Optimize Local Therapy for Oligometastatic and Oligoprogressive Non–Small Cell Lung Cancer to Enhance Survival

Joe Y. Chang, MD, PhD,1 and Vivek Verma, MD1

ABSTRACT

Metastatic non–small cell lung cancer (NSCLC) is highly heterogeneous, and there are patients with limited areas of metastases (oligometastases) or progression (oligoprogression) whose natural history and prognosis can be considerably more favorable. As a result, local therapy may offer these patients a chance at clinically meaningful disease control and/or cure. This review begins by describing the current status of the existing prospective data, including evidence of overall survival improvements from multiple randomized trials. Given the nascent nature of this domain, the review then examines ongoing controversies and unresolved issues regarding local therapy for oligometastatic and oligoprogression. First, the role of local therapy in the setting of targeted therapies and immunotherapy is discussed, because most published randomized trials of local therapy have been performed in the context of chemotherapy, which is no longer the standard of care for most patients with metastatic NSCLC. Refining patient selection for local therapy is then reviewed, including clinical factors (such as control of the primary and regional lymph node sites, the heterogeneous definitions of oligometastases/oligoprogression, and the underrepresentation of brain metastases in existing randomized data) and novel pathologic/molecular biomarkers. Next, because there also remains no consensus regarding the optimal modality of local therapy, the advantages and disadvantages of stereotactic radiotherapy, surgery, and other ablative techniques are discussed. Subsequently, methods to optimize radiotherapy are examined, including controversies regarding the optimal dose/fractionation and timing/sequencing scheme. A discussion regarding potentially extending the existing data to polymetastatic NSCLC follows. The review concludes with remarks regarding prudently designing randomized trials of local therapy going forward, including the benefits and drawbacks of specific endpoints meriting further testing in this unique population.

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Metastatic non–small cell lung cancer (mNSCLC) has historically been thought as a homogeneous entity that is incurable. In the contemporary era, however, numerous efforts have contributed to debunking this dogmatic notion, most notably the discovery that a subset of patients with mNSCLC with limited areas of metastasis (oligometastases) or progression (oligoprogression) experience considerably improved outcomes. Consequently, more aggressive therapy for these patients may offer a chance at clinically meaningful disease control and/or cure (Figure 1).

For the purposes of this review, the definitions of oligometastasis and oligoprogression are based on adequate representation in existing randomized trials and the inclusion criteria of ongoing phase III trials. Oligometastasis refers to the initially treatment-naïve setting (or after first-line systemic therapy) and is most commonly defined for patients with ≤3 metastatic areas (not including the primary tumor and regional lymph nodes). Oligoprogression refers to non–newly diagnosed patients who have had prior (or ongoing) systemic therapy and ≤3 metastatic areas that have progressed in size (and/or avidity). Oligorecurrence is a subtype of oligoprogression in which the primary tumor has been previously treated in a definitive manner.

The primary rationale for local therapy (most commonly stereotactic ablative radiotherapy [SABR, also called stereotactic body radiotherapy] and less commonly surgery or thermal ablative therapy) for oligometastatic and oligoprogressive disease is to provide potentially curative-intent therapy to the limited existing sites of gross disease, assuming that systemic therapy can address micrometastatic disease. For patients who have received systemic therapy, local therapy can eliminate cancer clones that are resistant to chemotherapy, targeted therapy, or immunotherapy. Second, in the immunotherapy era, ablative radiotherapy may also release tumor-associated antigens and stimulate a tumor-specific immunologic response. Third, because systemic therapy is less locally effective compared with dedicated local modalities, another rationale is to better preserve subsequent-line systemic options in case future...
relapses occur. Fourth, local therapies (especially RT) continue to play an important role for symptomatic palliation in these patients. Finally, for patients who cannot tolerate or want a break for systemic therapy, local treatment to the only visible gross tumor can delay systemic therapy and improve quality of life in addition to offering the benefit of local control.

Table 1 displays comparative studies of local therapy for limited mNSCLC that have been published or presented as of the time of writing. Of these studies, 5 have shown an overall survival (OS) benefit for local therapy, whereas the remainder have insufficient follow-up for robust OS assessment. A recent meta-analysis has also been performed corroborating the encouraging results of the aforementioned publications.

Figure 1. (A) An 80-year-old man with lung squamous cell carcinoma and a synchronous isolated metastasis at the thoracic spine. His PD-L1 expression was >70% and there were no driver mutations. He was treated using definitive concurrent chemoradiotherapy, followed by adjuvant durvalumab. He has remained without evidence of disease for approximately 2 years. (B) A 65-year-old man with right lung adenocarcinoma and hilar/mediastinal lymph node involvement, a PD-L1 expression of 10%, and no driver mutations. He presented with a symptomatic isolated brain metastasis and underwent surgical resection, followed by radiosurgery (15 Gy). He was treated using carboplatin/pemetrexed for 4 cycles with progression, followed by nivolumab for >1 year with isolated progression in the primary site. He was then treated on protocol with nivolumab and consolidative SABR to the primary disease. He has since remained without evidence of disease for 2.5 years. (C) A 75-year-old woman presented with diffuse metastatic lung adenocarcinoma, a PD-L1 expression of 75%, and no driver mutations. She was treated using carboplatin/pemetrexed and consolidative chest RT in 2016. She subsequently developed progression in the left humerus in 2017 and was treated using pembrolizumab and palliative RT to that area. She then developed isolated progression in the left upper lobe in 2018 and received pembrolizumab with SABR on protocol. She developed another isolated progression in the left hilum in 2019 and underwent proton therapy, followed by consolidative RT to a clavicular metastasis in 2020. Altogether, she has survived for >5 years since the initial diagnosis.

Abbreviations: chemo, chemotherapy; fx, fraction; met, metastasis; RT, radiotherapy; SABR, stereotactic ablative radiotherapy; SRS, stereotactic radiosurgery.

Local Therapy in Immunotherapy and Targeted Therapy

Arguably the largest limitation of many of the existing data (Table 1) is that they were designed when chemotherapy was the standard of care for stage IV mNSCLC. In the most contemporary time periods, however, new systemic agents have been shown to improve OS over chemotherapy alone. These include immune checkpoint inhibitors for non–small cell lung cancer (NSCLC).
and third-generation tyrosine kinase inhibitors (TKIs) for driver mutation-associated NSCLC.\textsuperscript{14}

Thus, the additional value of metastasis-directed local therapy in the setting of these new systemic agents remains uncertain. Specifically, it is unclear whether the enhanced local effect of new systemic therapies dampens the benefit of local control, or whether dedicated local therapy could be even more beneficial because systemic control is improved (which could be more likely given the promising results of a single-arm phase II trial\textsuperscript{15}). Part of this ambiguity arises because the unique tumor biological signature for any given histology will result in a variety of possible responses to a given form of systemic therapy. As a result, further studies should focus on mechanistic patterns of interaction between a patient’s cancer biology and the systemic agent received and use that information to design a local therapy approach.

In efforts to account for this relatively rapid change in the systemic standard of care, several trials have made protocol amendments. For instance, NRG LU002 and Table 1. Selected Comparative Studies to Date of Local Therapy Versus No Local Therapy for Oligometastatic or Oligoprogressive* NSCLC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Histology</th>
<th>Population</th>
<th>Sample Size</th>
<th>Follow-Up</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheu et al\textsuperscript{2}</td>
<td>Retrospective</td>
<td>NSCLC</td>
<td>Oligometastatic disease (≤3 metastases not including the primary)</td>
<td>49</td>
<td>3.9</td>
<td>First-line chemotherapy or concurrent chemoradiation in all patients; maintenance therapy/observation vs SABR/surgery</td>
<td>Higher PFS and OS with local therapy on propensity-matched analysis</td>
</tr>
<tr>
<td>Gomez et al\textsuperscript{3}</td>
<td>Randomized</td>
<td>NSCLC</td>
<td>Oligometastatic disease (≤3 metastases not including the primary)</td>
<td>49</td>
<td>3.2</td>
<td>First-line chemotherapy in all patients; maintenance therapy/observation vs subsequent RT (62%) or surgery (4%) or both (24%)</td>
<td>Higher PFS and OS with local therapy</td>
</tr>
<tr>
<td>Iyengar et al\textsuperscript{4}</td>
<td>Randomized</td>
<td>NSCLC</td>
<td>Oligometastatic disease (≤6 lesions including the primary with ≤3 metastases in lung or liver)</td>
<td>29</td>
<td>0.8</td>
<td>First-line chemotherapy in all patients; maintenance chemotherapy vs SABR</td>
<td>Higher PFS with local therapy; incomplete follow-up for OS</td>
</tr>
<tr>
<td>Xu et al\textsuperscript{5}</td>
<td>Retrospective</td>
<td>EGFRm NSCLC</td>
<td>Oligometastatic disease (≤5 lesions excluding the primary)</td>
<td>145</td>
<td>3.2</td>
<td>First-line, first-generation TKI in all patients; maintenance therapy/observation vs subsequent RT, surgery, both, or RFA (liver metastases only)</td>
<td>Higher PFS and OS with local therapy to all sites of disease on propensity-matched analysis</td>
</tr>
<tr>
<td>Palma et al\textsuperscript{6}</td>
<td>Randomized</td>
<td>Mixed</td>
<td>Oligorecurrent disease (≤5 metastases)</td>
<td>99</td>
<td>4.3</td>
<td>Palliative standard of care vs SABR</td>
<td>Higher PFS and OS with local therapy</td>
</tr>
<tr>
<td>Wang et al\textsuperscript{7}</td>
<td>Randomized</td>
<td>EGFRm NSCLC</td>
<td>Oligometastatic disease (≤5 lesions excluding the primary with &lt;3 metastases in any 1 organ)</td>
<td>133</td>
<td>2.0</td>
<td>Up-front RT followed by first-generation TKI vs up-front first-generation TKI</td>
<td>Higher PFS and OS with local therapy</td>
</tr>
<tr>
<td>Tsai et al\textsuperscript{8}</td>
<td>Randomized</td>
<td>NSCLC and breast cancer</td>
<td>Oligoprogressive disease (≤5 areas of progression) after ≥1 lines of systemic therapy</td>
<td>102</td>
<td>1.0</td>
<td>Palliative standard of care therapies vs SABR</td>
<td>Higher PFS with local therapy; findings significant in NSCLC but not in breast histology</td>
</tr>
</tbody>
</table>

Abbreviations: EGFRm, EGFR-mutant; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; RFA, radiofrequency ablation; RT, radiation therapy; SABR, stereotactic ablative radiotherapy; TKI, tyrosine kinase inhibitor.

*Including oligorecurrent.
ClinicalTrials.gov identifier: NCT03137771 now allows first-line immunotherapy and uses it as a stratification criterion; it is anticipated that enough patients receiving first-line immunotherapy will be enrolled, resulting in a robust analysis based on that subgroup. Similarly, the unpublished randomized SINDAS trial in oligometastatic epidermal growth factor receptor–mutated NSCLC showed a progression-free survival (PFS) and OS benefit to SABR, but it was conducted in the setting of first-generation TKIs.7 However, the randomized NORTHSTAR trial is designed to evaluate this question in the setting of third-generation TKIs (NCT03410043).

Despite the lack of consensus regarding the degree of benefit from local therapy in the setting of new systemic agents, enrollment into these randomized trials is highly recommended. If local therapy is being considered off protocol, then a thorough discussion of this unresolved clinical issue should ensue to exercise joint decision-making between patients and providers.

Patient Selection

Although oligometastatic and oligoprogressive settings are appropriately labeled as disease that is an intermediate stage between locally advanced/micrometastatic and widely disseminated disease, it must be acknowledged that oligometastatic or oligoprogressive conditions remain very heterogeneous and hence all such patients will not benefit from local therapy to the same extent. As a result, it is highly consequential to refine patient selection for local therapy.

Clinical predictors of post–local therapy outcomes are essential for refining patient selection, including those pertaining to the number, size, timing, and location of metastatic lesions (Figure 1A). For instance, it is unclear whether optimally defining limited metastatic disease should encompass the number of lesions in a given organ, which some studies do3,7 but others do not.3,5 In addition, brain metastases have historically been associated with a poorer prognosis and have been highly underrepresented in existing randomized trials (Table 1); whether these patients receive the same benefit from local therapy as patients with extracranial-only oligometastases remains an unresolved question (Figure 1B). It is possible that a separate definition of intracranial oligometastases may be required for further stratification. RTOG 9508 indicated that stereotactic radiosurgery improved OS for patients with a single brain metastasis,16 but a prematurely closed small randomized trial of patients with oligometastatic brain disease (1–4 lesions; not reflective of oligometastatic overall disease) showed no PFS/OS benefits when stereotactic radiosurgery was added to chemotherapy.17 Finally, nodal disease is often indiscriminately grouped and treated with the primary tumor regardless of the degree of nodal burden; this practice may not be prudent given that it is a reported prognostic factor in the limited mNSCLC population.18

There is no doubt that utilizing pathologic/molecular biomarkers to stratify patients at higher risk of developing further metastases after local therapy is crucial, and it has been a major focus of active investigation because

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Histology</th>
<th>Metastases</th>
<th>Systemic Therapy</th>
<th>Local Therapy</th>
<th>Primary Endpoint</th>
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<tbody>
<tr>
<td>OMEGA</td>
<td>NCT03827577</td>
<td>NSCLC</td>
<td>1–3</td>
<td>Chemotherapy, IO, targeted agents</td>
<td>RT, surgery, RFA</td>
<td>OS</td>
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<td>SARON</td>
<td>NCT02417662</td>
<td>NSCLC</td>
<td>1–5</td>
<td>Per physician discretion</td>
<td>RT</td>
<td>OS</td>
</tr>
<tr>
<td>NRG LU002</td>
<td>NCT03137771</td>
<td>NSCLC</td>
<td>1–3</td>
<td>Chemotherapy or IO</td>
<td>RT</td>
<td>PFS (phase II), OS (phase III)</td>
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<tr>
<td>CORE</td>
<td>NCT02759783</td>
<td>NSCLC, breast cancer, prostate cancer</td>
<td>1–3</td>
<td>Per physician discretion</td>
<td>RT</td>
<td>PFS</td>
</tr>
<tr>
<td>OITROLC</td>
<td>NCT02076477</td>
<td>NSCLC</td>
<td>1–5</td>
<td>Chemotherapy</td>
<td>RT</td>
<td>ORR</td>
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<td>SABR-COMET-3</td>
<td>NCT03862911</td>
<td>Mixed</td>
<td>1–3</td>
<td>Per physician discretion</td>
<td>RT</td>
<td>OS</td>
</tr>
<tr>
<td>LONESTAR</td>
<td>NCT03391869</td>
<td>NSCLC</td>
<td>1–3 (subset)</td>
<td>Ipilimumab/ nivolumab</td>
<td>RT</td>
<td>OS</td>
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<td>HALT</td>
<td>NCT03256981</td>
<td>Oligoprogressive NSCLC with driver mutation</td>
<td>1–3</td>
<td>TKI</td>
<td>RT</td>
<td>PFS</td>
</tr>
</tbody>
</table>

Abbreviations: IO, immunotherapy; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RFA, radiofrequency ablation; RT, radiation therapy; TKI, tyrosine kinase inhibitor.

*Including oligorecurrent.
patients who rapidly experience new metastases likely do not benefit from local therapy. It has been suggested that for patients with NSCLC, PD-L1 status may be a promising such biomarker. The proportional efficacy of immunotherapy seems to be correlated with the degree of PD-L1 expression,12,13 and as a result it has been postulated that RT for oligometastatic (or polymetastatic) NSCLC may benefit patients with low PD-L1 to a greater degree.19 Although immunotherapy is not a local modality, it can exert independent local effects; for patients with low PD-L1, it is unlikely that immunotherapy would prove to exert adequate local effects, so dedicated local therapy may be more useful in those circumstances and could change immunotherapy-resistant “cold” cancer to immu

therapy-sensitive “hot” cancer.1 Similarly, other circumstances associated with a high likelihood of harboring targeted therapy-resistant clones may prove to be best managed with additional local therapy, although further study is required to address long-term survival.

Another emerging form of pathologic/molecular analysis for purposes of risk stratification is with circulating tumor cells, circulating tumor DNA, or microRNA profiling.20,21 Translational work has shown promising findings in that these candidate biomarkers may be able to predict outcomes and hence guide the use of local therapy (or lack thereof) on an individualized level. These approaches require standardization and validation by larger studies going forward, but they nevertheless remain an attractive future approach with which to further refine and individualize patient selection for this circumstance.

Altogether, owing to the relatively recent emergence of local therapy for oligometastatic and oligoprogressive NSCLC, populations of existing studies are substantially heterogeneous, and to this extent there is an expanding need for methods with which to better select patients who may benefit the most from local therapy. Further refinement of clinical parameters and ongoing work on pathologic/molecular biomarkers represent highly important ways to avoid both overtreatment and undertreatment.

**Modality of Local Therapy**

The goal of local therapy in oligometastatic or oligoprogressive disease is to eradicate all known areas of gross disease. There are several potential modalities that could accomplish this purpose, including SABR, surgery, or other nonradiotherapeutic ablative approaches. Although the vast majority of existing trials have used SABR for this purpose (Table 1) and most ongoing trials also use SABR (Table 2), the optimal modality for this purpose remains unknown.

Metastasectomy for limited-metastatic disease has the advantage of surgical extirpation, which generally yields very high rates of local control; the high tissue yield can also be useful for genomic/molecular analyses. This procedure has also been performed for more than a half-century and has a considerable amount of associated observational (nonrandomized) data.22-23 Its main disadvantages are associated with the invasiveness of the procedure, including a nontrivial rate of surgical complications and the resulting impact on quality of life. However, using contemporary surgical approaches at centers of excellence could reduce this risk considerably.

A primary advantage of SABR is its noninvasive approach. In addition, there may be a potential synergy between the antitumoral immune system and RT. It is postulated that RT-mediated tumoricide leads to enhanced tumor antigen release; as a result, the galvanization of the immune system by immune checkpoint inhibitors may become even more pronounced and yield a greater degree of systemic tumoricide.1 The combination of local control with RT and improved systemic control with the combination of RT and immunotherapy could drive outcome benefits over immunotherapy alone.19 The primary disadvantage of SABR is a potentially lower local control for certain lesions (eg, large lesions or those close to radiation-sensitive organs). SABR is also associated with a nontrivial rate of high-grade adverse events in lesions close to critical normal tissues.5,24

Nonradiotherapeutic ablative techniques (eg, radiofrequency or thermal ablation) have not been well tested for oligometastatic or oligoprogressive NSCLC but have been extensively used for liver metastases from colorectal cancer. The single-arm RAPTURE trial evaluated this modality for 106 patients with primary lung cancer or lung metastases,25 but there was no requirement for specifically oligo-

metastatic disease. Eighty-eight percent of tumors had a complete response lasting at least 1 year (without differences between lung metastases and primary lung cancer), and the rate of parenchymal damage was minimal. However, major complications occurred in 31 patients (largely pneumothorax) and the study only followed patients for up to 2 years. As a result, the utility of this approach remains exploratory until further trials are published.

Taken together, although the vast majority of published and ongoing randomized trials for oligometastatic or oligoprogressive NSCLC have used SABR, multidisciplinary review is strongly recommended in light of the unique advantages and disadvantages of each modality. In particular, individualized decision-making should be conducted in light of the metastases’ size and location at minimum, because local control between modalities may be highly sensitive to these 2 factors. Because the most contemporary systemic therapies also exert some level of independent local effects, the value of local control must be carefully balanced with the potential for treatment-related adverse events.

**Optimizing RT**

Another limitation of the existing data on RT for oligometastatic or oligoprogressive NSCLC is the wide heterogeneity
in RT management. Despite this issue, further refining RT is essential to maximize any potential interactions between radiation and the immune system while not overly increasing the risk of toxicities.

To date, there is no single most accepted dose/fractionation regimen for oligometastases (or to the primary disease). Existing studies (Table 1) have used a wide variety of schemes, including ablative SABR regimens consisting of high (≥100 Gy) biologically effective doses (BED) and lower hypofractionated doses.

It has been suggested by preclinical data that there may be a certain optimal dose/fractionation of RT (12 to 18 Gy/fraction) that best promotes immunostimulatory effects—whereas low doses may not optimally stimulate the immune system, very high doses may not do so either.26 It is difficult to translate that data into human patients, and to that extent an exploratory analysis of a prospective trial has suggested that ablative SABR dosing (50 Gy in 4 fractions with BED >100 Gy) may be associated with enhanced immune effects compared with lower fractional doses.20-27 However, unplanned exploratory analyses likely carry unforeseen biases, and further corroboratory data are required.

On the other hand, ablative dose/fractionation schemes are not always feasible because the size and/or location of the irradiated lesion largely dictates the maximum allowable dose delivered. It remains uncertain whether increasing the radiation dose in lesions amenable to either higher- or lower-dose irradiation always offers additional clinical benefits over lower doses.28

In addition, results of one preliminary prospective trial have indicated a potential benefit of intentionally delivered very-low-dose RT (as low as 7.5 Gy total dose) together with ablative SABR regimens (eg, 50 Gy in 4 fractions), which improves clinical response rates compared with ablative SABR alone.29 Very-low-dose RT is hypothesized to operate via a distinct mechanism from that of ablative RT, aiming to improve immune infiltration of the tumor microenvironment and thereby enhancing clinical response rates.30 This concept is in its nascence, however, and further data for validation are required for more credence.

It has also been suggested that various organs are differentially immunogenic. In other words, metastases located in different organs could elicit varied degrees of immune responses.31 The mechanisms and reasons for this phenomenon are unclear and could relate to the degree of immunosuppressive signals produced by the microenvironment of each particular organ; to that extent, it merits further investigation to determine whether different RT dose/fractionation schemes are required for different sites of metastasis.

Finally, if it is proven that a particular type of ablative dose/fractionation regimen is most optimal but cannot be applied to disease that is in close proximity to radiation-sensitive organs, then it may be feasible to test the utility of partial-volume RT. This approach would use the most optimal ablative dosing to a portion of the tumor and a lower dose to the remainder. This technique is rarely performed currently, and further data supporting its utility are required.

With regard to dosing of the primary tumor, limited data support dose escalation. One such retrospective publication reported that definitive-dose or high-BED hypofractionated RT was associated with improved survival, but these data are prone to a wide variety of biases and shortcomings that limit interpretation.32 Until more robust and causative data are presented, primary tumor dosing will continue to remain heterogeneous and individually determined.

Overall, despite an increasing number of reports describing the synergism between RT and systemic agents (eg, immunotherapy), there is much left to be elucidated regarding how best to prescribe and deliver RT so that the systemic effects are maximized. Until robust data addressing this unresolved issue are reported, the wide heterogeneity in such approaches will likely continue. However, based on preclinical and preliminary clinical data, to maximize immunologic effects, ablative dosing for oligometastatic NSCLC should be considered for at least some lesions if the location and/or size permits.

**Extrapolation of Polymetastatic Disease**

Whether patients with >3 metastases benefit from local therapy to the same degree as oligometastatic cases is currently unclear, because this population has been highly underrepresented in existing randomized trials (Table 1). Although some of these trials enrolled patients with up to 5 metastases, it should not assumed that the benefits of local therapies extend to this underrepresented population.

Historically, due to concerns regarding toxicity associated with combined immunotherapy and RT, the majority of initial prospective clinical studies in the multimetastasis setting used immunotherapy with a single site of SABR. Although pooled randomized studies showed that this strategy improved the response rate, PFS, and OS,19 comprehensive multisite irradiation may be needed to activate/prime a stronger and broader anticancer immune response to address the issues of cancer antigen heterogeneity and the immunoresistant microenvironment in different tumor locations.15,33,34

To address the limitations of the existing randomized trials, the accruing SABR-COMET-10, NIRVANA-LUNG, NORTHSTAR, and LONESTAR (ClinicalTrials.gov identifiers: NCT03721341, NCT03774732, NCT03410043, NCT03391869) trials are expected to answer much of the controversy surrounding whether SABR benefits patients.
with polymetastatic disease. SABR-COMET-10 is enrolling patients with a variety of cancers with 4 to 10 metastatic lesions receiving investigator-chosen systemic therapy, whereas NORTHSTAR and LONESTAR are enrolling patients with both polymetastatic and oligometastatic NSCLC receiving combined nivolumab/ipilimumab or osimertinib (for patients with EGFR mutations). The primary endpoint of these trials is OS, and they include extensive translational analyses to address the utility of patient-specific biomarkers, as mentioned earlier.

Although treating a large number of polymetastatic lesions off protocol is currently not recommended, it may be postulated that patients who are polymetastatic also have highly heterogeneous disease and may include subpopulations that may benefit from local therapy similar to patients who are oligometastatic (Figure 1C). While patients are undergoing systemic therapy, clinicians should evaluate their biological and clinical status continuously and intervene with local therapy as clinically and biologically indicated. In addition, in the setting of polymetastasis, it may not be necessary to deliver RT to all lesions at one time because of potential toxicities. In fact, immunologically, there could be an advantage to delivering multiple separate rounds of RT, so-called pulsed RT to different lesions, to boost the “tumor vaccine” effect and/or eliminate new treatment-resistant clones. Even for the same lesion, pulsed RT to deliver each fraction of SABR during the interval of immunotherapy (every few weeks), instead of consecutive delivery of each fraction, may not only improve SABR tolerance, but also facilitate a stronger immune response and overcome immunotherapy resistance, the latter of which is a major limitation of current immune checkpoint agents.

To summarize, the throughput for RT target delineation, planning, and delivery has rapidly increased in the modern era. As a result, it is now possible to treat numerous areas in a relatively short time frame, which naturally facilitates the treatment of polymetastatic lesions. However, careful patient selection and dynamically monitoring/evaluating patient status are essential. Subgroup analyses of trials such as SABR-COMET-10, NORTHSTAR, and LONESTAR will also help identify which subsets of the polymetastatic population could benefit from aggressive local therapy.

Designing Future Randomized Trials
The randomized trials of tomorrow should be constructed prudently and should be based on the several controversies and unresolved issues discussed herein. They should be designed with important endpoints that are clinically meaningful yet not prohibitive in terms of accrual. All endpoints have unique advantages and disadvantages and should be weighed against each other when designing trials.

The endpoint of many published randomized trials of oligometastasis is OS, which should be considered the gold standard of outcomes research. This parameter requires the largest expected sample sizes, but positive OS findings can likely signal a high degree of insurance approval in the future. It is recommended that OS continue to be the primary endpoint of randomized oligometastasis trials, especially because PFS may not be adequately correlated with OS in this population, especially with the high utilization of salvage therapies. In addition, trial populations that remain “unrefined” (such as those of present-day trials) likely result in a substantial number of events (deaths) that would allow for feasible sample sizes that are not prohibitive to accrual. If, however, trials enroll a more “enriched” population with better-than-expected prognosis for oligometastatic disease (eg, based on known prognostic factors in stage IV NSCLC), then larger sample sizes may be required.

Oligoprogresion represents a different circumstance for which detecting OS differences may be more difficult for a given sample size, because metachronous metastases generally exhibit a higher OS than synchronous disease, so these trials should be powered according to the expectation that the event rate would be lower and a greater sample size would be required to see the desired effect size.

For both oligometastasis and oligoprogresion, other endpoints that may be of clinical importance include the rate of new metastases and/or the necessity to switch to another line of systemic therapy. The rate of success (or futility) of local therapy for this population is, in large part, dictated by the rate of additional metastases (out of the irradiated area); moreover, from a practical standpoint, patients only have a finite number of adequate lines of systemic therapy. Thus, this endpoint may represent an example of a clinically meaningful endpoint that may correlate with patient quality of life and may require smaller sample sizes than trials with OS endpoints; however, this endpoint could come at the expense of payors potentially not deeming the endpoint as being “clinically meaningful.”

The importance of adequately powered prespecified subset analyses in trials of the oligometastatic and oligoprogresive population cannot be understated, mainly owing to its impact on sharpening patient selection for local therapy in the future. It is well recognized that only a limited number of important subsets should be adequately powered and evaluated, so as not to require prohibitive sample sizes. We encourage trials to enroll patients with a wide variety of ages and performance statuses, not to promote generalizability but rather to involve subsets based on known clinicopathologic prognostic factors such as disease burden and/or location, the type of delivered systemic therapy, molecular profiling, the presence of brain metastases, PD-L1 status, the...
degree of nodal involvement, RT dose/fractionation schemes, and the type of local therapy. Because these factors are all related to many of the unresolved areas in this realm as described throughout this review, subset analyses based on these factors may considerably help address these knowledge gaps.

Secondary endpoints are most commonly PFS or toxicities, but others such as cost-effectiveness and quality of life would lend greater credence to local therapy, especially from a practical standpoint and for payors. Translational endpoints are also helpful for the purposes of refining patient selection but may not always be feasible. Nevertheless, it is important to construct randomized trials in this population given the limitations and controversies of the existing data so as to meaningfully move this burgeoning field forward.

Conclusions

Local therapy for oligometastases and oligoprogression is rapidly expanding and has clearly showed promise (including OS improvements) in existing randomized trials. Optimization of local therapy, including patient selection, local modality (SABR vs surgery vs other ablative techniques), and SABR regimen/timing/sequencing, is crucial to maximize those benefits. The unique biological nature of each malignancy mandates different combinations of systemic and local therapy strategies. Limited data indicate that ablative dosing is preferred if feasible/tolerable to achieve maximal immune activation/priming, whereas the utility of very low doses remains under active investigation. For polymetastatic NSCLC, it may be possible in the immunotherapy era to convert some patients to oligometastatic status through effective systemic therapy and/or multiple rounds of pulsed local therapy, and possibly eliminate all lesions to achieve a possible cure. More studies are needed to explore biological/molecular markers to define true oligometastatic status in addition to diagnostic imaging modalities, and the status could be dynamic, depending on the interaction between individual tumor biology with both systemic and local treatment.

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