The Evolving Modern Management of Brain Metastasis

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Abstract

The incidence of brain metastases is increasing as cancer therapies improve and patients live longer, providing new challenges to the multidisciplinary teams that care for these patients. Brain metastatic cancer cells possess unique characteristics that allow them to penetrate the blood brain barrier, colonize the brain parenchyma, and persist in the intracranial environment. Additionally, brain metastases subvert the innate and adaptive immune system, permitting evasion of the anti-tumor immune response. Better understanding of the above mechanisms will allow for development and delivery of more effective therapies for brain metastases. In this review, we outline the molecular mechanisms underlying development, survival, and immunosuppression of brain metastases. We also discuss current and emerging treatment strategies, including surgery, radiation, disease-specific and mutation-targeted systemic therapy, and immunotherapy.

Keywords

Glioblastoma; brain cancer; brain metastases; immunotherapy

Introduction

Brain metastases are the most common intracranial tumors in adults, and portend significant morbidity and mortality(1). Depending on the primary tumor, median survival ranges from

just 2 to 27 months(2). The most common cancers metastasizing to brain include lung (~50%), breast (15–20%), melanoma (5–10%), kidney (7%) and colon (4–6%). Ironically, as cancer therapies improve and patients live longer with their primary tumors, the incidence of brain metastases is increasing and now approaches 200,000 per year in the U.S.(3).

Patients harboring brain metastases often present with neurologic symptoms such as headache, cognitive impairment, seizures, and focal deficits, all precipitating declines in quality of life and survival(1). Effective therapies are limited by poor understanding of metastasis tropism, growth, and survival in the brain microenvironment. Furthermore, many systemic therapies fail to penetrate the blood-brain barrier (BBB) and therefore do not accumulate at therapeutic doses(4). A new focus on brain-specific considerations and therapies is warranted.

In this review, we outline the molecular mechanisms favoring brain metastasis and the peculiarities of the brain immune environment that allow metastases to persist and immunotherapies to suffer. Finally, we outline the most current treatment strategies, including surgery, radiation, and systemic therapies.

Molecular Pathways Favoring Brain Metastasis

Cancer cells metastasizing to brain are often molecularly and phylogenetically distinct from their primary tumor source(5), possessing added capacities for penetrating the BBB and colonizing the brain microenvironment. Mechanistic considerations are outlined below.

Extravasation and traversing the BBB—The BBB is composed of endothelial cells, pericytes, basement membrane proteins, and astrocytes. To cross the BBB, metastatic cells employ diverse processes, including proteolysis of tight junction proteins by cathepsins and matrix metalloproteinases(6) (Figure 1). Alternatively, metastatic cells elaborate inflammatory cytokines, chemokines, and soluble factors to disrupt intercellular junctions. These include transforming growth factor-β (TGF-β), interleukin-1β (IL-1β), vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (b-FGF)(7) (Figure 1). Finally, some metastatic cells disrupt the BBB by inducing endothelial cell death(8).

Following BBB disruption, metastatic cells primarily employ paracellular migration to enter the brain parenchyma (9). Studies using a cranial window mouse model coupled with multiphoton laser scanning microscopy have permitted visualization of the process(10). Essential steps include: 1) size-restricted arrest of tumor cells at vascular branch points; 2) active extravasation by the tumor cell from the abluminal vessel surface into the perivascular space; 3) positional maintenance of the tumor cell within the perivascular space; and 4) angiogenic growth (lung cancer cells and renal cell carcinoma) or vascular cooption (breast cancer cells and melanoma) (10,11).

Mouse models of brain metastasis have identified several molecules required for tumor cell extravasation, including L1-Cell Adhesion Molecule (L1CAM), a protein implicated in axon guidance. Elevated expression of L1CAM by arrested tumor cells within the abluminal space of the brain microvasculature promotes tumor cell adhesion to endothelial cells and facilitates vascular cooption(12) (Figure 1 and Table 1). Through vascular cooption, cancer

cells interact with the pre-existing vasculature, permitting access to angiogenic factors, nutrients, and oxygen. Studies using mouse models suggest that the cancer cells remaining near the perivascular space after extravasation predominantly give rise to proliferating metastases(10).

ADAM9, a member of the disintegrin and metalloprotease family, regulates lung cancer brain metastasis by targeting vascular remodeling at the BBB through regulation of *VEGFA*, *ANGPT2*, and *PLAT* expression(13). Increased ADAM8 expression in triple-negative breast cancer (TNBC) stimulates angiogenesis through the release of VEGF and increases transendothelial migration by activating β1-integrin(14). Activation of the c-MET receptor tyrosine kinase in brain metastatic breast cancer cells promotes perivascular adhesion and neoangiogenesis, in part through increased expression of IL-8 and CXCL1(15). Cyclooxygenase-2 (COX-2), HB-EGF ligand, and ST6 N-Acetylgalactosaminide Alpha 2,6 Sialyltransferase 5 (ST6GALNAC5) promote breast cancer cell migration across the BBB(16) (Figure 1 and Table 1). Factors secreted by activated brain microvascular endothelial cells such as angiopoietin-2 (Ang-2) disrupt tight junctions and increase BBB permeability to breast cancer cells in mouse models(17). Thus, inhibition of Ang-2 can enhance BBB function and impair progression of brain metastases. Similarly, signaling by the chemokine stromal cell-derived factor 1α (SDF-1α; also known as CXCL12) and its receptor CXCR4 promotes migration of breast cancer cells across the BBB. Treatment with AMD3100, a small molecule antagonist of SDF-1α, inhibited lung cancer brain metastasis by protecting the BBB(18).

Despite these insights, many questions remain. The majority of the mechanistic studies described above have focused on breast carcinoma and non-small cell lung cancer (NSCLC) as little is known regarding the mechanisms employed by other commonly metastasizing tumor types, including melanoma, renal cell carcinoma (RCC), and small-cell lung cancer (SCLC). Future research may reveal new targets for preventing extravasation of metastatic cells into the brain parenchyma. Moreover, future studies are needed to develop drugs that can effectively cross the BBB, which remains a therapeutic delivery barrier despite the partial opening observed by the intracranial accumulation of small molecules such as gadolinium and other contrast agents. Drug delivery to brain metastases may be prevented in part by the abnormal and heterogenous blood vessels surrounding the metastases and increased tumor interstitial hypertension leading to decreased perfusion thereby impairing drug accumulation at the metastatic sites(19).

Role of astrocytes—Colonization and outgrowth of cancer cells requires adaptation to the brain microenvironment. Such adaptation is mediated by dynamic inter-cellular interactions between metastatic cells and astrocytes, glial cells that serve to prevent neuronal damage. Reactive astrocytes destroy metastatic cells by producing plasminogen activators (tPA and uPA) that convert plasminogen into plasmin, a protease that can induce Fas ligand (FasL)- mediated apoptosis of cancer cells(12). Plasmin also inactivates L1CAM, restricting vascular cooption by metastases. Metastatic cells, in turn, counteract the effects of plasmin by expressing serpins (neuroserpin and serpin B2) thereby facilitating metastatic colonization(12) (Table 1 and Figure 2).

While astrocytes can indeed restrict brain metastases, they also induce growth-promoting survival pathways within cancer cells, including via STAT3 expression(20). Inactivating STAT3 signaling in reactive astrocytes can decrease brain metastasis in mouse models and humans (Figure 2 and Table 1). Astrocytes also promote proliferation of breast cancer cells through increased expression of Reelin, a secreted glycoprotein that regulates neuronal migration and growth(21). Likewise, activation of c-MET in breast cancer cells promotes brain metastasis, eliciting bidirectional signaling with astrocytes(15). Enhanced tumor cell IL1β secretion following c-MET activation promotes neighboring astrocytes to secrete HGF, the c-MET ligand, enhancing metastatic cell growth and colonization (Figure 2 and Table 1). IL-1β also elicits enhanced expression of Jagged-1 (JAG1), a Notch ligand(22). Interaction of JAG1 in astrocytes and Notch in breast cancer stem-like cells (CSCs) enhances self-renewal and promotes brain metastasis in mouse models(22) (Figure 2).

Astrocytes may also protect brain metastases from chemotherapy. Metastatic breast and lung cancer cells engage directly with astrocytes by establishing gap junctions through upregulation of protocadherin 7 and connexin 43(23). Gap junctions are usurped to transfer c-GAMP to astrocytes, stimulating production of interferon-γ (IFN-γ) and tumor necrosis factor (TNF). These cytokines activate transcription factors NF-κB and STAT1 in brain metastatic cells, resulting in enhanced tumor growth and chemoresistance(23) (Figure 2 and Table 1). Finally, gap junction signaling between breast cancer cells and astrocytes enhances production of IL-6 and IL-8 in cancer cells, upregulating endothelin-1 (ET-1) production by astrocytes and leading to chemoprotection(24) (Table 1).

Adaptation of metastatic cells to the brain microenvironment—Survival and growth of brain metastases require adaptations to the unique microenvironment of the brain. Cancer cells must effectively compete with neurons for oxygen and nutrients, often by acquiring neuronal characteristics. To maintain sufficient oxygenation, metastatic cells employ vascular cooption or neoangiogenesis, a target of anti-angiogenic therapies(25). Compared to primary tumors, some brain metastases express high levels of hexokinase-2 (HK2), an enzyme that phosphorylates glucose to generate glucose-6-phosphate(26). Brain metastatic cells originating from lung and breast tumors can acquire metabolic adaptations characteristic of neuronal cells including increased expression of the gamma-aminobutyric acid (GABA) transporter and use of GABA as a metabolite to promote metastatic cell growth(27). Brain metastatic cells also upregulate acetyl-CoA synthetase enzyme 2 (ACSS2) to use acetate as a carbon energy source allowing for increased growth in the brain parenchyma(28). Likewise, similar to neurons and glial cells, some metastatic cancer cells release glutamate and uptake glutamine, resulting in an enhanced ability to colonize the brain(29).

Immune Evasion

Intracranial tumors, including metastases, offer unique challenges to the antitumor immune response. A deeper understanding of these challenges can help alter the balance from tumor immune-evasion to tumor destruction.

Primary brain tumors subvert the innate immune response by secreting cytokines that skew glioma-associated macrophages/microglia (GAM) toward the M2 phenotype and suppress the M1 phenotype(30). Brain metastases can elicit a similar phenomenon to create a tumor-permissive environment. In the presence of lung cancer brain metastases, microglia often lack inducible nitric oxide synthase (iNOS) and tumor necrosis factor-alpha (TNF-α), rendering them unable to facilitate phagocytosis and antigen presentation(31). Meanwhile, astrocytes release exosomes containing microRNA-19a (miR-19a), which can decrease expression of the PTEN tumor suppressor in cancer cells (Figure 2 and Table 1). Metastatic cells lacking PTEN release CCL2, recruiting Iba1+ macrophages that promote cancer cell proliferation and survival(32).

T-lymphocytes are the mainstay of cancer immunosurveillance and are subject to profound disturbances within the intracranial tumor environment. Regulatory T-cells (T_{reg}) predominate in the tumor microenvironment in patients and mice with melanoma, breast, or colon cancer brain metastases as well as with primary tumors(33,34). Reactive astrocytes with activated STAT3 signaling restrict T-cell activities during brain metastasis, impairing their activation through secreted factors that decrease immune function(20).

Bone marrow sequestration is a recently characterized phenomenon involving trapping of T-cells in the bone marrow in the setting of intracranial tumors specifically, both primary and metastatic(35). Sequestered T-cells cannot traffic to the brain and exert their anti-tumor function. Such sequestration follows loss of the receptor S1P1 from the T-cell surface. In mouse models, stabilization of T-cell S1P1 abrogates sequestration, licensing immunotherapies targeting intracranial tumors. Sequestration occurs in experimental models of glioma, as well of intracranial breast, melanoma, and lung cancers (35), suggesting this phenomenon hampers the immune response to brain metastases.

T-cell exhaustion is a hypofunctional state that follows chronic, suboptimal antigen exposure and is characterized by expression of multiple alternative immune checkpoints on the T-cell surface(36). It has now been described in the setting of gliomas and intracranial metastases(37). A more robust understanding of the prevalence and mechanisms of T-cell dysfunction in brain metastases will permit development of more rationally designed immunotherapies in this setting.

Brain Metastases: Adjusting our Approach to Treatment

A diagnosis of metastatic cancer, particularly involving the central nervous system (CNS), was formerly considered to signal imminent end of life, with expected survival of less than six months. Advances to the treatment of disseminated cancer, however, are substantially extending survival and challenging the often nihilistic attitudes of patients and providers. For example, a recent single-armed Phase II trial of ipilimumab/nivolumab for patients with untreated melanoma brain metastases touted median survivals that had not been reached at 30 months. Furthermore, OS at 12 months was 81.5%(38). Likewise a number of recent studies demonstrate high rates of "freedom from local recurrence," with these extending over years(39,40) While these numbers are perhaps not yet broadly representative, the implication is clear – close attention must be paid to treatment regimens for these patients that control disease while preserving neurocognition and quality of life. Current treatment

approaches toward brain metastases often utilize a local therapy (surgery, SRS or a combination of the two) to aggressively control discrete lesions and avoid the deleterious effects of whole-brain radiotherapy (WBRT), recognizing that the omission of WBRT increases the risk of developing new brain lesions. Various modalities, specific clinical scenarios, and histological considerations are discussed below. Selecting the patients most likely to benefit from initial operative management is important, and factors contributing to decision-making include age, Karnofsky performance status (KPS); the number, size, location, and histology of intracranial lesions; symptoms; and the distinction between new disease, recurrent disease, and radiation necrosis(41).

Approach: Modalities

Radiation Therapy—Radiation therapy, either alone or following resection, remains the mainstay of treatment for brain metastases. Historically, WBRT was utilized to treat both the lesions and the "normal" brain parenchyma at risk for subclinical micrometastatic disease. WBRT, however, is associated with neurocognitive decline and even dementia in some cases(42–44). Nonetheless, the complications of WBRT were frequently deemed preferable to uncontrolled or new brain metastases, given the limited survival of patients with metastatic cancer. Initially, SRS was utilized as a means of improving local control in patients with brain metastases treated with WBRT. RTOG 9508, a large, randomized trial of WBRT with or without immediate SRS in patients, demonstrated improved survival with the addition of SRS for select patients with one brain metastasis, high performance status, or a favorable histology(45).

SRS as monotherapy for treatment of brain metastases, however, has become increasingly popular over the past 15 years. Several studies comparing SRS alone versus SRS with WBRT showed no disadvantage in overall survival (OS) when WBRT was omitted, though there was an increase in the rate of new brain metastases(46–48). A small, randomized study from M. D. Anderson suggested a decrease in cognitive decline when SRS monotherapy was employed rather than the combination with WBRT(47). More recently, a multi-institutional randomized trial of SRS alone versus SRS and WBRT revealed significantly better retention of neurocognitive ability in the SRS monotherapy arm (20 versus 51% deterioration in delayed recall at 3 months post treatment, $p < 0.001$)(49). As part of its "Choosing Wisely" initiative, the American Society of Radiation Oncology now suggests that WBRT NOT be routinely add to SRS for the treatment of limited numbers of brain metastases.

Twenty years ago, Patchell et al showed that WBRT following resection of a single brain mestastasis significantly reduced the rate of local and distant brain recurrence compared to post-operative observation alone(50). In combination with surgical resection, SRS is also effective at reducing local recurrences, either when administered post-operatively to the resection cavity or pre-operatively to an intact lesion(51–54). For example, Mahajan et al demonstrated a significant improvement in local control in a randomized trial of "SRS alone" versus "no radiotherapy" to the resection cavity(54). In addition, a randomized trial of SRS versus WBRT to resection cavities by Brown et al showed that the risk of neurocognitive decline was substantially higher in those patients treated with WBRT (52 vs

85% 6 mos post-radiotherapy, p<0.0003)(55). None of these trials demonstrated a significant difference in OS between the study arms.

While the above studies were limited to a few (<4) brain metastases, SRS monotherapy may be appropriate for larger number of brain metastases, as well. A large study by Yamamoto et al of patients undergoing SRS for up to 10 brain metastases revealed no difference in OS compared to those being treated for 2–4 tumors, and only slightly worse OS than those harboring a solitary metastasis(56). An additional study by our group revealed that the aggregate volume of lesions is a more important predictor of outcome than total number of lesions undergoing SRS, with 10 cc representing an important demarcation(57). Single-fraction SRS is clearly limited in its ability to treat large metastases with an acceptable balance of toxicity and efficacy, however, as shown in RTOG 9005(58).In such situations, treatment via SRS in a few large fractions (termed "hypofractionated SRS") appears to offer effective local control with minimal damage to normal brain parenchyma(59,60).

WBRT is still preferred in the setting of numerous brain metastases, carcinomatous meningitis, or primary histologies prone to micrometastatic disease (e.g., small-cell lung cancer), as SRS in these instances often cannot effectively target all of the disease visualized on MRI and/or any disease that is present but not observed. Strategies to comprehensively irradiate the brain while protecting neurocognitive function via hippocampal sparing(61) or via the use of neuroprotectants(62) are being explored. For example, a recently opened trial at our institution administering a novel superoxide dismutase is evaluating the ability of this compound to preserve neurocognition in patients with more than 10 brain metastases receiving WBRT(63,64).

Surgery—The role of surgery for brain metastases is well-established by a variety of now largely historical studies(65–69). Surgery confers several long-recognized benefits, including the unique ability to expediently relieve debilitating or life-threatening mass effect and/or CSF obstruction. Lesions larger than 3 cm or those causing symptoms from local compression benefit from surgical resection(70). Furthermore, surgery confers the capacity to obtain tissue, ever important in the growing age of molecular and precision medicine. Tumor markers and mutations elucidated from surgical pathology specimens frequently guide the selection of targeted therapies, with one study finding that 53% of patients had a clinically actionable mutation in a brain metastasis that was not present in their primary tumor(5).

Importantly, early studies highlighting the role of resection generally proffered recommendations for surgery as an adjunct to WBRT when lesions were solitary, large, and/or symptomatic in patients with good functional status (67,68,71). The classic trial by Patchell et al in 1990(67), for instance, enrolled 48 patients with a solitary brain metastasis, and KPS ≥ 70. Patients were randomized to "surgical resection + post-operative WBRT" versus "WBRT alone." The surgical group survived significantly longer (40 vs 15 weeks) and enjoyed longer periods of functional independence (KPS>70, 8.8 months vs 1.8 months); freedom from death due to neurological compromise; and time to brain recurrence. While unambiguously establishing surgical value, early studies advocating resection alongside WBRT are now seemingly passé, with the declining role for WBRT and ever-

increasing role for SRS (discussed above). Likewise, any question of surgery's utility as a lone modality is equally moot, with local intracranial recurrence rates following resection alone proving unacceptable at 46–68%. This was perhaps most definitively demonstrated in a 2017 publication by Mahajan et al.. In their prospective randomized controlled trial (RCT) examining local recurrence rates, patients undergoing resection alone attained freedom from local recurrence (FLR) rates of just 43% at 12 months; patients receiving post-operative SRS, however, achieved 12 month FLR rates of 72% (40).

More relevant questions in the current climates of SRS and aggressive therapy now surround the role for surgery in conjunction with SRS or in instances of multiple metastases. Regarding the former, while no trials have compared "surgery + SRS" to "SRS alone," as noted previously, various recent RCTs have established the inarguable value of post-operative SRS versus both observation (40) and WBRT (52). The latter question of multiple metastases is somewhat more weakly addressed by studies that are now more than a decade old (72–74). Consensus therefore remains unreached, and newer studies are needed (75). No randomized studies have evaluated the role of surgery in this population, as they were historically excluded from trials due to a shorter life expectancy and presumed limited benefit to treatment. Given the improving survival in this group, however, resection of multiple metastases likely does provide benefit in the appropriately selected patient. In perhaps the most pertinent study examining the topic, Paek et al. reviewed 208 patients with either solitary or multiple brain metastases treated at a single institution. They uncovered no difference in survival between patients operated for one metastasis versus 2–3, and neurological symptoms were stabilized in each group. Factors impacting survival were instead KPS and RPA Class I assignment (73). In general, then, when surgically approaching multiple metastases, the best evidence to date is that traditional principles apply: in patients with good functional status and multiple lesions, resection of large, dominant, symptomatic metastases (up to 2–3) may benefit performance status without worsening survival.

Systemic Therapy—While the initial treatment of brain metastases relies heavily on local therapies (radiation and/or resection), systemic therapy plays a role in multi-modality care for CNS recurrence. Studies illustrate improved survival amidst brain metastases for those who receive subsequent systemic therapy compared to those who do not(76). Critical goals of systemic therapy, agnostic of tumor histology, include extracranial disease control and prevention of cancer seeding the untreated brain. For intracranial progression following local therapy, brain-permeable systemic compounds are preferred. For those experiencing life-threatening extracranial disease progression, systemic therapy may be indicated prior to local therapies to stabilize extracranial disease. In each of these clinical scenarios, well-coordinated, multidisciplinary care involving neurosurgical, radiation and medical oncology partners is paramount.

The BBB remains a challenge to effective systemic therapy for brain metastases, and novel delivery platforms to overcome this barrier are eagerly anticipated. Preclinical studies in breast cancer show brain metastases accumulate higher concentrations of ^{14}C-paclitaxel and ^{14}C-doxorubicin than normal brain, yet far below that within extracranial metastases(77). This has led to the classification of the BBB as a blood-tumor-barrier (BTB) in the setting of metastases. One strategy to bypass the BTB is the encapsulation of standard

chemotherapeutics, their prodrugs or active metabolites, into nanoparticles or liposomes to enhance accumulation in brain metastases. This has been implemented with several cytotoxics including doxorubicin, irinotecan and taxanes(78), and clinical translation is ongoing in several early phase trials (NCT02915744 and NCT01770353). Transcytosis across the BTB via receptor-mediated interactions is another strategy to enhance intratumoral concentrations. ANG-1005 is a novel drug conjugate consisting of 3 molecules of paclitaxel covalently linked to Angiopep-2, designed to cross the BTB via endocytosis after binding to LRP-1. Results from a phase II study of ANG-1005 for breast cancer brain metastases and/or leptomeningeal disease illustrate clinical benefit of 71%, with partial responses in 14% (8/58) of patients with brain metastases, and 22% (5/23) with leptomeningeal disease(79).

In the current era, a discussion of systemic therapies must include the role of immunotherapy, particularly checkpoint blockade. Employment of monoclonal antibodies against CTLA-4 (ipilimumab) and PD-1 (nivolumab, pembrolizumab) function to remove inhibition of the anti-tumor immune response and have been approved for use in melanoma and NSCLC(80,81). While patients with intracranial metastases were historically excluded from systemic and immunotherapy trials, intracranial responses are increasingly observed following checkpoint blockade, prompting newer interest in harnessing immunotherapy for these patients. For instance, a meta-analysis of studies for melanoma brain metastases found treatment with SRS + ipilimumab increased survival compared to SRS alone(82). In dedicated prospective studies, a recent phase II study found nivolumab to be effective alone or in combination with ipilimumab for patients with untreated asymptomatic melanoma brain metastases, with 46% of patients in the combination group and 20% of the patients on nivolumab alone showing intracranial responses(83). Another landmark phase II study found 52% of patients with previously untreated melanoma metastases obtained an objective intracranial response following combination therapy; interesting, extracranial response was similar at 47%. At 6 months, rates of intracranial progression-free survival were somewhat lower at 64.2% than extracranial progression-free survival at 75.9%. OS in this study was 81.5% at 12 months, and median survival had not been reached at 30 months(38). Meanwhile an early combined analysis of both lung and melanoma brain metastasis patients from a further phase II study illustrated intracranial response rates to pembrolizumab monotherapy of 33% and 22%, respectively, again with near identical extracranial response rates (84). These dramatic results may shift the paradigm for systemic therapies to one of up front rather than salvage therapy, as a number of these studies were conducted in patients receiving no prior therapy for their intracranial disease, and high concordance between intracranial and extracranial disease is noteable. Numerous studies are ongoing to continue to define the role and timing (pre-, post- or concurrent with radiation) of immunotherapy in solid tumor brain metastases (NCT02696993, NCT02886585) (Table 2). A recent review outlines additional considerations for generating anti-tumor immunity against brain metastases(85).

Approach: Specific Clinical Scenarios

Recurrent metastases—Radiographic progression following radiation generally indicates one of two diagnoses: recurrent/progressive disease, or radiation necrosis, a

delayed inflammatory process that involves apoptosis of endothelial cells, peritumoral edema, chronic tissue hypoxia, and disruption of the blood brain barrier(86). While it is impossible to distinguish between these pathologies on imaging alone, the distinction is important, as recurrent disease necessitates further radiation, whereas radiation necrosis contraindicates it. A recent retrospective study examined 35 patients with radiographic progression of previously irradiated brain metastases who underwent biopsy. When radiographic progression occurred within 9 months of SRS, approximately 50% of biopsies identified disease recurrence. When radiographic progression occurred after 9 months, however, greater than 90% of the biopsied lesions proved to be radiation necrosis(87). Radiation necrosis is pervasive, particularly at later time-points after radiation, and it is critical to distinguish it from true disease progression. In addition to distinguishing disease progression from radiation necrosis, biopsy allows for the detection of actionable mutations in the brain metastasis, which are often distinct from the primary tumor(5).

Surgical resection for previously resected recurrent brain metastases prolongs survival in RPA class 1 patients(88) and can be considered for recurrent lesions that are accessible and symptomatic. However, one of the most promising emergent strategies, effective for both recurrent disease and radiation necrosis, is laser interstitial thermal therapy (LITT). LITT uses a robotically controlled laser probe introduced through a small incision to propagate thermal energy and cause cellular damage, including protein denaturation and coagulative necrosis(89). Temperature data is calculated from phase change data obtained from a continuously running MRI. The minimally invasive approach is useful in patients or brain areas that may be less amenable to open resection, and it avoids problems with wound healing plaguing previously irradiated areas. Furthermore, biopsy is obtained simultaneously to distinguish between recurrent disease and radiation necrosis. Limitations to LITT include a lesional size limitation per trajectory of ~3cm diameter, as well as morbidity associated with LITT-induced edema. Ali et al recently published their results using LITT in 23 patients with recurrent brain metastases following SRS and found that when >80% of the lesion is ablated, no additional tumor growth was observed(90). While further prospective, randomized studies are clearly needed, LITT offers significant promise for patients with progressive metastases or radiation necrosis.

Approach: Disease-Specific Therapeutic Considerations

NSCLC—Present standard of care involves molecular testing to include epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) at diagnosis of lung adenocarcinoma, as multiple targeted therapies are approved. The incidence of brain metastases among those whose non-small cell lung cancer (NSCLC) harbors a mutation in *EGFR* or *ALK* is approximately half, while a third of those with *ROS-1* positive NSCLC will recur in the CNS.

While several targeted agents are approved in NSCLC harboring an *EGFR* mutation, resistance emerges through the *T790M* mutation(91). Osimertinib, a second-generation EGFR tyrosine kinase inhibitor, has activity against the *T790M EGFR* mutation and crosses the BBB. In the phase III FLAURA trial, over 500 patients with activating *EGFR* exon 19 deletions or exon 21 *L858R* mutations were randomized to osimertinib versus gefitinib or

erlotinib. PFS favored osimertinib (18.9 months vs. 10.2 months), and PFS benefit was consistent across patients with and without brain metastases(92) (Table 2). Osimertinib is approved in the front-line treatment of EGFR-mutant NSCLC regardless of *T790M EGFR* mutation status and is favored among those with brain metastases.

The identification of *ALK* and *ROS-1* translocations and activity of *ALK* inhibition in this molecular subset of NSCLC led to approval of crizotinib(93). Newer second-generation ALK inhibitors have shown superior activity compared to crizotinib and enhanced brain permeability. Alectinib, a brain permeable second-generation ALK inhibitor, illustrates improved PFS and time to CNS progression compared to crizotinib, with a more favorable toxicity profile(94). Another second generation ALK inhibitor, ceritinib, improves PFS over platinum-based chemotherapy for those with brain metastases (10.7 vs. 6.7 months)(95). Finally, lorlatinib is a third generation, CNS permeable ALK/ROS1 inhibitor with FDA breakthrough designation designed to overcome *ALK* resistance mutations. Intracranial response rates for ALK-inhibitor-pretreated patients is approximately 45 – 60%(96) (Table 2). Specific to *ROS-1* mutations, crizotinib remains a mainstay of therapy, but has poor BBB permeability. Thus, in the setting of brain metastases, second and third generation ALK/ROS-1 inhibitors including ceritinib and lorlatinib are favored(97).

Melanoma—Systemic therapy for melanoma has transformed over the past decade to include targeted and immunotherapeutic approaches. Targeted therapies utilizing combined inhibition of the mitogen-activated protein kinase (MAPK) pathway, namely BRAF and MEK, in *BRAF* mutant melanoma yield improved outcomes. Combination dabrafenib and trametinib illustrated intracranial response rates of 58% for BRAF *V600E* mutant, radiation therapy-naïve, melanoma brain metastases(98). In this analysis, the median extracranial response was more durable (10.2 months, 95% CI 5.8 – not estimable) compared to intracranial duration of response (6.5 months, 95% CI 4·9–10·3). A newer generation BRAF inhibitor, vemurafenib, yields intracranial response rates of 25% for progressive, *BRAF*-mutant melanoma brain metastases(99) (Table 2). As discussed above re: immunotherapy in melanoma, combination therapy with ipilumumab and nivolumab yielded near identical intracranial and extracranial response rates (52% and 47%, respectively), with 1 year OS rates of 81.5% in patients with metastatic melanoma (of which 57% harbored a mutation in *BRAF*)(38). In the era of both targeted and immunotherapy for melanoma brain metastases, clinical trials addressing the most effective sequencing of these strategies, taking mutation status into account, are needed.

Breast Cancer—Treatment for breast cancer brain metastases is subtype-dependent, based on hormone receptor (HR) and/or HER-2 expression. Inhibitors of cyclin-dependent kinase 4/6 (CDK4/6) have altered the approach to the treatment of HR-positive, metastatic breast cancer with significant improvements in PFS. Of the 3 approved agents (Palbociclib, ribociclib, and abemaciclib), abemaciclib illustrates the greatest CNS permeability with intracranial response rates of 17%(100).

The incidence of brain metastases in advanced HER2-positive breast cancer is ~30%. While larger monoclonal antibodies do not traverse an intact BBB, studies illustrate delayed time to CNS relapses by adding pertuzumab, a monoclonal antibody targeting HER2-HER2

dimerization, to trastuzumab(101). Intracranial responses to the antibody drug conjugate, trastuzumab emtansine (TDM1), are observed in several small studies(102), and TDM1 was shown to significantly improve survival in patients with CNS metastases compared to capecitabine-lapatinib(103). Brain permeable small molecule inhibitors targeting HER1 and HER2, lapatinib or neratinib, combined with capecitabine, yield intracranial response rates of 67% and 49% respectively(104,105). A newer generation, HER2-specific small molecule inhibitor, tucatinib, is currently under investigation for treatment of metastatic HER2 positive breast cancer with and without brain metastases (NCT02614794) (Table 2).

There are no approved targeted therapies to treat TNBC brain metastases, despite the fact that nearly half of those diagnosed with metastatic disease experience recurrence in the CNS. Systemic therapies under investigation include inhibition of poly-ADP-ribose polymerase (PARP) with DNA damaging platinum chemotherapy (NCT02595905), and a pegylated prodrug of irinotecan (NKTR-102, NCT02915744) (Table 2).

Future perspectives

Brain metastases are an increasingly prevalent challenge confronting multiple disciplines. Development of effective therapies to treat brain metastases requires greater understanding of the means by which metastatic cells adapt to the distinct metabolic, chemical, and cellular composition of the brain microenvironment. Likewise, greater insight is needed into the mechanisms blocking passage of therapeutic agents across the BBB, as well as into the immunologic proclivities of the brain microenvironment and the immune-evasive strategies implemented by brain metastases. A new focus on these problems will be required to improve survival and quality of life for patients with brain metastases.

Acknowledgements

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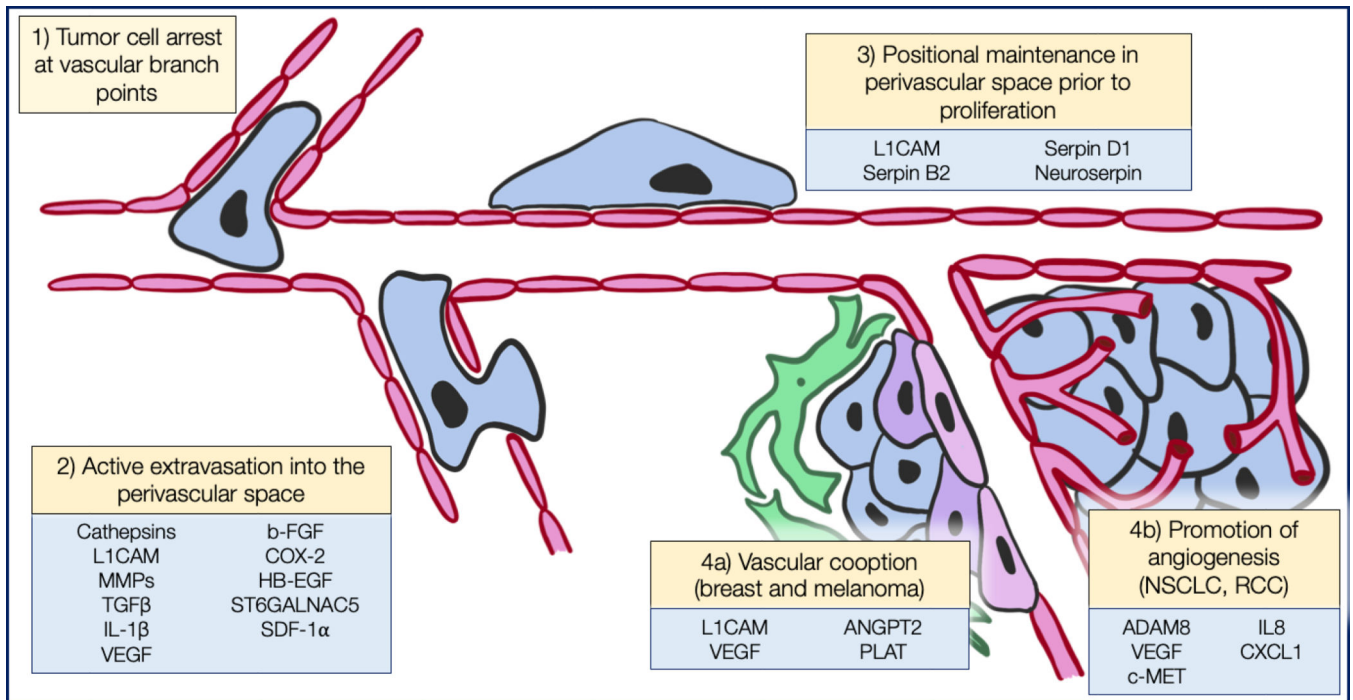
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Figure 1:

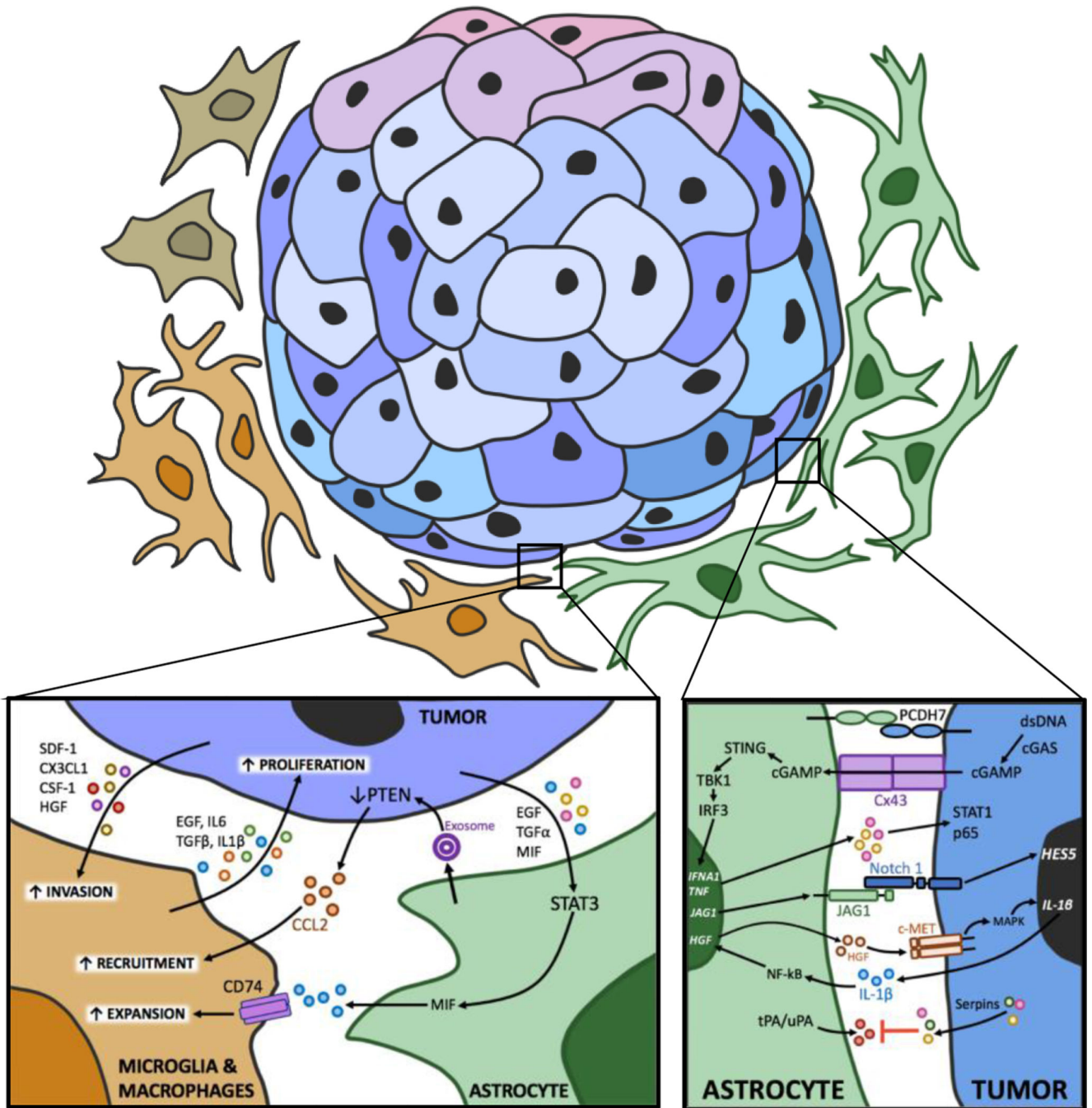Several steps are required for the initiation and maintenance of brain metastasis of lung cancer, breast cancer, melanoma, and renal cell cancer. Molecules involved at each step are indicated.

Figure 2:
Intercellular crosstalk between tumor cells, astrocytes, microglia and macrophages in the
brain parenchyma regulates metastatic outgrowth. Signalling pathways in each interaction
are indicated.

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Table 1.

Molecular Targets of Brain Metastasis and their functions.

Target	Function	Cancer Type	Reference
ST6GALNAC5, COX2, HBEGF	Adhesion to brain endothelial cells and extravasation	Breast	16
SDF-1/CXCR4	Migration, extravasation and BBB permeability	Lung, Breast	18
Serpins, L1CAM	Vascular co-option and survival	Breast, Lung	12
PCDH7, Cx43	Forms tumor cell-astrocyte gap junctions, promotes outgrowth	Breast, Lung, Melanoma	23
Notch signaling	Self-renewal of cancer stem cells in brain	Breast	22
Astrocyte-secreted exosomes	Myeloid recruitment, proliferation, outgrowth	Breast, Melanoma	32
ACSS2	Outgrowth in brain	Breast, Lung, Melanoma	28
cMET	Adhesion to brain endothelial cells, angiogenesis	Breast, Lung	15
ADAM9	Migration, Angiogenesis	Lung	13
ADAM8	Transendothelial migration, angiogenesis	Breast	14
Endothelin receptors	Promotes survival and interaction with brain microenvironment	Breast, Lung, Melanoma	24
Angiopoietin-2	Disrupt BBB	Breast, Lung	17
STAT3 signaling	Immune cell expansion and activation	Breast, Lung Melanoma	20
Hexokinase 2	Outgrowth in brain	Breast	26

Table 2.

Therapies for Brain Metastasis. Several clinical trials are underway to investigate disease-specific therapies for brain metastasis, as well as checkpoint blockade for brain metastasis. When available, outcomes are summarized

Cancer Type	Drug/Target	Clinical Trial	Clinical Trial Outcome	References
Lung	Osimertinib (EGFR)	FLAURA	PFS=18.9 months, HR 0.46, 95% CI 0.37–0.57	92
Lung	Alectinib (ALK)	Global ALEX	CNS RR=81%, Response duration=17.3 months	94
Lung	Ceritinib (ALK)	ASCEND-4	PFS=10.7 months, HR=0.70, 95% CI 0.44–1.12	95
Lung	Lorlatinib (ALK)		IC-ORR=40–75%	96
Melanoma	Dabrafenib+trametinib (BRAF)	COMBI-MB	IC-ORR=59%	98
Melanoma	Vemurafenib (BRAF)		IC-ORR=15%, PFS 4.0 months, OS 9.6 months	99
Breast	Abemaciclib (CDK4/6)	NCT02308020	In Progress	100
Breast	Pertuzumab +trastuzumab +docetaxel (HER2)	CLEOPATRA	OS=34.4 months	101
Breast	Trastuzumab emtansine (HER2)	EMILIA	OS=26.8 months	103
Breast	Tucatinib + capecitabine + trastuzumab (HER2)	HER2CLIMB	In Progress	
Breast (TNBC)	Cisplatin +/− veliparib	NCT02595905	In Progress	
Breast	Etirinotecan Pegol (NKTR-102)	NCT02915744	In Progress	
Melanoma	Ipilimumab + nivolumab (CTLA-4+PD-1)	NCT02374242	Intracranial ORR=46%	83
Lung, Melanoma	Pembroluzimab (PD-1)	NCT02085070	Intracranial RR=33% for NSCLC, Intracranial RR=22% for melanoma	84
NSCLC	Nivolumab +/− Ipilimumab +Radiation (PD-1, CTLA4)	NCT02696993	In Progress	
Brain Mets (any solid tumor)	Pembrolizumab (PD-1)	NCT02886585	In Progress	