Management of Oligoprogressive and Oligopersistent Disease in Advanced NSCLC

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Abstract: The oligometastatic disease state is defined as an intermediate state between localized cancer and widespread systemic metastases. Oligoprogression is defined as a subgroup in which limited metastatic areas are progressing in the background of oligometastatic or polymetastatic disease, whereas oligopersistent disease refers to an induced state in which formerly polymetastatic disease responds to treatment and decreases to fewer than 5 sites of active disease. With modern improvements in systemic therapy for patients with non–small cell lung cancer, including immunotherapies and targeted therapies, there may be a role for local therapy in selected patients with limited metastases—a subset of patients with potentially curable metastatic disease. Improved imaging techniques and advancements in highly conformal delivery of radiotherapy with stereotactic body radiation therapy have increased interest in using ablative radiotherapy or surgery as local consolidation therapy to improve patient outcomes. In this review, we define the oligoprogressive and oligopersistent disease states in patients with non–small cell lung cancer and discuss the evidence for the treatment and management of this patient population, including recent prospective trials and future directions in the selection of patients who will benefit most from local therapy.

Keywords
Local consolidative therapy, NSLC, oligometastatic, oligopersistent, oligoprogressive

Introduction

The idea of oligometastatic disease as a discrete clinical state was first introduced by Hellman and Weichselbaum in 1995.[1] This concept arose from an increased understanding of the multistep character of cancer progression, whereas previous schools of thought suggested that cancer spread in a contiguous manner (Halsted theory) or that all cancers, even limited primary tumors, are a sign of early systemic disease that may have already metastasized. Weichselbaum and colleagues suggested that these theories of cancer spread were too limited and that many intermediate states exist between localized cancer and systemic disease, adding that malignancy also evolves

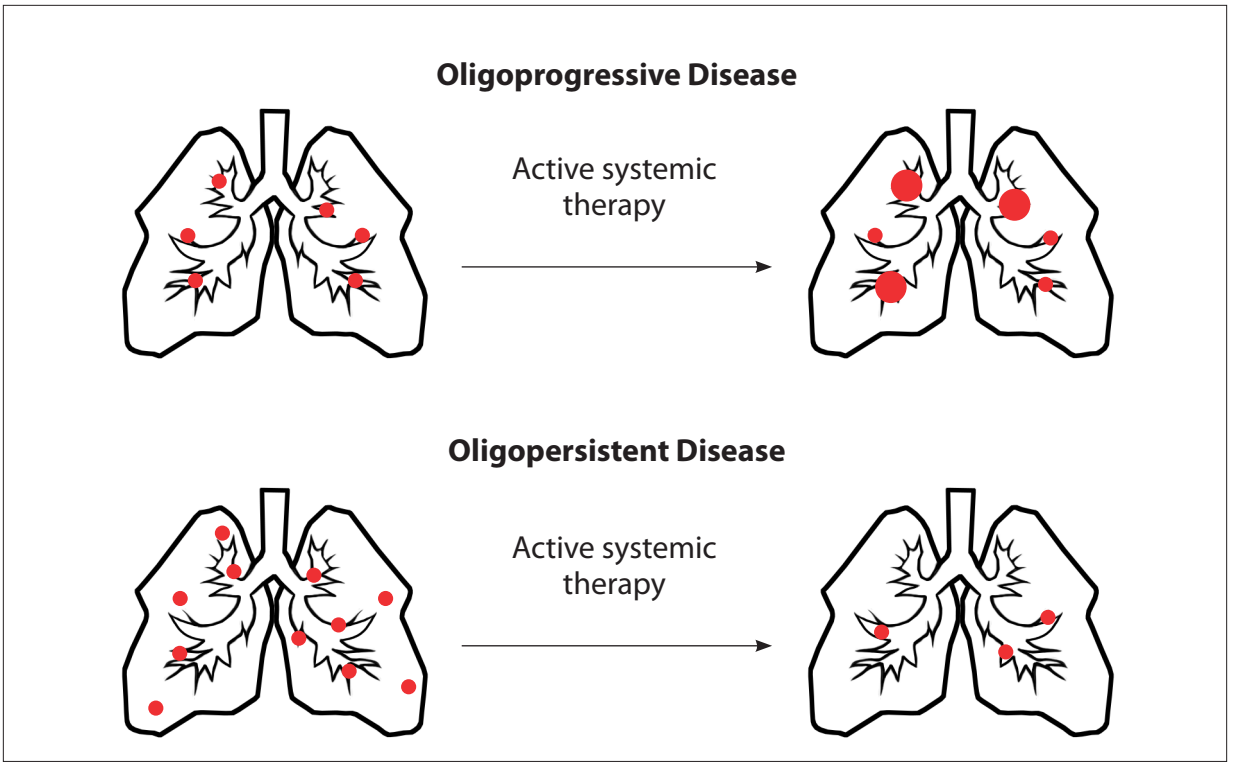

Figure. *Oligoprogression* is defined as a state in which limited metastatic areas are progressing in the background of oligometastatic or polymetastatic disease (top). *Oligopersistence* is defined as an induced oligometastatic state in which a patient with formerly polymetastatic disease has responded to treatment, with the result of fewer than 5 sites of active disease (bottom).

and progresses during cancer spread. They proposed the existence of an oligometastatic state, in which metastases are limited to one or a finite number of organs as a consequence of anatomy or physiology. They also indicated that tumor progression is related to primary tumor size and grade, which are functions of tumor biology. As a tumor grows and metastasizes, it becomes more efficient at metastasizing and seeding organs. This leads to the conclusion that oligometastatic disease does not occur by chance; rather, it is a state during the multistep process of tumor progression during which a cancer has a limited ability to metastasize.[1]

An example of early research is the SABR-COMET trial, which investigated the benefit of local therapy with stereotactic ablative radiotherapy (SABR) in patients who had oligometastatic disease (defined as 1 to 5 metastatic lesions in patients with a controlled primary malignancy). In SABR-COMET, SABR achieved a 22-month median benefit in overall survival (OS) in patients with oligometastatic disease.[2]

In the modern era, we have made much progress in the realm of management of patients with limited metastatic disease. However, the ability to define oligometastatic disease is limited by the lack of biomarkers available to identify patients with true oligometastatic disease, such that imaging is used as the main diagnostic modality. A growing body of work has sought to anatomize the different forms of oligometastatic disease. Guckenberger and colleagues characterized and classified oligometastatic disease, first by differentiating between patients with a history of polymetastatic disease before a diagnosis of oligometastatic disease to characterize induced oligometastatic disease (with previous history) and patients with genuine oligometastatic disease (without previous history). Genuine oligometastatic disease was then subclassified as repeat disease (with previous history of oligometastatic disease) or de novo oligometastatic disease (first-time diagnosis). Patients with de novo oligometastatic disease were further subclassified as those with (1) oligorecurrent disease, in which oligometastatic disease was diagnosed during a treatment-free interval; (2) oligoprogressive disease, in which signs of progressive disease were detected on imaging in patients undergoing active systemic therapy; or (3) oligopersistent disease, in which imaging indicated stable disease or a partial response in patients on active systemic therapy. This characterization is important as we further develop treatment goals and strategies for different forms of oligometastatic disease.[3]

We note that although current paradigms base definitions of oligometastatic disease on the number of active

lesions and timing, further work is needed to explore how histology, genomics, and other factors can help define the disease setting better.

This review focuses on the oligoprogressive and oligopersistent disease states in patients with non–small cell lung cancer (NSCLC) and on the management of these patients.

Definition of Oligoprogressive and Oligopersistent Disease

In the oligometastatic state, patients have controlled primary tumors and 5 or fewer sites of metastatic disease. Oligoprogression is defined as a subgroup in which limited (≤5) metastatic areas are progressing in the background of oligometastatic or polymetastatic disease.[4] Oligopersistence is defined as an induced oligometastatic state in which a patient with formerly polymetastatic disease responded to treatment that resulted in 5 or fewer sites of active disease.[5] These are described graphically in the Figure.

Management of Oligoprogressive and Oligopersistent Disease

The techniques used to manage oligoprogressive or oligopersistent disease include systemic therapy, local ablative therapy, surgical resection, radiofrequency ablation, and stereotactic body radiation therapy (SBRT).

Systemic Therapy

Systemic therapies for metastatic NSCLC are determined by the histologic subtype and molecular profile of the cancer. Screening for *EGFR*, *KRAS*, *ALK*, *BRAF*, *NTRK1/2/3*, *MET*ex 14 skipping, *RET*, and *HER2* mutations and programmed death–ligand 1 (PD-L1) testing are the standard of care (SOC) for all patients with newly diagnosed metastatic disease. Tyrosine kinase inhibitors (TKIs) have been the mainstay first-line treatments for most patients with NSCLC mutations. Exceptions are targeted monoclonal antibodies, which are used in patients with particular mutations (eg, amivantamab [Rybrevant, Janssen] for *EGFR* mutation insertions and trastuzumab for *HER2* mutations). If none of the aforementioned biomarkers are deemed actionable, treatment is guided by PD-L1 status. For patients with a PD-L1 status of 50% or higher, immunotherapy with pembrolizumab (Keytruda, Merck) or atezolizumab (Tecentriq, Genentech) is given with the option of chemotherapy (pemetrexed plus platinum-based treatment).

In cases of disease progression or persistence, first-line systemic therapy is continued or a second-line systemic agent within the same drug class is initiated. Given recent data, further described in later sections of this article, the addition of local therapy to progressive or persistent sites of limited metastatic disease may be recommended for improved disease control. The goal of pursuing local ablative therapy, such as radiation, is to eliminate cancer clones that have become resistant to initial therapy, to stimulate a tumor-specific immune response in the body, and to avoid the use of second- or subsequent-line systemic therapies in order to save these options for use in the scenario of relapse further down the line.[6] The use of local therapy to control limited sites of metastatic disease can mitigate disease progression and allow patients to continue on systemic therapy.[4]

Local Ablative Therapy

Local therapy, especially radiation therapy, historically has been used for palliation in advanced NSCLC. Improved systemic therapy—including immunotherapy and targeted therapy—is behind the rationale for supporting local therapy to control limited metastatic disease. For example, the addition of pembrolizumab to standard chemotherapy resulted in significantly longer OS and progression-free survival (PFS) vs treatment with chemotherapy alone.[7] With improvements in systemic therapy, patients who have limited sites of metastatic disease may not experience progression or may experience progression only in sites of initial disease.

Modern diagnostic tools also allow the detection of early metastatic disease. These improvements in the modern era suggest that local therapy has a role in selected patients and that metastatic disease in a subset of patients may be curable. Improved imaging techniques and advancements in highly conformal delivery of radiotherapy with SBRT have resulted in increased interest in using ablative radiotherapy or surgery as local consolidation therapy (LCT) to improve patient outcomes. Meta-analyses of patients with true oligometastatic disease have shown that they can benefit from ablative local therapy, with an increase in 5-year OS.[8]

Surgical Resection

The concept of using local therapy in the management of metastatic disease was first derived from surgical metastasectomy. Historically, metastatic sites of disease were definitively managed with radical resection. Patchell and colleagues demonstrated a benefit in both local control and OS in patients who underwent surgical resection of limited brain metastases in addition to whole-brain radiotherapy vs patients who underwent whole-brain radiotherapy alone.[9] Pastorino and colleagues looked at 5206 patients from the International Registry of Lung Metastases who underwent complete metastasectomy and found 5- and 10-year survival rates of 36% and

26%, respectively. Notably, the 5-year survival rate in patients who underwent a complete resection was 43% in those with single lesions and 27% in those with 4 or more lesions.[10] Patients with liver metastases from colon cancer are often treated with liver resection, with reported 10-year survival rates of 20% to 26%.[11]

The existence of the oligometastatic state is well supported by surgical literature, and surgical resection of oligometastatic sites of disease has been used in patients with NSCLC. A retrospective review of 185 patients with NSCLC who underwent resection of brain metastases at Memorial Sloan Kettering Cancer Center from 1974 to 1989 found a 5-year OS rate of 13% and a 10-year OS rate of 7%. Notably, multivariate analysis demonstrated that complete resection of primary disease resulted in significantly prolonged survival.[12] Nonetheless, prospective data supporting the use of surgical resection in oligometastatic NSCLC are limited.

Extracranial sites of metastatic disease in NSCLC have also been treated with surgical resection. Porte and colleagues retrospectively reviewed the records of 43 patients with NSCLC who were treated with surgical resection for synchronously (n=32) or metachronously (n=11) discovered adrenal gland metastasis. They found that median survival was 11 months and that the 4-year OS rate was 11%.[13] A meta-analysis performed by Ashworth and colleagues examined data on 757 patients with NSCLC who had 1 to 5 metastases treated with local therapy (surgical metastasectomy, SBRT, radical external-beam radiotherapy, and curative treatment of the primary lung cancer) and found that the median OS was 26 months. In this patient group, surgical resection was the most commonly used local treatment (n=635; 83.9% of patients).[14]

Adding to this body of work, one prospective phase 1/2 study looked at the role of radical local treatment (surgery or radiotherapy) in 40 patients with oligometastatic NSCLC. They found that the median PFS was 12.1 months, with a 1-year PFS rate of 51.3% and a 3-year PFS rate of 13.6%.[15] A single-arm, phase 2 prospective trial from Memorial Sloan Kettering Cancer Center looked at patients with NSCLC and a solitary metastasis who were treated with chemotherapy (mitomycin, vinblastine, and cisplatin) and resection of all sites of disease. The authors reported a median OS of 11 months, with 2 of 23 patients (9%) surviving at least 5 years.[16] These studies demonstrate the role of local therapy in the form of radical resection for patients who have NSCLC with limited metastases.

Radiofrequency Ablation

Radiofrequency ablation (RFA) is a technique in which thermal ablation is administered via a conductive probe inserted into a tumor under imaging guidance. High-frequency alternating current is delivered through the probe and heats tissues to a temperature that causes cellular destruction and necrosis.[17]

Historically, RFA has been used in medically inoperable patients and has shown efficacy in those with early-stage NSCLC. Simon and colleagues published data on 71 patients who had stage I primary lung cancer treated with RFA and reported 1- and 5- year OS rates of 78% and 27%, respectively. Notably, PFS rates were higher at all time points in patients with smaller lesions (≤3 cm) than in those with larger lesions (>3 cm): 83% vs 45% at 1 year and 47% vs 25% at 5 years, respectively.[18]

A multicenter prospective trial, ACOSOG Z4033, evaluated medically inoperable patients with stage IA NSCLC who underwent RFA for local therapy. The 1- and 2-year OS rates were 86.3% and 69.8%, respectively. Patients with lesions smaller than 2 cm had a statistically significant improvement in 2-year OS of 83%. The local tumor-free recurrence rate was 68.9% at 1 year and 59.8% at 2 years. These rates were worse for larger tumors. Overall, RFA was well tolerated, was not associated with worsening of pulmonary function test results, and yielded 2-year OS rates similar to those of patients treated with SBRT.[19]

Other minimally invasive local ablative therapies include microwave ablation, cryoablation, and percutaneous cryotherapy. These therapies, although not used as commonly as RFA, have shown comparable outcomes in recent data. Yang and colleagues examined patients with medically inoperable stage I NSCLC who underwent microwave ablation and reported 1- and 5-year OS rates of 80% and 16%, respectively. Once again, patients with smaller tumors (defined as ≤3.5 cm) had better outcomes. The local control rate was 96% at 1 year and 48% at 5 years.[20] Moore and colleagues looked at medically inoperable patients with stage I NSCLC who underwent cryoablation and reported a 5-year OS rate of 67.8% and a 5-year PFS rate of 87.9%.[21]

These reports indicate that ablative techniques such as RFA and cryoablation are safe and efficacious for the local control of early-stage primary NSCLC. Further work should be done to elucidate efficacy and survival outcomes in patients with oligometastatic NSCLC who are treated with RFA for local therapy.

Stereotactic Body Radiation Therapy

The development of SBRT, a radiotherapy technique that delivers highly conformal ablative doses of radiation, has made possible less invasive local ablative treatment of oligometastases in patients who are not surgical candidates. SBRT achieves high rates of local control and outcomes comparable with those of surgical resection.

An initial retrospective review from the University

Table. Clinical Studies of Importance in Oligoprogressive and Oligopersistent Non–Small Cell Lung Cancer

Study	Design and Results
Retrospective Studies in Oligoprogressive NSCLC	
Gan et al[27]	14 patients with *ALK*-mutated NSCLC whose disease progressed in ≤4 extracranial sites on crizotinib were treated with local therapy. Local control rates were 100% at 6 months and 86% at 12 months. Median PFS was 14 months for patients who received local therapy vs 7.2 months for patients who were not treated with local therapy.
Yu et al[28]	18 patients with *EGFR*-mutated NSCLC and oligoprogressive disease in whom resistance to EGFR inhibitors developed were treated with local therapy. Median PFS was 10 months, and median OS was 41 months.
Weickhardt et al[29]	25 patients with *ALK*- or *EGFR*-mutated NSCLC and oligoprogressive disease who continued systemic therapy with crizotinib or erlotinib received local therapy, with a median PFS of 6.2 months.
Prospective Studies in Oligoprogressive NSCLC	
Iyengar et al[30]	24 patients with NSCLC whose disease progressed on first-line systemic therapy were treated to a total of 52 sites of metastatic disease with SBRT and concurrent erlotinib, with a median PFS of 14.7 months and mean OS of 20.4 months.
CURB: Tsai et al[31]	31 patients with oligoprogressive NSCLC received SBRT + SOC treatment, and 28 patients with oligoprogressive NSCLC received SOC treatment alone. Median PFS was 10.0 months in the SBRT group vs 2.2 months in the SOC group.
Ongoing Prospective Studies in Oligoprogressive NSCLC	
SUPPRESS-NSCLC (NCT04405401)	2-arm prospective phase 2 study aims to randomize 68 patients with oligoprogressive NSCLC to SOC approach vs addition of SBRT to continued systemic therapy. Coprimary endpoints are PFS and OS.
HALT (NCT 03256981)	2-arm randomized phase 3 trial aims to randomize patients with oligoprogressive NSCLC and an initial response to TKI therapy followed by progression in 1 to 3 sites of extracranial disease to TKI therapy alone vs SBRT and continued TKI therapy.
STOP (NCT02756793)	Multicenter randomized phase 2 trial aims to randomize patients with oligoprogressive NSCLC in a 1:2 ratio to SOC therapy or SBRT to all sites of oligoprogression. Primary endpoint is PFS.
Prospective Studies in Oligopersistent and Oligorecurrent NSCLC	
Iyengar et al[24]	29 patients with limited metastatic NSCLC (primary plus ≤5 sites of metastatic disease) who achieved a partial response or had stable disease after induction chemotherapy were randomized to maintenance chemotherapy alone or to SBRT followed by maintenance chemotherapy. PFS was 9.7 months in the SBRT group vs 3.5 months in the maintenance-alone group.
Gomez et al[23]	74 patients with stage IV NSCLC and ≤3 metastatic lesions after first-line systemic therapy without evidence of disease progression were randomized to LCT or maintenance treatment alone. Median PFS was 11.9 months in the LCT group vs 3.9 months in the maintenance group.
Meta-analysis Comparing Oligoprogressive and Oligopersistent NSCLC	
Chen et al[36]	Analysis of 1750 patients with oligometastatic NSCLC from 20 different studies that stratified patients by synchronicity, oligopersistence, and oligoprogression/recurrence. On comparison of OS, pooled odds ratios were 3.981 (P<.001) for patients with synchronous oligometastatic disease, 3.355 (P<.001) for patients with oligopersistent disease, and 1.726 (P=.373) for those with oligoprogression/recurrence.

EGFR, epidermal growth factor receptor; LCT, local consolidative therapy; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; SBRT, stereotactic body radiation therapy; SOC, standard of care; TKI, tyrosine kinase inhibitor.

of Chicago examined 25 patients with oligometastatic NSCLC who were treated with SBRT. A total of 62 lesions (median, 2 lesions per patient) were treated with SBRT (most commonly 50 Gy in 10 fractions) administered to all sites of active disease (<5 sites of disease) after first-line systemic therapy. Median PFS was 7.6 months, and median OS was 22.7 months.[22]

The randomized, prospective phase 2 trial SABR-COMET enrolled patients with a controlled primary malignancy and 1 to 5 metastatic lesions. Patients were randomized in a 1:2 ratio to SOC palliative treatment or SOC treatment plus SBRT. The primary end point was OS. Of 99 patients, 18 (18%) had a primary lung cancer. The 5-year OS rate was 17.7% in patients who received SOC palliative treatment vs 42.3% in patients who received SBRT in addition to SOC treatment. The long-term analysis demonstrated that aggressive local therapy with SBRT had a durable effect on OS and indicated that it may be possible to achieve long-term disease control in patients with oligometastatic disease if all sites of limited disease are amenable to ablative therapies.[2]

Gomez and colleagues performed a randomized controlled phase 2 trial of patients who had stage IV NSCLC with 3 or fewer metastatic lesions after first-line systemic therapy without evidence of disease progression. Patients were randomized in a 1:1 ratio to local consolidative therapy (LCT) with SBRT, chemoradiation, or surgical resection or to maintenance treatment alone (including observation only). Among 74 patients who were enrolled, median PFS was 11.9 months in the LCT group vs 3.9 months in the maintenance treatment group, suggesting that LCT nearly tripled PFS in comparison with maintenance therapy alone. LCT was well tolerated and not associated with an increased incidence of serious adverse events. Notably, the study also found that time to the appearance of new sites of disease was prolonged in the LCT arm, suggesting that LCT may play a role in increasing time to recurrence or progression.[23]

A single-institution, randomized phase 2 study performed at UT Southwestern Medical Center randomized patients with limited metastatic NSCLC (primary tumor plus ≤5 sites of metastatic disease) who had achieved a partial response or stable disease after induction chemotherapy to either maintenance chemotherapy alone or SBRT followed by maintenance chemotherapy. Among 29 patients who were enrolled, a significantly improved PFS was noted in those treated with SBRT followed by maintenance chemotherapy vs those treated with maintenance chemotherapy alone: 9.7 months vs 3.5 months, respectively. SBRT was well tolerated, with similar toxicities in the 2 treatment arms. Notably, patients treated with SBRT experienced zero failures within the radiation field and had fewer overall recurrences, whereas patients who were treated with maintenance chemotherapy alone experienced both distant recurrence and progression at existing sites of disease.[24] This study once again demonstrated an almost tripling of benefit in PFS in patients with oligometastatic NSCLC treated with aggressive local therapy. Interestingly, the analysis also demonstrated that SBRT may have prevented local failure at sites of gross disease observed at presentation, which are thought to be the most likely sites of first recurrence according to data from studies of patterns of failure.[25]

As a result of the promising findings of these studies, the idea that local therapy may significantly affect outcomes in patients with limited metastatic disease gained traction and allowed development of the NRG LU002. This phase 2/3 randomized controlled trial compared patients with oligometastatic NSCLC (with ≤3 sites of extracranial metastasis whose disease did not progress after first-line systemic therapy) who received LCT with radiation and/or surgery (n=134) followed by maintenance systemic therapy vs patients who received maintenance therapy alone (n=81). Notably, immunotherapy was allowed, and 90% of patients were treated with immunotherapy-based systemic therapy. Preliminary results after enrollment of 215 patients, presented at the 2024 American Society of Clinical Oncology Annual Meeting, showed that 1- and 2-year PFS rates were 48% and 36% in the maintenance systemic therapy arm and 52% and 40% in the SBRT plus maintenance therapy arm. The 1- and 2-year PFS and OS rates were not found to be significantly different in the 2 arms. Work is ongoing to further elucidate these findings, which are the first results available of a randomized comparison of LCT and maintenance systemic therapy vs maintenance therapy alone in the era of immunotherapy.

Role of Palliative Treatment in Patients With Oligometastatic Disease

It is important to note that many approaches to oligometastatic disease, often including oligoprogressive and oligopersistent disease, are correctly guided by palliative intent. In these cases, we often allow the patient's symptoms, imaging findings, and functional status to guide decision making in terms of which lesions are most likely to benefit from local treatment. However, recent evidence provides compelling evidence in favor of a more nuanced approach to local treatment for oligoprogressive and oligopersistent disease.[26]

Management of Oligoprogressive and Oligopersistent Disease

In subsequent sections, we describe what is known about

the data guiding specific treatments for oligoprogressive and oligopersistent disease, acknowledging that these disease states are likely different from de novo oligometastatic and oligorecurrent disease.

Management of Oligoprogressive Disease

As previously mentioned, patients with oligoprogressive disease seem to be a distinct population deserving of separate discussions and studies to investigate the role of local therapies in improving their outcomes. Data suggest that each site of metastatic disease can undergo distinct clonal evolution, so that individual sites of disease develop treatment resistance. Such clonal evolution is independent of the behavior of other sites of metastatic disease, or even the behavior of the primary disease.[8] This understanding has led to retrospective studies evaluating the role of local ablative therapies in patients with progression of disease at limited sites.

Several retrospective studies have explored the role of local therapy in patients with oligoprogressive NSCLC. Gan and colleagues investigated the use of local therapy in patients with *ALK*-mutated NSCLC that had progressed on crizotinib (Xalkori, Pfizer) in 4 or fewer extracranial sites. Patients who received local ablative therapy underwent hypofractionated radiotherapy, SBRT, or surgical resection. Of 33 patients with oligoprogressive disease, 14 were treated with local therapy. Local control rates in the lesions treated with local ablative therapy were 100% at 6 months and 86% at 12 months. Moreover, a dose-response relationship was observed with local control, with a 12-month local control rate of 100% in patients who received a single-fraction equivalent dose of more than 25 Gy vs a 12-month local control rate of 60% in patients who received a single-fraction equivalent dose of 25 Gy or less. The median PFS was 14 months in patients who received local therapy vs 7.2 months in patients who were not treated with local therapy. These data suggest that local ablative therapy produced a durable response in the oligoprogressive lesions that were treated. An interesting point is that the median overall time on crizotinib in the patients who were treated with local ablative therapy was 28 months vs 10.1 months in the patients who were not able to receive local therapy, suggesting that local ablative treatment allowed patients to be treated with systemic therapy for an extended duration. Notably, the OS rate at 2 years was significantly better in the patients who received crizotinib for longer than 1 year (72%) than in those who received crizotinib for 1 year or less (12%).[27]

Another retrospective study, performed by Yu and colleagues at Memorial Sloan Kettering Cancer Center, examined patients with *EGFR*-mutated NSCLC in whom resistance to epidermal growth factor receptor (EGFR) inhibitors, including erlotinib and gefitinib, developed and who were treated with local ablative therapy. In this patient population with acquired resistance, who may not have had further options for targeted systemic therapies, local therapy (surgical resection, radiofrequency ablation, or radiation) was well tolerated and may have been associated with improved outcomes. Median PFS in 18 patients who had oligoprogressive *EGFR*-mutated NSCLC with acquired resistance to EGFR inhibitors was 10 months, and the median OS was 41 months.[28]

Weickhardt and colleagues looked at patients with *ALK*- or *EGFR*-mutated oligoprogressive NSCLC who continued treatment with crizotinib or erlotinib. They found that median PFS was 9.0 months for patients with *ALK*-mutated NSCLC vs 13.8 months for those with *EGFR*-mutated NSCLC. Of 65 patients with oligoprogressive disease, approximately half (n=25) received local therapy while continuing systemic therapy. Of these 25 patients, 19 later experienced progression, with a median subsequent PFS of 6.2 months.[29]

Patients with stage IV NSCLC that progresses through first-line chemotherapy are known to have a poor prognosis, with a median survival of 12 months and poor PFS and OS. Additionally, as previously described, recurrence after treatment with chemotherapy is most likely to develop at the original sites of gross disease. Iyengar and colleagues conducted a single-arm phase 2 study of patients with stage IV NSCLC and no more than 6 extracranial sites of disease that had progressed through first-line platinum-based chemotherapy and were amenable to treatment with SBRT to all sites and concurrent erlotinib until disease progression. Of note, erlotinib is an EGFR TKI that was originally approved for all patients with locally advanced NSCLC that had failed to respond to at least first-line chemotherapy. A total of 24 patients with progression on first-line systemic therapy were treated at a total of 52 sites of metastatic disease, most commonly in the lung parenchyma. Median PFS was 14.7 months, and mean OS was 20.4 months. An interesting finding from a patterns-of-failure analysis in this study was that most patients experienced distant progression in new sites of disease, and only 3 of 47 recurrent lesions were within the radiation field. This analysis suggests that the use of local therapy (SBRT) in addition to erlotinib not only yielded considerably increased PFS and OS in comparison with historical rates in patients treated only with second- or third-line systemic therapies but also resulted in a striking shift in patterns of failure.[30]

CURB (NCT03808662) was a randomized controlled phase 2 trial of SBRT in patients with oligoprogressive metastatic breast cancer or NSCLC with a primary endpoint of PFS. Enrolled patients received at

least first-line systemic therapy, and oligoprogression was defined as the presence of 5 or fewer progressive lesions on computed tomography or positron emission tomography/computed tomography. Patients were randomized in a 1:1 ratio to SOC treatment or to SBRT plus SOC treatment (SBRT group). A total of 28 of 51 patients (55%) in the SOC group had NSCLC, and 31 of 55 patients (56%) in the SBRT group had NSCLC. Overall, median PFS was 3.2 months in patients who received SOC treatment vs 7.2 months in patients in the SBRT group. Notably, no difference in PFS was found for the patients with breast cancer, but median PFS for the patients with NSCLC was 10.0 months for patients in the SBRT group vs 2.2 months for those in the SOC group. This striking result illustrates that the use of SBRT as a local ablative treatment in oligoprogressive NSCLC was effective and resulted in more than a 4-fold increase in PFS in comparison with the SOC approach. Further studies are needed to understand the differing results in patients with metastatic breast cancer.[31]

Several ongoing prospective studies aim to investigate further the role of local ablative therapy in improving outcomes in patients with oligoprogressive NSCLC in the immunotherapy era. The 2-arm, prospective phase 2 SUPPRESS-NSCLC (NCT04405401) study aims to randomize 68 patients with oligoprogressive NSCLC, defined as 1 to 5 extracranial lesions 5 cm or less in size and involving 3 or fewer organs, in a 1:1 ratio either to an SOC approach (including continuation of systemic therapy, moving to next-line therapy, or observation) or to SBRT to all lesions in addition to their continued systemic therapy. The co-primary endpoints are PFS and OS, with the goal of providing randomized evidence to further elucidate the role of SBRT in oligoprogressive NSCLC.[32] HALT (NCT03256981), which is currently enrolling patients, is a 2-arm randomized phase 3 trial that aims to evaluate the effect of local ablative therapy on PFS in patients with oligoprogressive NSCLC who had an initial response to a TKI but then had progression in 1 to 3 extracranial sites of disease. Patients are being randomized to continuation of TKI therapy only or to continuation of TKI therapy plus SBRT. STOP (NCT02756793) is a multicenter phase 2 trial that aims to randomize patients with oligoprogressive NSCLC (defined as documented progression in ≤5 individual lesions) in a 1:2 ratio either to SOC therapy or to SBRT to all sites of oligoprogression. Patients will be followed until the next disease progression, with a primary endpoint of PFS.[33] These studies are summarized in the Table.

Management of Oligopersistent Disease

Oligopersistent (whether repeat oligopersistent or induced oligopersistent) disease is stable or responds partially in a limited number of sites. In induced oligopersistent disease, a complete or prolonged partial response is noted in the remaining polymetastatic lesions.[34] The 2 earlier prospective studies of oligometastatic NSCLC (Gomez and colleagues and Iyengar and colleagues) both enrolled patients after completion of systemic therapy.[23,24] Because these patients were defined as having oligometastatic disease at the time of randomization, both patients with genuine oligometastatic disease resistant to systemic therapy and patients with induced oligopersistent disease may have been included. Similarly, in NRG-LU002, patients underwent induction systemic therapy and were included if they had oligometastatic disease. Therefore, patients with synchronous oligometastatic, oligopersistent, or rapidly oligorecurrent disease may have been included.

Oligopersistence suggests the existence of mutations in the persistent sites that remain resistant to systemic therapy, paralleling the biological underpinnings of induced oligorecurrent disease. It could be reasoned—although future work is needed to evaluate this hypothesis—that induced oligopersistent disease represents a more indolent entity than induced oligoprogressive disease, given the stability (and nonprogression) of the residual lesions. The goal of local therapy in oligopersistent disease would be to eliminate these resistant clones, potentially improving the depth of response to systemic therapy.

A recent analysis pooled 1750 patients with oligometastatic NSCLC from 20 different studies evaluated the role of local therapy in their management, stratifying patients by synchronicity, oligopersistence, and oligoprogression/recurrence.[35] On comparisons of OS, the pooled odds ratios were 3.981 (P<.001) for patients with synchronous oligometastatic disease, 3.355 (P<.001) for patients with oligopersistent disease, and 1.726 (P=.373) for patients with oligoprogression/recurrence. These data recapitulate findings from Chen and colleagues, who retrospectively analyzed patients with oligometastatic disease in the setting of the European Society for Radiotherapy and Oncology (ESTRO)/European Organisation for Research and Treatment of Cancer (EORTC) guidelines and found significantly worse survival for patients with oligorecurrent disease than for those with oligopersistent disease.[36] The data suggest distinct behavior (and possibly distinct underlying biology) in these entities, strengthening the argument for future work evaluating the role of consolidation, especially in oligopersistent disease.

Future Directions in the Management of Oligoprogressive and Oligopersistent Disease

The next steps in determining the optimal management of oligoprogressive and oligopersistent disease involve developing an understanding of the underlying factors

that drive specific lesions to become oligoprogressive or oligopersistent. For example, the ability to identify specific clones that are resistant to systemic treatment might be beneficial in guiding clinical decision making to determine which patients and lesions would benefit from aggressive local ablative therapy. In addition to heterogeneity in response to systemic therapy for induced oligometastatic lesions (progressive or persistent), further work must explore factors beyond direct tumor genetics that an influence response. For example, the location of the tumor, the tumor microenvironment, and anatomic considerations (an obvious one being the blood-brain barrier) must be explored. Further studies are also needed to elucidate how sites of oligoprogressive disease affect prognosis and to understand how the timing of oligoprogression can affect patient outcomes.

In the era of immunotherapy and other systemic advances, the role of systemic therapy on its own for limited progression as well as the possible abscopal effects of its use in combination with radiotherapy must be considered. Further data are necessary to understand how immune system modulation related to local therapy such as SBRT may be harnessed. Studies are also needed to determine how we can optimally deliver radiotherapy to incite the desired abscopal effects, including dosing, fractionation, and timing (sequential or concurrent) in relation to systemic therapy.

Future Directions in Defining the Oligometastatic State

The definitions of oligometastatic disease and its subsets, including oligoprogressive and oligopersistent disease, are currently often based on clinical characteristics, including the number of metastatic lesions and timing. However, an optimal definition of oligometastatic disease would take into consideration factors that predict disease biology and behavior. This is illustrated by the fact that outcomes are not always worse in patients with a greater number of metastatic sites than in patients with more limited metastases. Further work is needed to identify biological and clinical markers that can predict the metastatic potential of specific patients or lesions.[37]

In an updated review by Weichselbaum and Hellman, the authors discuss how a patient's primary tumor may contain genetic clones with the ability to metastasize that do not necessarily cause growth of the primary tumor.[38] They pose that the genetic instability of the primary tumor allows growth, invasion, and the creation of cells with the ability to metastasize distantly.

In a review by Pitroda and Weichselbaum, the authors describe evidence that supports the existence of a wide biological spectrum of metastatic disease and heterogeneity in metastatic virulence. The heterogeneity of metastatic virulence indicates that many clinical, molecular, and host factors are likely yet to be identified that can help us optimize staging, treatment, and outcome prediction in patients with metastatic disease. Large-scale genomic sequencing analyses of primary tumors can be used to study the biological heterogeneity of metastases further and how disease biology affects patient outcomes.[39] One study demonstrated that microRNA expression can be used to identify patients with oligometastatic disease who are likely to remain free of disease or continue to have oligometastatic disease after local treatment with SBRT, and to distinguish these patients from those in whom widespread metastases will develop. This work provides evidence that there is a biological basis for the proclivity to maintain the oligometastatic disease states.[40] New techniques in the identification of circulating tumor cells can also be used to discover patients in the oligometastatic state earlier in the course of their disease.[38]

Studies in patients with pancreatic cancer analyzed the distinct clonal variations within the primary tumor and indicated that disease progression may occur in a stepwise manner with the existence of an intermediate state, perhaps the oligometastatic state, in which tumors have limited metastatic capacity. The ability to identify patients whose disease is limited in its capacity to metastasize would significantly help clinicians to determine which patients truly have oligometastatic disease and would benefit from local ablative treatment.[38]

The meta-analysis of 757 individual patients with oligometastatic NSCLC conducted by Ashworth and colleagues found significant OS differences in patients who were partitioned into 3 prognostic risk groups on the basis of 2 factors: synchronicity of metastasis (synchronous vs metachronous) and nodal involvement. These data provide evidence that clinical factors can be used to guide clinical decision making during a determination of whether a patient may benefit from local therapy.[14]

Ultimately, we should aim to use our increased understanding of how clinical, molecular, and host factors affect the evolution of oligometastatic disease to guide our management of these patients. This has already been accomplished in the staging of patients with primary oropharyngeal cancer, in which disease positive for human papillomavirus is identified as a separate entity. We can harness our understanding of the molecular characteristics of metastases to identify mechanisms that are susceptible to therapeutic intervention and potentially affect the metastatic potential of certain sites. In their review, Pitroda and Weichselbaum pose the idea that the disease of patients with low-risk metastases (those of lower metastatic virulence) may be curable with locally ablative

therapies alone, whereas patients with highly virulent metastases may benefit from further systemic therapy instead of local therapy. Our work to further understand the biological basis of a lesion's predilection to metastasize will fundamentally guide our understanding of how each patient's disease will act along the wide spectrum of metastatic disease.[28]

To deepen our understanding of molecular markers that influence metastatic potential, it is imperative that we harness the tools at our disposal, including next-generation sequencing and artificial intelligence (AI), to facilitate multimodal data analysis. Multimodal data analysis will allow us to combine outputs from tumor genomics, tropism, radiology, and pathology to predict outcomes. We can also integrate AI analysis of outcomes such as response to initial treatment and patient characteristics such as functional status and social determinants of health to predict treatment outcomes. AI-based methods can allow us to identify molecular factors that predict response to systemic treatment. For example, AI-based methods have made possible the creation of algorithms that integrate histopathological data to predict response to immunotherapy in patients with gastric cancer.[41] Similarly, AI-based biomarkers have been used to predict the benefits of androgen deprivation therapy in patients with prostate cancer, ultimately sparing many of them the adverse effects of unnecessary treatment.[42]

We expect that this work will lead to progress in the utilization of data such as circulating tumor DNA and changes in serum levels of measurable residual disease to guide clinical decision making. It will also provide better knowledge of the oncogenotypes that drive the oligometastatic state and the mechanisms by which host tissues respond to this disease state. These advancements in our understanding of the oligometastatic disease paradigm are critical in our ability to identify and optimize, with a more nuanced approach, the selection of patients and metastatic lesions that will most benefit from local therapy.

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