Review of Treatment Options for Oligometastatic Non–Small Cell Lung Cancer

Michael R. Folkert, MD, PhD, and Robert Timmerman, MD

The authors are affiliated with the University of Texas Southwest Medical Center in Dallas, Texas. Dr Folkert is an assistant professor in the Department of Radiation Oncology. Dr Timmerman is a professor in the Departments of Radiation Oncology and Neurological Surgery.

Address correspondence to:
Robert Timmerman, MD
Department of Radiation Oncology
Simmons Comprehensive Cancer Center
UT Southwestern Medical Center
5323 Harry Hines Blvd
Dallas, TX 75235
Tel: 214-645-7651
E-mail:
robert.timmerman@utsouthwestern.edu

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Abstract: Our understanding of metastatic disease is constantly evolving. Although outcomes for patients with stage IV non–small cell lung cancer (NSCLC) are poor, aggressive/radical local intervention may be effective in a subset of patients with limited or "oligometastatic" disease. Here we review and compare the range of available treatment options that are specific to oligometastatic NSCLC, and discuss potential directions of future clinical research.

Introduction: Stage IV NSCLC

Two-thirds of patients with non–small cell lung cancer (NSCLC) present with stage IV disease. Stage IV NSCLC remains poorly controlled, with a median survival of up to 12 months following first-line chemotherapy.[1-5] Distant metastatic patterns for NSCLC are fairly well characterized, with the lung (ipsilateral and contralateral), bone, brain, and adrenal gland being the most common sites for spread.[6-9] It recently has been hypothesized that driver oncogenes affect the pattern of this spread. In a recent study by Doebele and colleagues,[10] NSCLC with common gene mutations—including those in epidermal growth factor receptor (*EGFR*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), and anaplastic lymphoma kinase (*ALK*)—was compared with wild-type NSCLC. Compared with patients who had the classic pulmonary, adrenal, bone, and brain metastases noted in wild-type NSCLC, *ALK*-mutant NSCLC patients were more likely to have pericardial or pleural metastases. Furthermore, *EGFR*- and *ALK*-mutant patients were more likely to have liver metastases than those with wild-type NSCLC, in which liver involvement is infrequent. For patients in an Asian population enriched for *EGFR* mutations treated with gefitinib,[11] this pattern was recapitulated, with lung being the most common site of failure (66%), followed by bone (18%), brain (16%), and liver (9.5%). Other sites included the adrenal glands, peritoneum, pericardium, and skin.

Stage IV NSCLC is evolving as a defined disease state; a recent multinational collaborative effort was organized by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) to develop and analyze large databases to revise the staging system for lung cancer.[12] A total of 81,015

analyzable cases from 46 sources in 19 countries were entered into the International Association for the Study of Lung Cancer (IASLC) database, including 67,725 patients with NSCLC. Analyses led to changes in the T and M descriptors in the TNM (tumor, node, metastasis) system, including subdivision of the M1 category into M1a (containing contralateral lung nodules and malignant pleural and pericardial effusions) and M1b (containing distant metastases).[13] Stage groupings also changed to reflect the relationship between the new T and M descriptors and overall survival,[14] and have been incorporated into the 7th edition of the AJCC staging guidelines.

Even with these changes, the M descriptor is still fairly simple in NSCLC and most other histologies, discriminating only among relatively local spread to the lung or pleura (contralateral lung nodules or pleural effusion), distant spread, and the absence of spread. The survival difference between M1a and M1b is still considerable (8-10 months vs 6 months, respectively, in the IASLC studies),[13] but the new grouping does not capture the relatively favorable prognosis of a patient with several small isolated metastases (especially extracranial-only metastases). Furthermore, as with all staging systems, this is just a snapshot in time, and does not describe how the history of disease unfolds for a particular patient after initial assessment. For NSCLC patients with metastatic disease, the actual story is far more complex.

Oligometastatic Disease

Our appreciation and understanding of the concept of metastatic disease has undergone significant evolution over the past 100 years. Following on the early Halsted hypothesis of orderly contiguous spread from a primary location,[15] the systemic hypothesis arose suggesting that any clinically apparent cancer already represented widespread disease. A bridging hypothesis advanced by Hellman and Weichselbaum in 1995 suggested that cancer comprises a spectrum of localized and systemic disease with many intermediate states.[16] This hypothesis was supported by a number of clinical observations made during the aggressive local management of metastatic disease, with the strongest observations made in the treatment of liver and lung metastases, primarily from colorectal cancer and sarcoma.[17-23]

Patients with limited metastatic disease of various histologies may potentially have prolonged progression-free survival (PFS) if all sites of clinically apparent malignant deposits are controlled locally with surgery or radiation.[24-30] Review of patterns of relapse after chemotherapy alone has demonstrated that the majority of systemic treatment failures in the stage IV setting occur at the sites of original gross disease.[31] Given the advances in imaging that allow for earlier detection and more precise delineation of targetable disease, our ability to pinpoint targets for local therapy will continue to improve.

The question is whether this proposed oligometastatic state—in which local intervention will yield clinically relevant benefits—exists for NSCLC. Although aggressive management of metastases to the lung from nonlung histologies has been shown to improve outcomes[22] and is now generally part of standard management for patients who can tolerate surgery, the converse also may be true for metastases from primary lung cancer. For example, NSCLC is one of the few disease states in which management of brain metastases is associated with a distinct survival advantage.[32] In the Radiation Therapy Oncology Group (RTOG) 95-08 trial, a randomized controlled trial comparing whole-brain radiation therapy (WBRT) alone vs WBRT plus targeted stereotactic radiosurgery (SRS) in patients with 1 to 3 brain metastases no greater than 4 cm in size, 63% of the patients treated had metastatic lung cancer. On multivariable analysis, only RTOG recursive partitioning analysis[33] class and squamous/non–small cell lung primary histology retained a significant association with survival. Although limited randomized evidence exists to confirm a similar survival advantage for extracranial disease in NSCLC, in the following sections discussing the range of interventions applied to the treatment of limited metastatic disease, retrospective and prospective nonrandomized studies have shown encouraging oncologic results that suggest that patients with limited metastatic disease burden do not "follow the curve" for their designated AJCC stage.

For the majority of stage IV NSCLC patients who progress through first-line or subsequent systemic therapy without an actionable mutation, supportive options and survival are insufficient.[34,35] Given the possibility that aggressive local control may provide some benefit in at least a subset of patients, exploring the use of local therapies is imperative, and may help bridge patients to subsequent effective systemic therapies. Only a well-designed prospective randomized trial can truly answer the question of whether the application of aggressive local therapy options will have a clinically relevant impact. When considering these options, an understanding of the role of surgery, interventional radiology techniques, and external beam radiation therapy is needed, along with knowledge about how these interplay with systemic treatment.

Systemic Treatments and Interaction With Local Therapy

A complete review of the role of and options for systemic treatment is beyond the scope of this work, which focuses on the management of limited local metastatic disease,

but the effect of systemic treatments (particularly targeted treatments) must be taken into consideration when deciding when and how to pursue aggressive local therapy. One theory of oligometastases is that progression of clinically detectable metastatic lesions in the face of targeted therapy represents the "escape" of a resistant subclone. Aggressive management of these resistant subclones may preserve the efficacy of a relatively nontoxic systemic treatment and leave the patient with more options over time.[27,36,37] Additionally, the use of local therapies as cytoreductive agents to debulk disease follows the Norton-Simon hypothesis, which suggests that the optimal efficacy of systemic therapy is dependent on natural tumor growth kinetics.[38,39] By eliminating large reservoirs of disease that are under increased pressure due to hypoxia or metabolic stress, the remaining disease burden may be more susceptible to systemic drug treatments.

Two targeted agents often used in the NSCLC population are erlotinib (Tarceva, Genentech/Astellas) and crizotinib (Xalkori, Pfizer). Erlotinib is an EGFR tyrosine kinase inhibitor originally approved for all locally advanced NSCLC patients after failure of at least 1 prior chemotherapy regimen, contributing to a median PFS and overall survival (OS) of 2.3 and 6.7 months, respectively.[40] Crizotinib is an orally available small-molecule inhibitor of ALK, a tyrosine kinase. Oncogenic fusion genes consisting of *EML4* and *ALK* are present in a subgroup of NSCLCs, representing up to 7% of such tumors.[41] For patients with this mutation treated with crizotinib, the overall response rate was 57%, the estimated probability of 6-month PFS was 72%, and the median for the study was not reached.

Patients with oncogene-dependent NSCLC treated with such tyrosine kinase inhibitors will still frequently experience limited sites of metastatic disease progression. A study by Weickhardt and colleagues[37] investigated the benefits of aggressive local ablative therapy for patients with central nervous system and/or limited systemic disease progression. They also described continuation of treatment with crizotinib or erlotinib in patients with metastatic *ALK* gene rearrangement (ALK+; n=38) or *EGFR*-mutant (*EGFR*-MT; n=27) NSCLC, respectively. In their study, the median PFS was 9.0 months for ALK+ patients on crizotinib, and 13.8 months for *EGFR*-MT patients on erlotinib. Twenty-five of 51 patients (49%) who progressed were deemed suitable for local therapy (15 ALK+, 10 *EGFR*-MT; 24 with radiotherapy, 1 with surgery) and continuation of the same targeted therapy. After receiving aggressive local therapy, 19 of 25 patients progressed again, with median subsequent PFS of 6.2 months. The authors concluded that the use of aggressive local therapy allowed effective continuation of relevant targeted therapy.

Local Therapies

Surgery for Oligometastatic NSCLC

Surgery is not always an option for patients with metastatic NSCLC, but it certainly has an established role even in stage IV disease, particularly in patients presenting with brain and adrenal metastases.[26,32,42-46] Radical treatment is supported by the European Society for Medical Oncology (ESMO) guidelines for selected patients with solitary metastases.[5]

Patchell and colleagues[43] established the role of surgical resection for solitary brain metastasis. In their prospective randomized trial, patients with single brain metastases (77% of whom had NSCLC) underwent surgery or biopsy and conventional WBRT. Overall survival was significantly enhanced in the surgery group (40 vs 15 weeks; $P<.01$). More recent studies, although not randomized, have begun to demonstrate the relative benefit of aggressive local surgical management of limited metastatic disease. Bonnette and colleagues[47] reported on 103 patients who underwent resection of primary and synchronous brain metastases from NSCLC, with survival of 56% at 1 year, 28% at 2 years, and 11% at 5 years. Collaud and colleagues[48] reported on 29 patients with synchronous single-organ metastatic NSCLC who underwent lung resection and local treatment of metastasis (brain, lung, adrenal). Their OS was 65% at 1 year and 36% at 5 years, and their median survival was 20.5 months. Congedo and colleagues[49] reported on 53 patients with oligometastatic disease treated primarily with surgery (in 42 patients); the most common involved sites were brain (n=39), followed by adrenal gland (n=7), bone (n=3), vertebrae (n=3), liver (n=1), and contralateral supraclavicular lymph node (n=1). OS was 73.1% at 1 year and 24% at 5 years, with a median survival of 19 months.

A concern is that many of the metastatic sites for NSCLC may not be amenable to surgery. For example, not all brain lesions are resectable—especially if there are multiple lesions, brainstem lesions, or lesions within eloquent brain—and resection of bone or spine lesions can have a high morbidity.[50] Resection of the limited number of liver lesions is an option for some, but not all, patients. The most common site for metastatic recurrence of NSCLC, the ipsilateral or contralateral lung, is only amenable to surgical treatment in a small number of patients. Local control rates are typically 85% to 95% if lobectomy can be performed, but more limited wedge resections typically offer local control rates of only 50% to 70%.[51,52] Adrenal metastases in relatively healthy patients are amenable to surgery using a minimally invasive approach.[26,44]

Interventional Radiology as Ablative Technology for Oligometastatic NSCLC

A number of focal ablative techniques have been tested in the management of focal lesions, including chemical

techniques (eg, ethanol ablation), thermal techniques (eg, radiofrequency ablation [RFA], laser ablation, focused ultrasound ablation, microwave ablation, and cryoablation), and irreversible electroporation. These are generally performed by practitioners from interventional radiology or in conjunction with an intraoperative procedure.[53-55]

In one of the largest reported studies for RFA, Simon and colleagues[56] reported on the treatment of 153 consecutive patients with primary or metastatic medically inoperable lung cancers treated with thoracic percutaneous fluoroscopic computed tomography (CT)-guided RFA. The overall 1-, 2-, and 5-year survival rates for stage I NSCLC were 78%, 57%, and 27%, respectively. The 1-, 2-, and 5-year local tumor control rates were 83%, 64%, and 47% for tumors 3 cm or smaller and 45%, 25%, and 25% for tumors larger than 3 cm, respectively. The overall pneumothorax rate was 28.4% (52 of 183 ablation sessions), with a 9.8% (18 of 183 ablation sessions) chest tube insertion rate. The overall 30-day mortality rate was 3.9% (6 of 153 patients), with a 2.6% (4 of 153 patients) procedure-specific 30-day mortality rate.

In addition to the lung, local interventional ablative strategies have been heavily investigated in the liver, with local control up to 90%,[57-60] as well as in adrenal lesions.[54] However, these strategies are limited by healthy tissue reserve, operability (still an invasive procedure with significant bleeding risks), the size of the target lesions, and the presence of vascular structures that can serve as a heat sink, preventing the effective delivery of cytotoxic thermal energy.[61-63] Osseous metastases also may be amenable to symptomatic treatment with thermal ablative techniques,[64-66] but care must be exercised close to nerve structures, which may be easily damaged by heat.[67] Furthermore, oncologic local control rates with ablative techniques have not been established. As such, access to other minimally invasive techniques—or, optimally, noninvasive techniques—is critical.

SRS and SBRT for Oligometastatic NSCLC

Stereotactic radiosurgery and stereotactic body radiation therapy (SBRT) are focal radiation techniques that deliver high doses of radiation in limited treatments to intracranial and extracranial malignant disease, respectively.[68,69] SRS is a standard tool for the treatment of intracranial metastases, with demonstrated safety and efficacy with and without the use of concomitant WBRT.[32,43,70,71] SBRT has proven efficacy in the treatment of patients with early-stage, medically inoperable NSCLC,[72] with an emerging indication in the setting of limited metastatic disease.[37,73-83] Because SRS is a well-established modality for intracranial lesions, we will emphasize current studies including oligometastatic NSCLC and advances in SBRT in this section.

SBRT has an established role in treating metastases of the adrenal gland, which is a common site for NSCLC metastases. With fractionation schedules ranging from 36 to 45 Gy in 3 to 5 fractions, local control between 87% and 100% at 1 year has been reported.[84-87] Holy and colleagues[87] reported a median OS of 23 months among NSCLC patients with isolated adrenal metastases treated with SBRT (40 Gy in 5 fractions), a rate comparable to that of similar patients managed with adrenalectomy. Casamassima and colleagues[86] achieved local control rates of 90% at 2 years in patients with various histologies, including NSCLC treated with SBRT (36 Gy in 3 fractions).

Focused prospective trials for lung[78] and liver[79] oligometastases were administered by the University of Colorado. The lung phase 1/2 trial enrolled patients with 1 to 3 pulmonary metastases from a solid tumor (13% from primary lung cancer), provided that the cumulative tumor diameter was less than 7 cm and the patients had adequate pulmonary function. The SBRT dose was escalated from 48 to 60 Gy in 3 fractions safely, and achieved 96% local control at 2 years, with a median OS of 19 months and limited toxicity (7.9% grade 3 toxicity).[78] The liver phase 1/2 trial enrolled patients with 1 to 3 hepatic metastases from a solid tumor (21% from primary lung cancer), provided that the cumulative tumor diameter was less than 6 cm and the patients had adequate liver and kidney function. The SBRT dose was escalated from 36 to 60 Gy safely, achieving a local control at 2 years after SBRT of 92% and median survival of 20.5 months. There was only 1 grade 3 toxicity observed, and no instances of classic radiation-induced liver dysfunction.[79]

Multiple trials that have not limited the target oligometastatic subsite also have also been performed. In a study from the Mayo Clinic by Milano and colleagues,[76] 121 patients with up to 5 sites of disease of any histology (including NSCLC) were treated with SBRT to all sites of disease using a preferred dose of 50 Gy in 10 fractions. The patients achieved 74% local control at 2 years in nonbreast primary histologies, with a median survival in that cohort of approximately 18 months. Only 1 patient experienced a grade 3 toxicity. They noted significantly improved rates of OS in patients who achieved a clinical response or had stable disease on systemic therapy prior to receiving SBRT. At the University of Chicago,[80] a prospective dose-escalation study was performed in which patients with 1 to 5 oligometastases of any histology (18% from primary NSCLC) were treated with SBRT to any site, escalating from 24 Gy in 3 fractions to 42 Gy in 3 fractions. They achieved a median PFS of 5.1 months and a median survival of over 2 years, with only 2 acute and 7 chronic grade 3 toxicities. Local control at 2 years (53%) was not as high as in other studies, likely owing to the lower administered dose in the early period of the study; the authors did note that in the higher-dose cohorts, local control at 2 years neared 90%. In Japan, Inoue and colleagues[88] conducted

a study of SRS and SBRT for patients with 1 to 5 sites of oligometastatic disease in the brain, lungs, or adrenal glands, including 41 patients (61% from primary lung cancer) treated with 15 to 25 Gy single-fraction or 20 to 40 Gy 4-fraction SRS for intracranial lesions, 48 Gy in 8 fractions for adrenal metastases, or 35 to 60 Gy in 4 to 8 fractions for lung lesions. They achieved local control at 3 years of 80%, and a median survival of 24 months. No grade 3 or higher toxicities were noted.

Focusing exclusively on oligometastatic disease from primary NSCLC, a recent phase 2 study was performed by our institution[89] in which SBRT in 1, 3, or 5 fractions with doses of 19 to 24 Gy, 27 to 33 Gy, or 35 to 40 Gy respectively was used to cytoreduce malignant metastatic NSCLC deposits, with erlotinib as the systemic therapy backbone. Enrolled patients were not selected for mutation, had limited metastatic NSCLC (<6 extracranial sites), and had progressed through first-line chemotherapy. SBRT was delivered to a range of extracranial sites, and to 2 or more sites in 62.5% of patients. The median PFS and OS for patients in this study were 14.7 months and 20.4 months, respectively, which compared very favorably to the 8- to 12-month median survivals noted following first-line chemotherapy,[1-5] the 6- to 9-month median survivals observed following progression through subsequent lines of cytotoxic chemotherapy,[34,35] or even the 18-month median survival reported for patients with stage IV NSCLC who responded to first-line therapy and received maintenance chemotherapy,[90] although it must be emphasized that this is a comparison with historical controls and does not account for selection bias or other potential sources of confounding. A change in the pattern of relapse was noted, with a shift in failure from treated sites of known disease to new sites of distant failure. By treating new sites of progression with SBRT, several patients in this study were able to remain on erlotinib for additional periods of 6 to 9 months. Toxicities were limited and included 2 grade 3 toxicities, 4 grade 4 toxicities (1 possibly from SBRT, and 3 definitely related to erlotinib), and 1 grade 5 toxicity (death) possibly related to SBRT.

Interstitial Brachytherapy for Oligometastatic NSCLC

A therapeutic technique that bridges the disciplines of Interventional Radiology and Radiation Oncology is image-guided interstitial high-dose-rate brachytherapy. A percutaneous interstitial high-dose-rate brachytherapy treatment directly irradiates the target lesion by placing a radiation source within the lesion under image guidance (generally ultrasound or CT), delivering ablative doses of radiation to the tumor while sparing nearby healthy tissues.[91]

Although limited data are available for the use of this technique in stage IV NSCLC, it does have demonstrated efficacy in the treatment of liver metastases, which is a more common site for patients with *EGFR*- or *ALK*-mutated NSCLC.[10,11] A prospective trial by Ricke and colleagues[92] treated 73 patients with 199 colorectal liver metastases to minimal lesion dose levels of 15, 20, or 25 Gy. A significant dose response for local tumor control was observed, with less than 5% risk of recurrence at prescription doses of 25 Gy. This dose was associated with an 8% rate of grade 2 and 3 complications. Similar results have been observed in the treatment of liver metastases from primary breast,[93] renal,[94] and gastric/gastroesophageal cancer.[95] Because the initial approach for this technique is the same as any other interventional radiology ablative technique, it could be applied to targets in the lungs, adrenal glands, and kidneys, and has already been applied with some success in osseous targets such as the spine.[96] Further development is warranted to determine the anatomic sites and populations in which this technique may be best applied.

Discussion and Future Directions

The pursuit of aggressive local therapy—including surgery, interventional radiology techniques, and external beam radiation techniques—has gained significant momentum in the treatment of selected stage IV patients with oligometastases. This aggressive therapy has resulted in dramatic improvements in local control, and many feel that it has led to measurable cure rates in patients previously thought to be incurable. Although this observation is grounded in clinical studies of colorectal and sarcoma primary histologies, in which the natural history of the disease can be quite prolonged, there is growing evidence that it also may apply to aggressive primary cancer subtypes in which the therapeutic window is very narrow, such as in advanced NSCLC. The current standard of care in advanced NSCLC without actionable mutations consists of systemic therapy alone regardless of the tempo of progression or number of disease sites and offers an unacceptable median OS of only 1 year.[1,2,4]

Given that most patients with stage IV NSCLC who fail first-line therapy experience progression in the original sites of gross disease,[34,35] pursuit of aggressive local control is reasonable. However, determining whether to use surgery, interventional radiology ablative techniques, or external beam radiation therapy techniques to do so is a complicated question. The optimal treatment should be minimally invasive (or noninvasive), administered quickly and efficiently, not have a lengthy recovery period, not impede delivery of other local or systemic treatment, and have a high rate of local control.[97,98] It must be noted that 80% of patients will develop additional metastases within 2 to 4 years of radical treatment,[82] so flexibility with the

treatment approach must be maintained. Options that retain the greatest degree of functional independence for the patient are necessary to bridge the patient from one treatment to the next, without impairing quality of life or future treatment options.

For medically fit patients with operable disease, surgery could be considered, but recovery time is a key limitation in this population; for example, patients with bone-based metastases may have significant impairment with long recovery times. Interventional ablative techniques are promising, but prospective oncologic outcome data for many of the sites often involved with metastatic NSCLC are limited. Efficacy is primarily seen in lesions smaller than 3 cm, and is impaired by the presence of vascular structures.[61-63] Although these procedures are minimally invasive, they are still invasive, with a high rate (>25%) of pneumothorax observed in the treatment of lung lesions and a 4% mortality rate.[56] SBRT, while not necessarily perfect for all scenarios, may offer the most versatile option for treating the widest range of disease sites in the largest portion of patients.

The reported experience thus far in the treatment of oligometastatic NSCLC has been primarily retrospective or as a subset of larger prospective studies. Despite these limitations, the data that are available support the use of aggressive local therapy.[74-77,80-83,99] With the addition of the recent study by our institution,[89] the excellent local control and relative improvements in median survival compared with historic outcomes have been validated in an NSCLC-only population. Additionally, studies have shown that more than half of advanced NSCLC patients have metastatic deposits amenable to SBRT after first-line therapy,[31] suggesting that a significant proportion of patients could potentially benefit from this approach. Given advances in imaging that allow for earlier detection and more precise delineation of targetable disease, this distribution will likely move further in favor of effective SBRT delivery. Furthermore, more localized dose deposition with charged-particle treatments (such as protons, helium ions, or carbon ions) may broaden eligibility for suitable patients.

Although it may be premature, we may have reached a point at which the M descriptor in the staging of NSCLC should be reexamined and potentially redefined. With a median survival of 20.4 months in our recent institutional study,[89] outcomes for mutation-unselected patients were far superior to the M1a (8-10 months) and M1b (6 months) reported by Postmus and colleagues[13] as part of the recent IASLC Lung Cancer Staging Project. Our results are more comparable to the outcomes for IIB or IIIA NSCLC reported in the updated TNM stage grouping by Goldstraw and colleagues[14] for the seventh edition of the AJCC staging guidelines. Significantly more data and follow-up will be needed before the oligometastatic disease state can be effectively incorporated into staging guidelines, however, as we still do not fully understand the temporal nature of the oligometastatic state or the underlying molecular mechanisms that drive it.[27,100]

We still need further prospective data to guide the treatment of stage IV NSCLC. The optimal integration of local therapy with systemic therapy for limited metastatic disease must be determined, as well as the efficacy of local therapy as a stand-alone treatment for oligometastases. At our institution, we have initiated trials comparing maintenance therapies vs SBRT plus maintenance therapies for limited metastatic disease in the extended first-line setting (NCT02045446), and currently have an open registry trial for patients with oligometastatic disease (NCT02170181) in which treatment with curative intent is offered to patients with 6 or fewer sites of metastatic disease (either on initial presentation or within the context of initial combined modality treatment). SABR-COMET (Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors) is a multi-institutional study (NCT01446744) currently accruing patients with advanced cancers. This study is randomly assigning patients to standard therapy alone or standard therapy plus SBRT given to up to 5 metachronous oligometastases.[101] We expect that these studies will help us identify the patients and sites most likely to benefit from local therapy, as well as firmly establish the oncologic benefit of aggressive local control.[24,102] In the interim, we will continue to refine and improve our techniques to ensure that our patients receive the safest and most effective treatment we can provide.

Disclosures

The authors have reported no relevant financial disclosures.

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