(Oligo)metastasis as a Spectrum of Disease

Stanley I. Gutiontov[1], Sean P. Pitroda[1], Phuoc T. Tran[2], and Ralph R. Weichselbaum[1]

ABSTRACT

Cancer metastasis is the leading cause of cancer-related mortality, and most patients with metastases from solid tumors have historically been considered incurable. Here, we discuss the evolution of our understanding of the oligometastatic state with an emphasis on the view that cancer metastasis represents a spectrum of disease. We highlight several recently published prospective clinical trials demonstrating improvements in cancer-specific outcomes with the utilization of metastasis-directed local therapies. We discuss biological aspects of oligometastases, including genetic, epigenetic, and immune determinants of the metastatic spectrum. Finally, we propose future considerations regarding clinical trial design for patients with oligometastatic disease.

Introduction

Cancer metastasis is the leading cause of cancer-related mortality, and most patients with metastases from solid tumors are considered incurable (1). Toward the last quarter of the 20th century, certain exceptions were found: For example, metastatic germ cell tumors exhibited high cure rates when treated with multi-agent systemic therapy (2). An increased understanding of signaling pathways influencing tumor progression resulted in the development and successful application of targeted therapies, first in the setting of hormonal blockade in breast and prostate cancer and later in a broader context (3, 4). Immunotherapy also demonstrated initial successes with rare cures when applying IL-2 in patients with metastatic renal cell carcinoma (RCC; ref. 5). More recently, a minority of patients with metastatic melanoma and other patient subsets are likely cured with immune checkpoint blockade (ICB; refs. 6, 7). However, it is important to note that although these systemic therapies have improved outcomes, the majority of patients with metastatic disease either do not respond or experience disease progression after initial response.

In 1995, a different conceptual paradigm was introduced—that of oligometastasis (8). This concept proposed that an intermediate state exists between locoregionally confined and widely disseminated malignancy. Some initial data that provided support for the oligometastatic hypothesis actually preceded its formulation by decades and included surgical reports that demonstrated long-term survival in a significant minority of patients treated with resection of metastases from a variety of primary solid tumors (9, 10). More recently, numerous prospective trials of ablative therapy have demonstrated meaningful improvements in cancer-specific outcomes in patients with limited metastatic disease. Our understanding of the molecular underpinnings of the oligometastatic state is increasing in step. This review aims to summarize the key clinical and biologic data supporting the existence of the oligometastatic state before delving into a detailed discussion of the opportunities that lie ahead.

[1]Department of Radiation and Cellular Oncology, University of Chicago, Chicago, Illinois. [2]Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Corresponding Author: Ralph R. Weichselbaum, University of Chicago, 5758 S. Maryland Avenue, Suite 1D, Chicago, IL 60637. Phone: 773-702-0817; Fax: 773-834-7233; E-mail: rrw@radonc.uchicago.edu

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The Oligometastatic State: Clinical Evidence

Several surgical series have demonstrated prolonged survival following resection of a limited number of metastases from a variety of primary solid tumors. In the setting of colorectal cancer metastasis to the liver, a retrospective cohort comprising 1,001 patients demonstrated a 10-year overall survival (OS) rate of 22% following hepatic resection (11). Another series of 929 patients demonstrated a 10-year cancer-specific survival (CSS) of 23% in the same setting (12). In an international, multi-institutional cohort of 5,206 cases of lung metastasectomy of a variety of histologies, the 5- and 15-year actuarial survivals after complete metastasectomy were 36% and 22%, respectively (13). Another cohort of 575 patients undergoing 708 lung metastasectomies, mostly for metastatic carcinomas and sarcomas, demonstrated a similar 5-year actuarial survival of 46% (14). More recently, a systematic review of 757 patients with oligometastatic non–small cell lung cancer (NSCLC) treated with either surgery or radiotherapy demonstrated a 5-year OS of 29% (15). Numerous smaller series with similar findings have been published (9, 10). Taken in aggregate, these results clearly demonstrate that a subset of patients with metastases from solid malignancies can be cured and/or experience long-term survival after metastasis-directed localized therapies (see **Table 1**).

The authors of the colorectal and pulmonary metastasectomy studies performed multivariate analyses to identify prognostic clinical factors. These were consistent across studies and included number of metastatic tumors, tumor size, tumor marker levels, metastasis disease-free interval (DFI), synchronicity of metastases, primary histology, control of the primary tumor, as well as the presence of lymphatic and/or multi-organ metastases. The identification of these factors has been important for several reasons.

First, risk stratification systems combining these factors further differentiate patient subsets by outcome. For example, in one of the colorectal cancer cohorts, the group with the most favorable versus the least favorable risk classifier experienced a 5-year CSS of 64% versus 2%, respectively (12). In the NSCLC cohort, those patients with metachronous distant-only metastases had a 5-year OS of 47.8% as compared with patients presenting with synchronous lymphatic and distant metastases, whose 5-year OS was only 13.8% (15). Second, the fact that it is these specific factors rather than others that predict clinical outcome has biological implications and has driven translational insights into the nature of oligometastasis. Finally, one of these clinical factors (number of lesions) has been used as enrollment criteria for completed and ongoing prospective clinical trials testing the benefit

Table 1. Selected studies demonstrating predictors of oligometastatic disease.

Study	Classifier	Key findings
Fong et al. (11)	Clinical	Developed a preoperative scoring system for predicting recurrence after hepatic resection of metastatic colorectal cancer, which included lymph node positivity, DFI from primary to metastases <12 months, number of hepatic metastases >1, largest metastasis >5 cm, and carcinoembryonic antigen level
Pastorino et al. (13)	Clinical	Large clinical cohort of lung metastasectomy patients demonstrated improved survival for patients with germ cell tumors, DFI ≥36 months, and single site of metastatic disease
Ashworth et al. (15)	Clinical	Systematic review of patients with NSCLC with 1 to 5 synchronous or metachronous metastases treated with local therapy that classified patients on recursive partitioning analysis into 3 risk groups: low risk with metachronous metastases, intermediate risk with synchronous metastases and no lymph node involvement, and high risk with synchronous metastases and lymph node involvement
Turajlic et al. (44)	Genetic	Classification of primary RCCs and matched metastases by somatic copy-number alterations and intratumoral heterogeneity identified a group with intermediate, oligometastatic potential that demonstrated high intratumoral heterogeneity
Iacobuzio-Donahue et al. (31)	Genetic	SMAD4 loss associated with widely disseminated rather than locally progressive pancreatic carcinoma (present in 78% of patients with polymetastases vs. 22% without)
Pitroda et al. (43)	Epigenetic	Similarity network fusion (SNF) analyses of mRNA and miRNA in patients treated with hepatic resection for limited metastases from colorectal cancer demonstrated 3 groups: "canonical," "immune," and "stromal"
		The combination of SNF group and clinical risk score predicted clinical outcomes better than either classifier alone
Oshima et al. (59)	Epigenetic	Induction of 14q32 miRNA expression *in vitro* abrogated liver metastasis development *in vivo* without affecting cell viability
		In the clinical setting (hepatic metastases from colorectal cancer), 14q32 miRNA expression directly correlated with overall survival
Lussier et al. (63)	Epigenetic	Enhanced function of miR-200c *in vitro* increased metastatic burden *in vivo*, and miR-200 family overexpression correlated with polymetastases clinically
Van den Eynde et al. (42)	Immune	The ImmunoScore (semiquantitative representation of $CD3^+$ and $CD8^+$ T-cell infiltration of tumor specimens) of the least immune-infiltrated colorectal cancer metastasis was associated with clinical outcome
Pitroda et al. (43)	Immune	Two of the SNF groups in the aforementioned study exhibited immune-related signatures

of local therapy in oligometastatic disease from a variety of primary tumors.

The site-agnostic, prospective phase II SABR-COMET trial randomized 99 patients with controlled primary tumors and ≤5 metastases to standard of care alone versus standard of care plus stereotactic body radiotherapy (SBRT), a form of ablative radiotherapy, to all sites (16, 17). After a median follow-up of 26 months, there was a 13-month improvement in OS in the SBRT arm. In the setting of oligometastatic NSCLC (defined as ≤3 metastases), a prospective phase II trial with a median follow-up of 38.8 months that randomized patients to local consolidative therapy (surgery or radiotherapy, including SBRT) + maintenance therapy versus maintenance therapy alone demonstrated a 2-year improvement in median survival in the SBRT arm ($P = 0.017$; ref. 18). In a phase II study, randomizing patients with colorectal cancer with up to 9 liver metastases to systemic treatment + local treatment (radiofrequency ablation and/or resection) versus systemic treatment alone, 8-year OS was 35.9% versus 8.9%, respectively ($P = 0.01$; ref. 19). More recently, the phase II ORIOLE study in oligometastatic prostate cancer (defined as ≤3 metastases) randomized 54 men 2:1 to SBRT versus observation; the median progression-free survival (PFS) was not reached in the SBRT group versus 5.8 months in the observation group (HR, 0.30; 95% confidence interval, 0.11–0.81; $P = 0.002$; ref. 20). Several other prospective studies in prostate cancer and NSCLC have been published with similar results (21).

Two other important points must be noted. The first is that not all data have been positive to date. For example, a recently published (albeit underpowered) randomized trial of pulmonary metastasectomy versus active monitoring in patients with metastatic colorectal cancer did not demonstrate a benefit to local therapy (22). The second is that the above data are specifically focused on the benefits of local therapy in either the *de novo* or metachronous oligometastatic state rather than in the setting of oligoprogressive disease, in which patients with metastatic disease experience progression in a limited number of sites. Studies have demonstrated a benefit to local ablation in this setting as well, for example, in patients with oligoprogressive EGFR-mutant NSCLC while on crizotinib or erlotinib (23), though we will limit most of our subsequent discussion to *de novo* or metachronous oligometastasis.

To confirm the benefit of local ablation in this setting, numerous phase III randomized control trials investigating standard of care ± local therapy for oligometastatic disease are ongoing. The results of these trials are eagerly awaited and should increase our insight into this clinical state. However, it is important to note that the definition of oligometastasis used as an inclusion criterion on these trials is usually based on number of metastases. These selection criteria may result in the enrollment of patients who have few metastases but biologically aggressive disease while excluding those with a greater number of more indolent lesions. Taken together, these two tendencies could lead to the dilution of the benefits of local therapy in this setting. At the same time, consideration of the biology implied by the other prognostic factors such as DFI and tumor marker levels can inform future trial design and secondary trial endpoints that should provide the field with more robust ways to define and track the oligometastatic state.

Tumor and Host

Primary tumors are made up of subpopulations of clonogens with different propensities to undergo the crucial steps of the metastatic cascade (24, 25). This fact, combined with discoveries implicating

specific molecular pathways in each of these steps, has led to significant interest in characterizing the tumor microenvironment in which these subpopulations first develop and the ways in which it shapes the metastatic phenotype (26, 27). Recent reformulations of the classic "seed and soil" hypothesis acknowledge the importance of the primary tumor "soil" and the complex tumor–host interactions that determine metastatic proclivity (28). At the same time, there has been an increasing understanding of the dichotomous role of host innate and adaptive immunity in the development of metastatic disease (29). A greater understanding of oligometastasis as part of a broader spectrum of metastasis may shed light on the involvement of these mechanisms. Using the clinical factors first identified in the surgical series outlined above, emerging preclinical and translational data are beginning to make inroads into this very question. We therefore now turn to this area of research.

Tumor burden

The number of metastases has long been considered one of the defining features of oligometastasis and features prominently in the recent ASTRO and EORTC classification recommendations (30). It is frequently used as a marker of the oligometastatic state both in clinical trial enrollment as well as in translational studies investigating the biology of metastatic disease. One early rapid autopsy series correlated patterns of failure with pathogenic mutations in 76 patients with locally advanced or metastatic pancreatic cancer (31). It found that *SMAD4*—an important mediator of TGF-β signaling, which in turn is important in the epithelial–mesenchymal transition (EMT) and invasiveness—was differentially lost from patients who died from tumors that underwent widespread metastatic dissemination (78% loss) as compared with those who died from local disease without metastases (22% loss). *SMAD4* has been implicated in other aspects of pancreatic cancer biology and progression in other clinical cohorts (32, 33), and these data provide a concrete example of how the biology of the underlying tumor can alter the metastatic phenotype (see **Table 1**).

More recent clinical data shed light specifically on the biology of the oligometastatic state and demonstrate the importance of an accurate determination of burden of disease using novel imaging techniques. The prospective phase II ORIOLE study in oligometastatic, hormone-sensitive prostate cancer (defined as ≤3 metastases) demonstrated significant benefits to 6-month PFS with SBRT over observation (20). Several secondary outcomes involving the use of molecular imaging and liquid biopsy correlatives lend additional insights. The first is that 36 participants underwent prostate-specific membrane antigen (PSMA)–targeted PET—which detects metastases more successfully than conventional imaging—before study therapy. Because of blinding to the PSMA-PET results, 16 of 36 patients treated with SBRT had baseline PET-avid metastases that were not treated. The proportion of men with untreated lesions with progression at 6 months was 38% compared with 5% for those with no untreated lesions ($P = 0.03$); the rate of new distant metastases at 180 days was 62.5% versus 15.8% ($P = 0.006$), respectively. This suggests that emerging technologies may allow for a true characterization of the number of lesions in oligometastatic disease and that this in turn can improve patient selection for local ablative therapies.

The authors also defined a high-risk circulating tumor DNA-based mutation signature by CAPP-seq; high-risk genes included *ATM*, *BRCA1/2*, *KRAS*, *PTEN*, *RB1*, and *TP53*, among others. Interestingly, when stratifying by the presence of these high-risk mutations, SBRT improved outcomes over observation in the high-risk mutation negative subgroup but not in the high-risk mutation positive subgroup. Given that the clinical benefit seen on prospective trials of locally ablative therapies in patients with presumed oligometastatic disease is the strongest evidence to date of the existence of the oligometastatic state, the lack of benefit in patients with high-risk mutations in this cohort of patients with 1 to 3 metastases implies that underlying biology trumps apparent clinical risk factors in some situations. These data also suggest the future possibility of using genetic classifiers to stratify patients for local ablation.

Although there is a growing body of evidence tying molecular features to tumor number in the oligometastatic state, another important marker of tumor burden—tumor size—awaits definitive study. However, it is suggestive that the presence of a metastatic tumor >5 cm was a negative prognostic factor in the colorectal hepatic metastasectomy series and large tumor size is associated with worse local control following definitive local ablative therapy in NSCLC (>5 cm) and hepatocellular carcinoma (>4 cm; refs. 34, 35). One plausible explanation behind the association between tumor size and oligometastasis invokes the host immune system. An increasing number of studies in melanoma and NSCLC have demonstrated that the response to ICB (anti–PD-1/PD-L1 and/or anti-CTLA4 monoclonal antibodies) is inversely correlated to tumor size. In metastatic melanoma, variable size cutoffs of <5 or <10.2 cm have been found to predict response (36, 37), and some of the greatest benefits of ICB have been found in the adjuvant setting in both melanoma and NSCLC, when the tumor burden is microscopic and therefore at its lowest (38, 39). Preclinical studies are also in line with this hypothesis: ICB response in melanoma is directly associated with the ratio of activated cytotoxic T cells to tumor burden. In fact, tumor burden in one study correlated with the ability of ICB to reinvigorate antitumor cytotoxic T cells (40). Though these results in aggregate are correlative rather than causal, they suggest a complex heterotypic tumor–host interaction that may influence the metastatic spectrum.

Interestingly, direct evidence of the interplay of the immune system and tumor burden is strongest in the setting of tumor number rather than tumor size. Using the ImmunoScore, which is a semiquantitative representation of $CD3^+$ and $CD8^+$ T-cell infiltration of colorectal tumor specimens that has been externally validated (41), researchers investigated outcomes in a cohort of patients with metastatic colorectal cancer treated with curative resection ± preoperative systemic therapy (42). Combining the ImmunoScore of the least infiltrated lesion with number of metastases resulted in improved predictions of outcome than number of metastases alone. Specifically, those patients with a high ImmunoScore and 1 to 3 metastases fared better than those with either a high ImmunoScore and ≥4 metastases or a low ImmunoScore. In the setting of the ORIOLE trial, greater peripheral baseline T-cell receptor clonality was associated with composite endpoint progression in the SBRT arm, and SBRT resulted in significantly more expanded clones than observation (20). Taken together, this suggests that host–tumor immune interactions can be harnessed in the setting of local ablation of oligometastatic disease (see **Table 1**).

Pace of progression

The potential influence of tumor immune-related signaling on the metastatic spectrum is further illustrated by a study investigating the pace of disease progression and other cancer-specific outcomes in colorectal cancer (43). Hepatic metastases from 134 patients with colorectal cancer treated with perioperative chemotherapy and surgical resection underwent detailed molecular characterization. Although primary tumor consensus molecular subtypes based on genomic analysis did not predict outcomes, a clustering analysis of parallel mRNA and miRNA data was able to stratify patients into three

markedly different risk categories. When these biologically defined groups (canonical, immune, and stromal) were incorporated with a previously validated clinical risk score, they performed better than either classifier alone. The distant metastasis-free survival was 59 months versus 35 months versus 13 months in the low-risk, intermediate-risk, and high-risk composite groups, respectively, and metastatic recurrences were limited (≤3 additional metastases) in number in 100% of low-risk patients, 87% of intermediate-risk patients, and 34% of high-risk patients. Importantly, the prognostic import of these molecular subtypes was externally validated in a separate clinical cohort. Interestingly, two of the risk categories had alterations in immune signaling pathways, with the immune subtype constituting the majority of the low-risk group and demonstrating molecular signatures related to T-cell activation and interferon signaling (see **Table 1**).

Other groups are investigating different aspects of metastatic biology over time in large cohorts of patients and thereby are inherently incorporating the concept of DFI into their biologic definition of oligometastatic disease. The Tracking Cancer Evolution through Therapy (TRACERx) project is using genomic and proteomic sequencing to characterize the evolution of several solid tumors, including RCC. In a publication matching 575 primary RCCs with 335 metastases, metastatic propensity was measured as a function of both number and time (44). The investigators defined a rapid progression group (multiple sites of disease progression within 6 months of nephrectomy) and an attenuated progression group (single-site progression <6 months or multisite progression >6 months), quantifying their intratumoral heterogeneity and somatic copy-number alterations (SCNA). The attenuated progression group demonstrated high intratumoral heterogeneity, whereas the rapid progression group demonstrated low heterogeneity in combination with high levels of SCNA (see **Table 1**).

Detailed study of the attenuated progression group yielded further insights. The first was that patients in this group had metastatic disease that was amenable to control through further local therapy, whether surgical or radiotherapeutic. The second was that tumors within the attenuated progression group were enriched for specific evolutionary subtypes that involved *PBRM1* mutations, further evidence that specific molecular aberrations can predict metastatic propensity in a clinical cohort. The third pertinent finding was that the course of these patients was one of initial oligometastatic progression followed by an increase in metastatic efficiency leading to disseminated metastases. This may suggest one reason why some series suggest that synchronous metastatic disease predicts for a worse outcome than metachronous disease: Perhaps the former patients simply have aggressive disease that has more in common biologically with a polymetastatic presentation rather than an oligometastatic one.

Epigenetic markers and specifically miRNA expression patterns are also linked with DFI and tumor number. Our group investigated a cohort of 63 patients with 1 to 5 metastases at time of treatment with lung metastasectomy (45). Patients were stratified into groups based on rate of progression following local therapy, with the low-rate group experiencing <0.6 new metastases per year, the intermediate-rate group experiencing 0.6 to 3.6 new metastases per year, and the high-rate group experiencing >3.6 new metastases per year. Downregulation of miRNAs associated with tumor-suppressor functions was found in the high-rate progression group and this was validated in a separate report (45). Other publications highlight the importance of the 14q32 miRNA locus, which is located in a region of the genome whose loss is associated with the metastatic phenotype in the TRACERx study discussed above (ref 46; see **Table 1**).

Looking Ahead

The optimization of inclusion criteria and endpoints for oligometastasis clinical trials

The major ongoing randomized clinical trials of locally ablative therapy to all metastases enroll patients primarily based on number of sites and generally limit this to either ≤3 or ≤5. Though such broad inclusion criteria are beneficial for rapid accrual, this results in a heterogeneous study population. For example, PCS IX, a phase II/III trial enrolling patients with castrate-resistant prostate cancer with 1 to 5 metastases, does not limit patients to those with bony metastases alone (NCT02685397). NRG LU002, a phase III trial enrolling patients with NSCLC with 1 to 3 metastases, does not limit patients to those without synchronous lymphatic metastases (NCT03137771). Given that expected 5-year OS can differ by approximately 15% between these two NSCLC patient groups and that local therapy is expected to have less impact on patients with polymetastatic prostate cancer with visceral disease, current inclusion criteria may dilute the benefits of local therapy and result in the premature rejection of the entire paradigm (15). These issues with patient heterogeneity are further amplified when studies enroll patients with multiple different cancer types. Indeed, the advisability of pooling data on disparate diseases with varying biology to make overarching statements regarding the role of local ablation in metastatic malignancy is unclear. Furthermore, ignoring the numerous clinical predictors of oligometastasis at both enrollment and progression limits our ability to gain further insight into the oligometastatic and oligoprogressive states.

A further limitation of current trial design is the use of endpoints not specifically tailored to the oligometastatic state. Given our current inability to accurately identify all sites of metastatic disease in most patients, the paradigm of local ablative therapy would be expected to result in modest but significant benefits in PFS and larger benefits in local control and OS. This is a pattern that has already been seen in the prospective phase II NSCLC trials and might be missed on larger randomized trials using PFS as the primary endpoint (18). It is also important to note that in many studies, patients frequently require and benefit from further local ablation to oligoprogressive disease. This may require the utilization of other clinical endpoints, such as metastasis-free survival or time to new metastasis. Finally, the inclusion of secondary endpoints focusing on biology (genomic, epigenetic, immunologic, etc.) is essential in order for the field to move to a combined clinicobiologic staging of metastatic disease (**Fig. 1**).

The utilization of molecular imaging, liquid biopsy, and single-cell sequencing

Molecular imaging and liquid biopsy hold significant promise for identifying and tracking oligometastatic disease. In the setting of PET, an increasing number of useful tracers are in development (HER2, PD-L1, FAPI, etc.), demonstrate high diagnostic accuracy, and can potentially accurately identify oligometastatic patients (47–49). The utilization of PSMA PET in the ORIOLE trial is a case in point: Patients with metastatic prostate cancer who received SBRT to all PSMA-defined lesions experienced a distant metastasis-free survival of 29.0 versus 6.0 months in those who had PSMA-positive disease left untreated (20). Molecular imaging may also increase the number of patients diagnosed with oligometastatic disease and allow for the measurement of treatment response.

Liquid biopsy and single-cell sequencing are also important tools for the future (see reviews by De Michino and colleagues and Marine and colleagues, respectively, for detailed discussions; refs. 50, 51). The likely utility of liquid biopsy in identifying and tracking oligometastatic

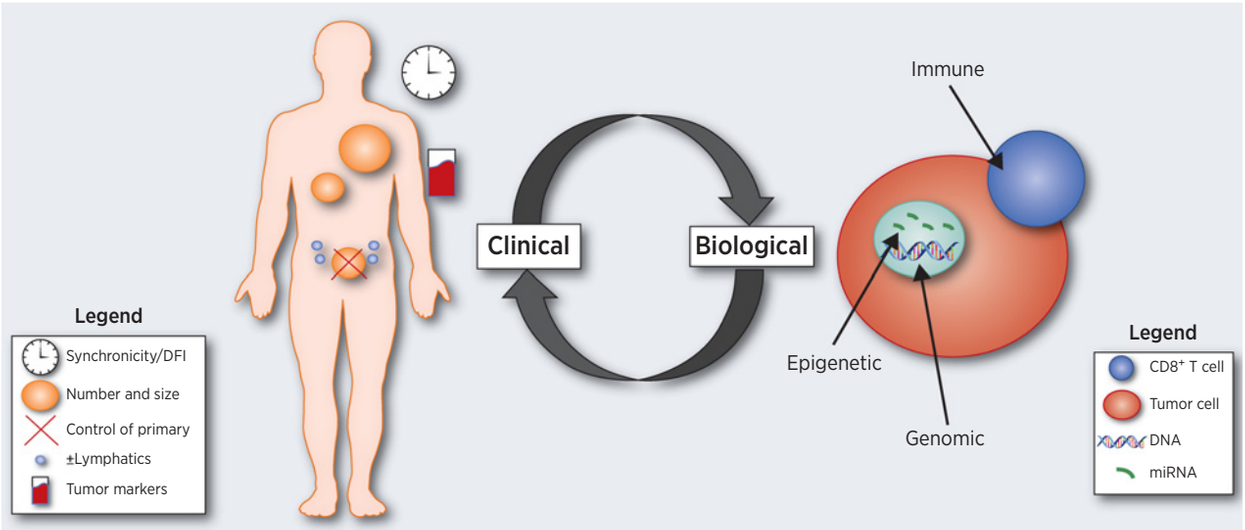

Figure 1.
Clinical and biologic determinants of oligometastasis.

disease is suggested by several data points, including the observation that high tumor marker levels in the original colorectal cancer hepatectomy series predicted for worse clinical outcomes (12). Since then, studies across many tumor types have found reliable markers of both high initial tumor burden and residual disease, from EBV titers in nasopharyngeal carcinoma to circulating tumor cells in small-cell lung cancer (52, 53). Already validated cutoffs could serve as enrollment criteria for patients on oligometastasis trials, whereas the inclusion of such biomarkers in exploratory secondary endpoints could result in novel signatures with which to track metastatic disease. Single-cell sequencing, on the other hand, may eventually allow for the identification and prediction of mechanisms behind the therapeutic resistance that will invariably arise in many patients treated for oligometastatic disease (51, 54). This, in turn, may result in an improved ability to select patients for local ablation and/or combine this modality with targeted systemic therapies.

Local therapy and the role of systemic therapy for oligometastasis

As our ability to accurately diagnose oligometastatic disease increases and assuming the benefits of local therapy in this setting are borne out in the phase III data, an important question arises: What role will systemic therapy play in this setting? Truly oligometastatic disease that is treated with either surgery or SBRT, modalities that can potentially achieve high local control rates, should theoretically not require further therapy. Early data to support this contention were presented above: The 2.5 year freedom from new metastatic disease off all therapy following SBRT in oligometastatic prostate cancer (20). As increasingly effective risk classifiers are developed and if molecular imaging and liquid biopsy demonstrate no residual disease, should we subject patients to the toxicity of systemic therapy? Furthermore, even if such patients harbor residual disseminated tumor cells, these are by definition dormant and therefore unlikely to be eradicated with cytotoxic therapies. In fact, if immunosurveillance plays a role in keeping these nascent metastases in check, cytotoxic and in particular myelosuppressive therapies may actually have detrimental effects.

On the other hand, long-term follow-up of a subset of the trials discussed earlier suggests that local control and therefore the efficacy of local ablation may decrease over time. In particular, the updated results of the SABR-COMET trial after a median follow-up of 51 months demonstrate a local progression rate of 37% in SBRT-treated lesions (17). If this result is replicated as other trials mature, it suggests that SBRT alone may be insufficient to control disease. Perhaps it is the combination of SBRT and novel systemic therapies that will optimize outcomes. One interesting experimental approach is the combination of immunotherapy with partial-lesion SBRT for large metastases, as demonstrated on a recently published phase I clinical trial. Seventy-nine heavily pretreated patients with a variety of metastatic solid tumors received SBRT to two to four metastases followed by the administration of pembrolizumab (55). Importantly, metastases larger than 65 cubic centimeters received partial tumor irradiation and local control at 1 year did not differ between partially irradiated and completely irradiated lesions (89.5% overall; ref. 56). Several other early trials of novel systemic therapy–SBRT combinations, including tyrosine kinase inhibitors (NCT02893332) and immune checkpoint therapies have been published (57, 58). However, a number of questions—including the optimal sequencing of local ablation and systemic therapy—remain unanswered. Prospective trials will be necessary to shed light on these and other important questions.

The development of therapeutics that alter the metastatic phenotype

On the other end of the spectrum remains the pivotal issue regarding the best treatment approach for polymetastatic, rapidly progressive disease. The current approach is to apply successive lines of systemic therapy until resistant clones outcompete susceptible clones and drive further progression, a process that tends to accelerate with each new therapy. Though novel systemic therapies and in particular immunotherapies have shown significant promise in this setting, patients with high tumor burden in most histologic subtypes tend to have low response rates. An alternative approach is to develop therapies that decrease the virulence of the metastatic phenotype. Importantly, the current heavy utilization of PFS as an endpoint limits

the ability to detect such effects and is another reason why novel endpoints in the metastatic disease setting should be investigated.

The actual existence of such therapeutics has been indirectly suggested by clinical observations of oligoprogression on targeted molecular therapies such as EGFR inhibitors in NSCLC (23). More direct support of the alteration of metastatic phenotype as a viable therapeutic strategy is provided by preclinical studies of epigenetic modifiers. In one series of experiments performed on the 14q32 locus miRNAs discussed above, investigators first discovered that transfection of metastatic cell lines with 14q32 locus miRNAs decreased metastatic lung colonization in murine models *in vivo* (59). The subsequent use of shRNAs to knockdown known 14q32 miRNA targets, led to reversal of a polymetastatic phenotype to an oligometastatic one. The group then demonstrated that DNA methylation controls the expression of 14q32-encoded miRNAs and treated HCT116 colorectal cells *in vitro* with decitabine, a commonly used antimetabolite in acute myelogenous leukemia and an inhibitor of DNA methylation. This induced 14q32 miRNA expression and abrogated the development of liver metastases *in vivo* without affecting cell viability (for a more in-depth analysis of the promise of epigenetic drugs in the treatment of solid tumors, see review by Morel and colleagues; ref. 60).

Other articles have recently demonstrated potential vulnerabilities in the molecular program regulating cancer metastasis. One series of experiments using 4-hydroxyacetophenone to activate non-muscle myosin-2C, alter actin organization, and inhibit the mechanical program of metastasis reduced metastatic burden in an *in vivo* model of colon cancer metastasis to the liver (61). Another set of experiments demonstrated the enhancement of CD44-mediated iron endocytosis during EMTs and found that interference with iron homeostasis using small-molecule inhibitors could alter epigenetic plasticity in tumor cells (62). Though this is preliminary work, the potential of such varied approaches and the subsequent possible long-term cancer-specific outcome benefit of combining these with locally ablative therapy should not be ignored.

Conclusions

The understanding of metastatic disease has increased in the 25 years since the oligometastatic state was first proposed. The original clinical predictors of oligometastatic disease continue to inform our investigations into the underlying biology of oligometastasis as well as current clinical trial design, though much remains to be learned. Safe and effective local ablation, new translational insights, and novel diagnostic technologies hold much promise. We believe that their creative application coupled with a bold willingness to question established paradigms in the treatment of metastatic disease will move the field forward even more rapidly in the 25 years to come.

Authors' Disclosures

S.P. Pitroda reports a patent for methods and kits for diagnosis and triage of patients with colorectal liver metastases pending. P.T. Tran reports grants and personal fees from RefleXion Medical and personal fees from Noxopharm, Janssen-Taris Biomedical, Myovant, and AstraZeneca outside the submitted work, as well as a patent for compounds and methods of use in ablative radiotherapy, and patent: 9114158 licensed to Natsar Pharm. R.R. Weichselbaum reports grants from Varian and Regeneron; other from Boost Therapeutics (stock), Immvira LLC (stock), Reflexion Pharmaceuticals (stock), Coordination Pharmaceuticals Inc. (stock), Magi Therapeutics (stock), Oncosenescence (stock), Aettis Inc. (consulting/advisory role), AstraZeneca (consulting/advisory role), Coordination Pharmaceuticals (consulting/advisory role), Genus (consulting/advisory role), Merck Serono S.A. (consulting/advisory role), Nano Proteagen (consulting/advisory role), NK Max America Inc. (consulting/advisory role), Shuttle Pharmaceuticals (consulting/advisory role), Highlight Therapeutics, S.L. (consulting/advisory role); and personal fees from AstraZeneca, Boehringer Ingelheim LTD, and Merck Serono S.A. outside the submitted work. No disclosures were reported by the other author.

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