tissue, and/or the visceral organs.

The study was activated in 2014 and was extensively discussed among multiple stakeholders even further back. Hence, advances in treatment planning and delivery technology and lack of equipoise by clinicians as to what is the best approach to use SBRT has, no doubt, occurred during the past decade.

The working hypothesis was that there would be acceptable short-term toxicity at 6 months after treatment of 3 to 4 metastases or 2 anatomically close metastases (ie, ≤5 cm of normal tissue between metastases) with or without surgical resection and using a 3- or 5-SBRT fraction schedule using Common Terminology Criteria for Adverse Events (AEs), version 4 criteria (ie, ≥grade 3). Hence, the primary aim was to define, within a multi-institutional setting, a recommended SBRT dose for each of the metastatic locations being treated with the caveat that there can exist individual and overlapping fields when multiple metastases are treated with SBRT.

In this study, of the 42 patients enrolled, the authors reported no protocol-defined dose-limited toxicities in 35 evaluable patients. There were 8 cases of grade 3 AEs in 7 patients, which were thought to be related to protocol treatment; these events occurred at least 18 months after treatment (range, 125-556 days). Hence, as shown in Figure 1 and Table 3, despite the results endorsing the working hypothesis that short-term toxicity was acceptable, it is clear that longer follow-up is necessary in these patients. Prediction of normal tissue toxicity from a conventional fractionation scheme (ie, 1.8-2.0 Gy per fraction over several weeks) may not be reliable for larger fractionation approaches (including hypofractionation and SBRT).

Furthermore, since the trial was activated, multiple systemic agents have been approved for patients with advanced lung, breast, and prostate cancer. Consequently, many of these patients may live long enough to eventually manifest radiation-induced normal tissue toxicity. Because these toxic effects, particularly bone fractures and pulmonary toxicity, can compromise daily quality of life, we strongly believe that clinicians must be sure to caution patients about the specific normal tissue toxicity profile that can occur depending on the anatomic site that is to be targeted with SBRT.

In summary, NRG-BR001 is a necessary first draft meant to generate discussion regarding the feasibility of SBRT in a cooperative group setting. Although this work is not perfect, it does provide evidence to guide patient care and serves as a framework in the development of next-generation, multi-institution, SBRT-based clinical trials for patients with oligometastatic disease.

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