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EDITORIAL

Cautioning Against Declaring Success Before the Finish Line

Michael T. Milano, MD, PhD,* and Steven J. Chmura, MD, PhD†

*Department of Radiation Oncology, University of Rochester Medical Center, Rochester, Minnesota; and †Department of Radiation and Cellular Oncology, University of Chicago, Chicago, Illinois

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There are famous occurrences of medical reversals after well-designed clinical trials contradicted the hopes of researchers exploring new and exciting technologies or interventions.[1] Until phase 3 trials in patients with oligometastases are complete, we will not know if the idea of aggressive metastasis-directed therapy will be another anecdote of medical reversal. In this issue, Amini et al from the American Radium Society (ARS) Thoracic multidisciplinary expert panel present evidence-based expert guidelines on the treatment of oligometastatic or oligoprogressive non-small cell lung cancer (NSCLC).[2] This work is laudable and appreciated from this group of highly regarded specialists.

The term *oligometastases* was coined by Hellman and Weichselbaum in 1995, reflecting a limited extent of clinically apparent metastatic disease. In their original paper, they called for this hypothesis to be studied from biology to clinical trials.[3] Twenty-five years later, the European Society for Radiotherapy and Oncology (ESTRO) and American Society for Radiation Oncology (ASTRO) published consensus definitions of oligometastases and addressed key questions related to oligometastatic disease (disease characteristics, disease burden, timing of oligometastases, relation to other treatments, endpoints, and the effect of technology).[4] ESTRO and the European Organization for Research and Treatment of Cancer (EORTC) also published recent consensus recommendations for the characterization and classification of oligometastatic disease, with an emphasis on developing terminology to better describe the timing of oligometastases over the course of disease and the clinical context of metastatic disease (ie, whether the patient previously had "polymetastatic" disease).[5]

Although the initial and longest-term outcomes data in this space come from surgical resections of lung metastases,[6] stereotactic body radiation therapy (SBRT) has emerged over the past 2 decades as a generally well-tolerated minimally invasive approach to irradiating oligometastases.[7] Data on SBRT for oligometastatic NSCLC have been emerging for over a decade.[8] Results from 2 randomized phase 2 studies,[9,10] both closed early after interim analysis, suggest that consolidative radiation therapy for the primary NSCLC site and oligometastases confers a progression-free survival benefit, and, in the study by Gomez et al,[10] prolongs overall survival and reduces the likelihood of developing new metastases (neither of which were primary endpoints). These 2 studies, along with the heralded SABR-COMET,[11] form much of the basis for voting in this ARS document. Notably, SABR-COMET was not specific to patients with NSCLC, nor for patients receiving chemotherapy before enrollment, and the phase 2 screening design necessitates a subsequent phase 3 trial (SABR-COMET-3) to best address the hypothesis of SBRT conferring a survival benefit.[12]

The ASTRO/ESTRO and ESTRO/EORTC provide no practical guidance on optimal treatment for patients with oligometastases. In contrast, the ARS guideline specifically addresses treatment options for patients presenting with metastases synchronously at the time of initial NSCLC diagnosis.[2] Clinical scenarios address the use of radiation therapy (without specifying technique) for oligometastases and the primary site, or limited sites of recurrence after initial presentation with more widespread disease (termed

Corresponding author: Michael T. Milano, MD, PhD; E-mail: Michael_Milano@urmc.rochester.edu

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"oligoprogression" in their guideline and common parlance, but "induced oligometastases" in the ESTRO/EORTC document).

Similar disease-specific guidelines were previously under the umbrella of the American College of Radiology and then transitioned to the ARS Appropriate Use Criteria guidelines. ARS methodology uses systematic review and objective grading of study designs and data reporting. Based on published evidence, panelists vote on the appropriateness of treatment options for specific clinical scenarios. The voting uses a 9-point scale, grouped into 3 broad categories of "usually appropriate," "may be appropriate," and "usually not appropriate." Panelists' votes do not necessarily reflect their specific recommendation for each clinical scenario (for which different treatment options may be appropriate), but rather how appropriate each option would be. Agreement versus disagreement is defined by the relative number of votes falling within the broad categories. After each of 2 rounds of voting, the panelists discuss areas of disagreement; subsequent voting may or may not resolve disagreement. Agreement does not necessarily equate to consensus because some individuals' votes may fall outside where most (a set number to be considered agreement) lie. Areas of disagreement default to "may be appropriate." The ARS guideline is not a democratic vote across the ARS or US radiation oncologists. Ultimately, voting depends on the panel makeup, reflecting mostly academic radiation oncologists with specific expertise in thoracic oncology (also 2 academic thoracic medical oncologists, 2 academic thoracic surgeons, and a medical physicist). Without strong level I evidence for guidance, some practicing oncologists not represented in this group may have voted differently.

The ARS panelists considered consolidative radiation therapy to the primary NSCLC site and 1 to 3 oligometastases usually appropriate in patients without disease progression after 2 to 3 cycles or 2 to 3 months of chemotherapy, chemo-immunotherapy, or targeted therapy. For targetable mutations, they conceded that published data are not robust and encouraged clinical trial enrollment. Treating all sites in patients with 6 to 10 oligometastases was considered usually not appropriate. For >5 metastases, SBRT to 2 sites of oligoprogression (after 6 cycles of chemo-immunotherapy) was considered usually appropriate, whereas treating all sites (7 in the specific scenario) was considered usually not appropriate. The panelists voted that no upfront radiation therapy may be appropriate in patients with 1 to 3 oligometastases who are candidates for immunotherapy. They also voted that upfront radiation therapy (before systemic therapy) to the primary sites and 3 oligometastases may be appropriate. Tjong et al[13] have also discussed the uncertainly in whether upfront versus consolidative radiation therapy is optimal for oligometastatic NSCLC, which to our knowledge is not being addressed in ongoing studies.

Areas of disagreement among the ARS panelists included the appropriateness of consolidative radiation therapy or continuing immunotherapy alone for a patient with 4 to 5 oligometastases; the appropriateness of maintenance therapy alone (ie, not upfront consolidative radiation therapy) for a patient with 2 to 3 oligometastases; and the appropriateness of second-line systemic therapy alone for a patient with 2 oligoprogressive metastases.

The ARS panel voting reflects the uncertainty in the importance of the number of oligometastatic lesions in treatment decision making. The EORTC/ESTRO consensus recommendation for classification of oligometastatic disease[5] only specifies "small" or "limited" number. "Number of metastatic lesions" fell out of consideration as a factor for their characterization of oligometastatic disease after the first of 3 rounds of voting. The ESTRO-ASTRO consensus document[4] defines oligometastases based on ability to safely deliver curative-intent metastasis-directed radiation therapy, as opposed to number. Much of the published data are based on patients with 1 to 3 oligometastases, even among those studies that included ≤5 oligometastases.

The ARS panelists' voting is aligned with the ASTRO Model Policy for SBRT (https://www.astro.org/ASTRO/media/ASTRO/Daily%20Practice/PDFs/ASTROSBRTModelPolicy.pdf) and National Comprehensive Cancer Network (NCCN) guidelines. The ASTRO Model Policy considers (and has done so since 2010) SBRT to select sites of limited (number not specified) metastases to be in accordance with accepted standards of care. The NCCN Clinical Practice Guidelines for NSCLC consider consolidative radiation an appropriate option for patients with oligometastatic NSCLC, with number characterized as "limited." Both the ASTRO Model Policy and NCCN guidelines emphasize the need for safe delivery of radiation therapy to justify medical necessity.

Despite the expressed opinion of the ARS thoracic multidisciplinary expert panelists, ASTRO Model Policy,

Table 1 Select randomized studies of standard of care versus consolidative radiation therapy for patients with oligometastases from non-small cell lung cancer without progressive disease after receipt of systemic therapy

Study	Country	Oligometastases (n)*	Primary endpoint(s)
NRG LU002 (NCT03137771)	US	≤3	OS, PFS
SARON (NCT02417662)	UK	≤5	OS
OMEGA (NCT03827577)	Italy	≤3	OS
SINDAS (NCT02893332)	China	≤5	PFS

Abbreviations: OS = overall survival; PFS = progression free survival.
* Extracranial metastases suitable for stereotactic body radiation therapy (with the recent LU002 update allowing for hypofractionated 15-fraction radiation therapy for oligometastases). †Specific to those harboring sensitizing EGFR mutation; in setting of de novo or recurrent non-small cell lung cancer.

NCCN guidelines, and many vocal proponents on social media, there is still not conclusive evidence to justify consolidative radiation therapy for patients with 1 to 3 metastases as a general therapeutic strategy. Well-designed phase 3 studies of standard of care versus consolidative radiation therapy for patients with oligometastatic NSCLC and without progressive disease after receipt of systemic therapy (Table 1), or with oligoprogressive NSCLC (summarized by Dohopolski and Iyengar[8]), will be definitive and provide that justification—or refute it. Physicians should have equipoise and continue to accrue to these clinical trials.

It is no secret that both of us are strong advocates of definitive radiation therapy for metastatic disease, as authors and investigators on retrospective analyses, prospective studies, and phase 1 to 3 clinical trials of SBRT for oligometastases. We both treat patients with oligometastases as a standard-of-care approach and expect that we would have voted in line with the ARS panelists (likely favoring consolidative radiation therapy for those with 4-5 metastases). Yet we both concede that without phase 3 data, how one scores the appropriateness of treatment can be subjectively based on how one interprets the available evidence. This is a limitation of the ARS approach. One of us (M.T.M.) is actively involved with the ARS in developing similar guidelines, some based on lower levels of evidence. Thus, we stress these limitations not to be critical (or hypocritical) but rather to emphasize that more work needs to be done. The ARS thoracic multidisciplinary expert panel recognizes this as well, strongly recommending clinical trial enrollment at the conclusion of their document.

Of course, our patients cannot await results from phase 3 studies and may not be eligible or willing to enroll on such studies. The great strength of these ARS guidelines is that they provide practical guidance from a multidisciplinary panel of experts who have evaluated the current evidence.[2] As phase 3 data emerge on the treatment of oligometastatic NSCLC and new questions arise (perhaps how to use genomic and biologic factors in decision making), we hope that the ARS continues this mission.

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