Published in final edited form as:

Neurosurg Clin N Am. 2020 October ; 31(4): 515–526. doi:10.1016/j.nec.2020.06.002.

The Role of Stereotactic Biopsy in Brain Metastases

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Keywords

Stereotactic techniques; Image-guided biopsy; Brain Metastasis

Introduction

Brain metastases (BrM) are the most common brain tumor in adults, affecting some 8–14 people per 100,000 population, and up to 20% of cancer patients will develop clinically- or radiographically-apparent BrMs^{1–5}. Some autopsy studies estimate the true incidence as higher still, up to some 30% of cancer patients⁶, and this represents a growing concern for oncologists and neurosurgeons. The most common primary brain-metastatic malignancies are lung and breast carcinomas and melanoma, largely reflecting their extra-CNS incidence, and colorectal and renal cell carcinomas are also seen in increasing numbers³. Although improvements in CNS and extracranial systemic control have resulted in steady gains in both survival and morbidity, the prognosis for BrMs remains poor with a median survival of between 4–8 months depending on cancer type^{3,7,8} and a 5-year survival rate of 2.4%⁹.

Prognosis and thus decision support for treatment remains partially defined with considerable variation amongst cancer types and molecular features, systemic manifestations, and treatment tolerance^{8,10}. Prognostic factors include age, performance status, extra-cranial metastases, treatment history and most importantly the extent of primary disease control^{1,9,11,12}. The degree of heterogeneity in primary cancer types and the patterns of BrM spread and presentations presents formidable challenges in terms of patient stratification and management. To this end, data driven prognostic models have been employed to better understand key risk factors. These have included Recursive Partition Analysis (RPA)^{11,13} and Graded Prognostic Assessment(GPA)^{14–16}, which takes into account histological grade, and now also integrates molecular subtype¹⁷. However the

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DISCLOSURE STATEMENT

The authors have nothing to disclose. NM has consulted for AstraZeneca. KY has consulted for BrainLab AG

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clinical value of these scoring systems has historically been limited due to the overall poor prognosis of BrMs^{1,9}.

Symptomatic patients are often referred to neurosurgical care for signs and symptoms of raised intracranial pressure such as headache and papilledema, focal neurological deficits such as weakness or paresthesias, obstruction of CSF flow, acute lesional hemorrhage (more frequently seen in renal cell carcinoma and melanoma), and for seizure. BrMs should always be suspected in patients with previous known primary cancers and diagnosis can be made on neuroimaging modalities such as CT and MRI. The gold standard for diagnosis remains histological diagnosis, which can be obtained either through surgical resection or stereotactic biopsy.

From a neurosurgical standpoint, resective surgery is offered for palliation, e.g. where significant mass effect is present, for local control of large or growing previously-irradiated tumors, and where cerebro-spinal fluid obstruction is present or imminent. Retrospective studies support the contention that RPA Class I patients benefit the most from surgical resection of solitary BrMs^{18–21}. This, along with the opportunity to concurrently obtain tissue diagnosis has made surgical resection a primary treatment option in solitary and oligometastatic BrM, with several studies showing no differences in surgical outcome for patients with solitary versus with up to 4 lesions^{22–26}. Neurosurgical considerations include patient fitness, extent of extracranial disease, and lesion site, number and proximity to eloquent brain circuitry.

In contrast, stereotactic biopsy for BrM is reserved for patients where there is diagnostic uncertainty, such as suspected BrMs of unknown primary, or ring-enhancing lesions in immunocompromised patients that could represent either infectious or neoplastic lesions, or in patients with conditions with lesions that can mimic BrMs, such as tumefactive multiple sclerosis (MS) or primary central nervous system lymphoma (PCNSL). Additional indications may also include patients with multiple primary cancers or those individuals who have undergone stereotactic radiosurgery (SRS) in order to differentiate between radiation necrosis and viable tumor growth. Recent advances in our understanding of the pathobiology of brain tumors however, may further expand the role of stereotactic biopsy.

Pathobiology of brain metastases

The formation of BrM requires successful adaptation to the CNS host environment through a process of intravasation of tumor cells into the circulation, followed by adhesive arrest in the circulation, extravasation and migration across the blood brain barrier, and successful growth within the brain. A growing literature is defining tumor-specific biologic adaptations that allow for CNS-specific colonization. For example, expression of specific adhesion molecules including the membrane glycosyltransferase ST6GALNAC5 in breast cancer tumor cells has been shown to facilitate circulating tumor cell adhesion to brain endothelial cells^{1,27}. Tumor and stromal angiogenic factors such as VEGF and matrix metalloproteinases, permeability factors and integrins all aid in the successful extravasation and establishment of a metastatic foothold in the CNS¹.

Significantly, recent studies have highlighted clonal divergence between primary lesions and their BrM counterparts. BrMs appear to harbor, with some frequency, targetable mutations that are not identifiable in the primary tumor, or in other sampled extracranial metastases. Examples include EGFR and ALK gene re-arrangements in lung cancer BrM formation, which are increasingly targetable CNS-penetrant tyrosine kinase inhibitors^{28–30}. Additionally, breast cancer subtype switching in the CNS has been established^{31,32}.

Data gleaned from comparative analyses of paired BrM and primary cancer tissue from individual patients may inform mechanisms of CNS-specific metastasis. Mutations, not yet targetable, which have been implicated in the development of BrMs in lung adenocarcinomas include upregulation of WNT signaling pathways via LEF1, HOXB mutation and mutations in the serpin family. The WNT/TCF signaling pathways have been shown to mediate chemotactic invasion in lung adenocarcinoma models³³, and tumor derived serpins suppress of stromal anti-tumor effects through inhibition of plasminogen activators³⁴. Breast cancer BrMs display differential patterns of BrM propensity depending on subtype, with HER-2 positive and triple negative subtypes most likely to metastasize to the brain however the extent to which this may be related to relative CNS inefficacy of established systemic treatment options remains to be determined. Genetic driver mutations commonly found in breast BrMs include the tumor suppressors TP53 and PTEN, as well as ERBB2, CCDN1, CDKN2A and CDKN2B, reflecting common alterations particularly in triple-negative and Her-2 positive subtypes. Activation of the PI3K-AKT pathway is correlated with poor prognosis in breast BrM patients and the presence of membranous HER-3 may provide an escape mechanism for PI3K pathway inhibitors³⁵. In melanoma BrMs, mutations in BRAF, CTNNB1 and RAS-family genes have been implicated^{36,37} with BrM response seen in patients treated with BRAF inhibitors such as dabrafenib³⁸. The PI3K-Akt pathway was again associated with poorer overall survival³⁹. There has also been interest in studying the immune cell infiltrate of melanoma and other cancer BrMs due to the efficacy of immune checkpoint inhibitors in systemic melanoma^{40,41}, and further understanding in the immune composition of BrMs, including how microglia/macrophages modulate the adaptive immune response^{42,43} may help guide immunotherapeutic options for BrMs going forward. Mutations in PTEN, CDKN2A and PIK3CA are also found in RCC BrMs but not in the primary tumor^{2,44}, and PIK3CA, KRAS and NRAS have been described in high frequency in CRC BrMs⁴⁵.

The most mature studies in this domain have identified non-concordance between primary and BrMs in both breast cancer and lung cancers^{46,47}. Specifically, squamous lung cancer patients harboring aberrations in the PI3K pathway had a much higher incidence of BrM. In addition, whole exome sequencing of two patients with paired primary and BrM samples suggested a high degree of clonal divergence⁴⁸. This view was reinforced in 86 paired primary-BrM samples from patients across a range of cancers². Consistent clonal divergence between primary and BrM mutations was again noted, however BrMs retained similarities between distinctly sampled BrMs within the same patient, suggesting although clonally divergent from their primary lesion, BrMs are relatively homogenous within the CNS. Overall, 53% of patients in their cohort had clinically actionable mutations exclusive to the BrM which were not detected in the primary tumor. The relative homogeneity of intracranial

lesions suggests that biopsy of even a single CNS BrM may yield significant information regarding the mutational profile of the BrM population as a whole within a given patient.

This information provides a paradigm shift in the way BrMs are viewed. Instead of considering BrMs as simply part of a monolithic primary disease which has spread beyond the confines of systemic treatment and control, these data suggest that BrMs harbor subclones which have specifically adapted to the brain host environment, which may harbor unique fitness attributes that cannot be identified by simply sampling their parent tumor.

Information regarding unique BrM specific-mutations is of high clinical value as it implies potential differential susceptibility to drug targeting and radiation treatment. The availability and rapid fall in the cost of genetic sequencing has led to many institutions, including our own, to offer targeted gene panel sequencing to patients in order to find actionable mutations. For example, the Memorial Sloan Kettering - Integrated Mutational Profiling of Actionable Cancer Targets (MSK-IMPACT) utilizes next-generation sequencing to target several hundred genes at depth^{49,50}. The increasing availability of such assays can provide BrM-specific mutation information with the potential to change neurosurgical management of BrMs in the future.

The role of stereotactic biopsy in brain metastases

Historically, BrM were treated with whole brain radiation therapy (WBRT) alone. However, despite good local and distant CNS control⁵¹ and in the setting of improved cancer survival overall making long-term considerations increasingly relevant, WBRT has fallen into disfavor for patients with few metastases owing to its associated significant long-term neurocognitive dysfunction⁵². In recent decades, the effectiveness of systemic therapies for cancers that commonly metastasize to the brain such as lung, breast and melanoma has significantly improved from the historical figure of less than 6 months frequently cited, with the advent of targeted therapies and checkpoint inhibitors^{51,53–55}.

The management of BrM can be divided into patient factors and disease factors - patient factors include age/performance status, concomitant disease and tolerance for a procedure under general anesthesia, disease factors include the status of extra-cranial disease, number and location of lesions and suitability for resective surgery. Neurosurgery is offered to patients who are able to tolerate an operation with stable extra-cranial disease and have a suspected primary cancer which is not considered highly radiosensitive, such as small cell lung cancer, germ cell tumors or leukemia^{26,56,57}.

Currently the predominant indication for BrM biopsy is diagnostic uncertainty, typically where concurrent patient features such as lack of other metastatic disease, immunosuppression/associated infections or autoimmune disease can give rise to plausible differentials. Surgery in these instances would provide definitive tissue diagnosis which could substantially alter the treatment goals.

The possibility of identifying targetable molecular lesions, exclusive to a given BrM, may increase the role of BrM sampling. While this is not currently common practice, advances in oncology drug design, and recent studies informing the evolution of BrM may alter this,

should drugs ultimately prove more effective/less toxic than current paradigms including whole-brain and targeted irradiation which are very effective at controlling individual BrM. Specifically, identification of alterations that are effectively treated with CNS-penetrant agents, or those that are associated with treatment resistance, have the potential to abrogate the need for potentially more toxic therapy, for example WBRT with its concomitant neurotoxicity, or to point to a change in targeted therapeutic strategy. Key examples include EGFR mutations and ALK rearrangement in NSCLC, with targeted and CNS-penetrant tyrosine kinase inhibitors (TKI) available^{58,59}. Specific EGFR mutations such as T790M are effectively targeted by third generation TKIs including osimertinib which have the added advantage of traversing the blood brain barrier and demonstrate clinical activity against BrM^{29,60}. Knowledge of specific resistance mutations such as C797S⁶¹ and EGFR L858R could potentially guide treatment decisions^{61,62}. Similarly, ALK-positive (EML4-ALK fusion) BrMs have seen responses to ALK inhibitors such as crizotinib, and newer drugs in the same family such as alectinib, ceritinib, brigatinib and lorlatinib have defined CNS penetration profiles⁶³. In breast cancer, HER-2 lesions constitute some half of all BrM patients, in part owing to the success of antibody-based (and non-CNS-penetrant) therapy including trastuzumab and its derivative antibody-drug conjugate ado-trastuzumab emtansine^{64,65}. In this setting, CNS-penetrant small molecule TKIs including tucatinib and neratinib have been developed with promising early data^{66,67}. Cell cycle inhibitors targeting CDK4/6 such as abemaciclib have been used in estrogen- or progesterone receptor positive breast BrMs^{68,69}. In BRAF-mutated melanoma BrMs, BRAF inhibitors such as dabrafenib and vemurafenib have shown efficacy, both alone and in combination with MAPK inhibitors such as trametinib, however response durability is unclear⁷⁰. Melanoma has also seen significant extracranial and CNS efficacy with immunotherapy. Immune checkpoint inhibitors such as drugs against PD-L1 (pembrolizumab and nivolumab) and CTLA-4 (ipilimumab) have conferred response rates of up to 60% when given in combination (ipilimumab and nivolumab)^{70,71}. An increased understanding of the underlying immunomodulatory mechanisms will help better identify biomarkers to help response prediction. Finally, as more BrM are treated with focused stereotactic irradiation modalities and immunotherapy, radiation necrosis and pseudo-progression are inflammatory entities that are increasingly encountered as radiographic differentials that can mimic disease progression, and raise more situations of diagnostic uncertainty which would require definitive surgical biopsy.

One of the key findings from BrM genome sequencing studies is the presence of private, discordant clinically actionable mutations in BrMs, which were found to be prevalent in 53% of lesions by Brastianos et al.². It should be noted however, that the term ‘clinically actionable’ was based on genes identified on the TARGET computational platform by Van Allen et al.⁷², which are not fully clinically validated. The decision to operate must therefore necessarily be multifactorial, taking into account the tumor’s location and ease with which a sample can be taken, the performance status of the patient, extent of disease and known features of the primary cancer, and likelihood of identifying a treatment-altering paradigm, against the risk of surgery and non-diagnostic yield, with the current mainstay indication remaining radiologically-inconclusive lesions.

Surgical Considerations

Although a detailed description of the different technical methods of brain biopsy is beyond the scope of this review, there are many different techniques for brain biopsy currently in use. In general, BrM biopsy follows the same principles as other forms of brain biopsy with the overall goal of providing a safe, consistent and reliable method of sampling lesional tissue. The principles of stereotaxy apply whether frame-based or frameless methods are employed, with consideration given to the depth and location of the lesion, relevant neurovascular anatomy and the constraints of stereotaxy based on preoperative imaging. Recent series have reported diagnostic yields of 84–100% with frame-based techniques and 86.6–100% with frameless procedures^{73,74}. Future diagnostic yields may improve with the increased utilization of sequencing for pathognomonic genomic alterations, which may prove more sensitive than histological diagnosis alone. Overall morbidity from stereotactic biopsy has been reported in 3.8–27.8% of frame-based procedures and 1.3–24.5% in frameless procedures^{73,74}. Postbiopsy radiographic hemorrhage rates ranged from 5.1–14.2% and 2.4–17.8% in frame-based and frameless methods, and lower for clinical neurologic deficits at 2.8–13.9% and 1.3–15.4% for frame-based and frameless biopsies, respectively⁷³. A more recent meta-analysis has described the morbidity associated with frame based biopsy to be between 0.7–13%, and mortality of 0–4%. Asymptomatic hemorrhages can be up to 59%, however symptomatic hemorrhages have been reported in some 0–8.6% of cases. Neurologic deficits are most frequently the result of larger hemorrhages^{73,74}. Freehand biopsy no longer has a role in the modern neurosurgical setting.

Biopsy has 4 important procedural steps: 1. identification of a safe trajectory, 2. burr hole placement, 3. maintenance of trajectory alignment, and 4. fixation at target point. Complications related to stereotactic biopsy are invariably caused by an issue with one or more of these factors.

Frame-based methods have advantages of being more accurate, but require rigid fixation of the patient while the patient undergoes cross-sectional imaging, typically computed tomography (CT) and in some cases magnetic resonance imaging (MRI). Frames used include the Leksell frame or Cosman-Roberts-Wallis (CRW) frame. Burr hole placement, maintenance of trajectory and fixation at target is facilitated by attachment of a targeting frame. The slightly higher accuracy for frame-based techniques has led to some surgeons preferring this approach for deep cranial lesions.

Frameless techniques employ alignment tools such as the Stealth Navigus (Medtronic, USA) or Brainlab Varioguide (Brainlab AG, Germany), and navigation systems based upon surface facial landmarks cross-referenced to an array fixed to the operating table allow matching of pre-operative imaging to the patient. Burr hole placement is planned using neuronavigation. The biopsy itself is typically performed through a linear scalp incision. Either a twist drill or high-speed drill is then used to make a burr hole. Some systems use burr hole anchors secured to the calvarium to help maintain the trajectory of the biopsy catheter (Figure 1) (Navigus, Medtronic, USA). Alternatively, manufacturers such as Brainlab have engineered a multi-articulated arm (Varioguide) connected to a fixed array to help neuro-navigate and maintain the trajectory (Brainlab AG, Germany). Use of intraoperative CT or MR imaging can be used to both improve registration and confirm biopsy location. These modalities can

also be utilized following completion of the biopsy to evaluate for intracranial hemorrhage. For suspected metastases, which are typically encapsulated, there is the additional possibility that a tumor could be deflected by a blunt needle end, a yielding nondiagnostic biopsy despite correct alignment. For this reason, our center advocates intraoperative pathologic assessment and in some cases intraoperative imaging. Intraoperative modalities such as simulated Raman scattering microscopy may increase the rapidity of pathologic evaluation⁷⁵.

The one significant drawback for both frame-based and frameless technologies is the reliance on historical images to plan trajectories. Brain compliance and its lack of rigid fixation to the dura allows for some deformation during surgery. In atrophic brains or those not harboring large/edema-inducing tumors, significant deviations can exist between the pre-operative image and the actual trajectory in a phenomenon known as brain shift^{76,77}. In principle it is therefore advisable when performing biopsies to minimize the dural opening to prevent CSF egress as much as possible when passing the needle. Alternatively, repeat imaging can be performed intra-operatively to verify neuronavigational registration and landmarks prior to cannula insertion.

Novel technologies such as interventional MRI (MRI Interventions, USA) use MR compatible, non-ferromagnetic instruments to perform biopsies while the patient is within the bore of the MRI scanner. Planning is first performed by scanning the patient with a series of fiducials to select the optimum entry point, then with the patient anesthetized and in the MR scanner, a linear incision is made and bone-anchored burr hole needle holder is placed, the trajectory is calculated and the needle is sequentially advanced and adjusted through serial imaging as it traverses the parenchyma to its target. This technique allows near real time visualization of the target and trajectory and can warn the clinician of any adverse complication during the procedure. An alternative but slightly more cost-effective method of providing real time guidance is to use ultrasound-guided biopsy. This method, which has been successfully used in other neurosurgical conditions^{78–80}, uses a combination of a burr hole ultrasound probe along with a needle attachment to the probe to provide real time image guidance to the target of interest. This can be used in after standard neuronavigation is used to plan the entry burr hole to achieve real-time image-guided sampling. The drawback of this technique is its poor resolution, particularly at depth and making it not suitable for some small lesions, however this technique when fused with intraoperative CT/MRI can help improve accuracy even further.

Robotic-assisted surgery is an area which has been gradually gaining acceptance in stereotaxy procedures. Although the procedure differs slightly between manufacturers, all currently available systems rely on pre-operative registration and calibration of the robot arm, with robotic assistance in maintaining trajectory and target guidance. Robotic-assisted stereotactic biopsy has been described in multiple case series combining to a total of over 290 procedures in a variety of different robotic systems. The quoted in vivo target error rate ranged from 0.81 ± 0.39 (ROSA, Zimmer Biomet) to 3.3 to 4.5 mm (Zeiss MKM). The non-diagnostic rate (NDR), hemorrhage rate (HmR) and mortality rate (MR) compares favorably to manual methods, with robotic series having an NDR = 2.2–4.3%, HmR = 8–10%, and MR = 0–0.5% compared to NDR = 0.3–4.2%, HmR = 3.7–8.8% and MR = 0–2% in

frameless manual case series, and NDR = 9%, HmR = 3.5–8.0% and MR = 0.7–1% in frame-based series⁸¹. The drawbacks however for these newer methods include the need for dedicated or adapted suites for equipment, and the time and resources required to perform these procedures may limit their use in the wider neurosurgical setting at least in the short term.

Other related surgical treatment options include laser interstitial thermal therapy (LITT). Available at several specialized centers, this technique relies on the guided insertion of catheters to the target lesions which provide target ablation through directed thermal energy (NeuroBlate, Monteris Medical Inc, USA). A 1024nm laser probe (which can be robotically advanced) in combination with real-time MRI thermometry predicts lesioning area. This approach has recently been used to treat patients who have undergone SRS for BrMs with evidence of progression and/or radionecrosis^{82,83}. With adequate planning for suspected LITT-responsive diseases (tumors, radionecrosis), stereotactic biopsy can be performed either within the bore of an MRI scanner just prior to LITT, or in an operating room immediately prior to transfer to a diagnostic MRI with the requisite LITT setup. Should sampling volume be a concern, another option is to use tubular-based stereotactic biopsy methods which permit sampling of greater volumes down the same trajectory path⁸⁴.

In rare cases where intraoperative pathology is not available or conclusive, intra-operative or immediate post-operative MRI can be useful to confirm that the correct location has been biopsied; in the absence of easily accessible MRI facilities, some surgeons have described gently introducing a small amount of air after biopsy in order to highlight the biopsy location on post-operative CT.

Finally, the capacity to obtain rapid histological diagnosis has the potential to increase diagnostic yield through immediate re-sampling in cases where the tissue obtained is non-diagnostic, and to reduce the risk of morbidity from over-sampling once a diagnosis has been made. Traditionally this has been performed through intra-operative frozen section analysis, however the practicalities and speed of obtaining an expert neuropathological opinion intra-operatively varies among institutions. Alternative intra-operative methods have been developed, including optical spectroscopy, such as Raman spectroscopy, which differentiates tissue types based on their light scattering properties. This modality provides the intraoperative pathologist with images within minutes, and a recent study has described its use in combination with machine learning classifier algorithms to identify malignant tissue types in the intra-operative setting to obtain near real-time tissue diagnosis^{75,82}. Other technologies currently in development include optical coherence tomography, multiphoton microscopy, video rate structured illumination microscopy, ex-vivo fluorescence confocal microscopy and ambient mass spectrometry, all aiming to improve the speed, accuracy and yield of stereotactic biopsies^{85,86}.

Clinical case studies

The following illustrative cases discuss clinical scenarios where the results of a stereotactic biopsy helped to guide therapy in patients with brain metastases.

Case 1—A 60 year old male with a history of metastatic melanoma presented subacutely with right hemiparesis. He had been receiving treatment with ipilimumab and nivolumab, but therapy was discontinued due to the development of hypophysitis. Brain MRI revealed a 2.5 cm ring-enhancing cystic mass in the left internal capsule without associated restricted diffusion (Figure 2, A and B). There were no other intracranial lesions. Given the cystic appearance in the setting of an existing immune-related adverse event from checkpoint inhibitor therapy, the differential diagnosis included a metastatic lesion as well as an inflammatory or infectious process. Given that surgical resection would carry significant risk of neurologic morbidity, consideration was given to stereotactic biopsy and cyst decompression which would permit simultaneous histological diagnosis and lesion size reduction which, if the lesion was confirmed to be metastatic, would also provide an attractive radiosurgical target. The decision was therefore made to perform a stereotactic biopsy of the cyst wall with aspiration of its intrinsic fluid. The biopsy and aspiration were performed through a single burr hole using a frameless technique. The pathology returned as metastatic melanoma, and the patient underwent post-operative stereotactic radiosurgery to a significantly reduced clinical treatment volume for definitive treatment of the metastasis. Two month post-treatment brain MRI revealed a resolving lesion (Figure 2C). The patient went on to develop progression of disease 10 months later confirmed on brain MRI with perfusion. He was retreated with proton beam radiotherapy at that time and continues to undergo regular radiographic surveillance.

Case 2—A 73 year old female with a history of recently-treated small cell lung cancer, previously treated stage I triple-negative breast cancer and anal cancer presented with headaches and double vision. MRI of the brain revealed a 1.5 cm right occipital mass centered around the calcarine sulcus (Figure 3A). The patient was advised to undergo stereotactic biopsy for diagnosis given the history of multiple primary cancers, with possible differential diagnoses including glioblastoma in the setting of a potential underlying germline cancer syndrome. In addition, the patient was hesitant to undergo resective surgery in part due to the risk of worsened post-operative vision, and the possibility that this tumor represented progression of small cell disease which is known to be both radiosensitive and likely to progress throughout the CNS. The biopsy was performed through a single burr hole using a frameless technique. The pathology returned as metastatic small cell lung cancer, and given this diagnosis, the patient received whole brain radiation therapy as opposed to stereotactic radiosurgery. Germline genetic testing was unrevealing. Brain MRI two months after whole brain radiation therapy revealed complete resolution of the metastatic lesion with no new areas of disease.

Case 3—An 83 year old female with a history of ALK-rearranged lung cancer and without active disease for over 10 years presented with left sided tremulousness, bradykinesia, and micrographia. Her symptoms responded to treatment with carbidopa-levodopa consistent with a diagnosis of Parkinson's disease, but MRI of the brain performed in workup for this revealed a multicystic peripherally enhancing mass in the right parietal lobe (Figure 3B). Systemic re-staging was negative for extracranial metastatic disease, and the differential diagnosis included BrM versus high grade glioma. Given the patient's advanced age, relative morbidity of open craniotomy and resection, and potential responsiveness of the lesion to

ALK inhibition via CNS-penetrant agents, the decision was made to proceed with stereotactic biopsy. The biopsy was performed through a single burr hole using a frameless technique. The pathology returned as metastatic lung adenocarcinoma with the same ALK rearrangement as the initial tumor. The patient subsequently underwent stereotactic radiosurgery for treatment of the lesion which was stable on repeat MRI one month following treatment. Confirmation of ALK rearrangement opened the option of treatment for her CNS-centric process with ALK-directed therapy should her disease progress despite radiosurgery.

Case 4—A 54 year old woman with a history of metastatic small cell lung carcinoma developed a right frontal lobe metastasis that was treated with single fraction stereotactic radiosurgery (18 Gy). A few months later, she developed left sided weakness. Brain MRI revealed an increase in the size of the treated lesion (Figure 3C). The time course and imaging characteristics were ambiguous, with the concurrent possibilities of either disease progression or radiation necrosis, which are managed differently. As a result, a stereotactic biopsy was recommended for diagnosis. The biopsy was performed through a single burr hole using a frameless technique. Pathology revealed predominantly radiation necrosis with a very small amount of viable tumor. As a result, the patient was advised to undergo laser interstitial thermal therapy for treatment which was performed as a separate operation two weeks later, and this achieved durable local control at 31 months follow up.

Discussion

Stereotactic biopsy is a safe and reliable procedure which has been a core part of neurosurgical practice. Its accuracy and yield have steadily improved with the advent of frame-based and frameless techniques, and associated morbidity and mortality are low⁷³. Clinically, stereotactic biopsy of BrM has traditionally been seldom performed except for specific indications such as lesions which are inconclusive on radiology and not amenable to open resection, or suspected BrMs with unknown primary source. This core diagnostic indication is unlikely to change in the near future.

However, the increasingly prominent role of surgical resection for oligometastatic BrM will provide molecular profiling data which will further increase our understanding of the pathobiology of BrMs. The finding that BrM harbor targetable mutations, in some cases divergent from the patients' primary tumor site, suggests that in the future a lower clinical threshold may be applied for biopsying lesions in easily accessible locations in order to gain knowledge of a BrM's molecular profile. Currently the overall proportion of clinically actionable genetic alterations detected exclusively in BrM via targeted genetic sequencing panels remains small. Whether such management strategies become more commonplace will depend on the establishment of clinically-validated and actionable mutations for BrMs. Knowledge of disease-specific BrM mutational profiles, along with an ever-expanding menu of CNS-penetrant agents targeting specific molecular pathways, will influence treatment decisions, and it is expected that the role of stereotactic biopsy will assume a more prominent role in the armamentarium of the neuro-oncological surgeon. It is anticipated that molecular profiling of both primary and BrMs will become *de rigueur* and our experience with routine tumor panel sequencing at our institution has highlighted situations where

biopsy may be particularly helpful. Currently however, the primary indication remains diagnosis for unresectable or ambiguous but otherwise treatable lesions.

From a surgical perspective, safety and good technique remain critical regardless of modality, and technological improvements in this domain including image guidance, robotic-assisted surgery, and simultaneous therapeutic strategies such as LITT are, together with improving survival of cancer patients in general, likely to usher an increase in the biopsy of BrMs. Therefore a good understanding of principles of stereotaxy, its utility and risk profile, and familiarity with a variety of techniques which obtain safe, reliable and accurate results are essential skills in modern neurosurgical practice.

Acknowledgements

This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748

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Key Points

- Stereotactic Biopsy plays an important role in the management of brain metastases and knowledge of underlying pathobiology of brain metastases can influence treatment decisions
- Neurosurgical oncology surgeons should be aware of the techniques available to perform stereotactic biopsies and the current and potential future indications of stereotactic biopsies
- Recent scientific research has uncovered differences in the underlying pathobiology of brain metastases compared to their primary counterparts.
- The utility of a stereotactic biopsy must be evaluated on a case by case basis and is influenced by a patient's history and radiographic findings.

SYNOPSIS

Brain metastases (BrM) affect up to 20% of patients with cancer and represent an increasing portion of surgical brain tumors patients owing to improving prognoses of cancer patients in general and in many cases even of those with brain metastases. With advances in molecular biology and targeted therapy, the indications for neurosurgical sampling and specifically stereotactic biopsy are likely to change in the future. In this review we address some of the scientific advances in BrM biology, the clinical rationale and range of techniques currently used to perform stereotactic biopsy, and how the advent of molecular interrogation may potentially alter the way BrM patients are managed in the future.

Figure 1:
(A) Navigus brain biopsy bone anchor. (Reprinted with the permission of Medtronic, Inc. ©). (B) Varioguide biopsy arm. (*Courtesy of Brainlab AG*).

Figure 2:

Axial T1 weighted post-contrast (A) and diffusion weight images (DWI, B) MRIs of the brain demonstrating a ring enhancing mass in the left internal capsule without restricted diffusion. Two month post-treatment axial T1 weighted post-contrast MRI of the brain (C) reveals a resolving cystic lesion.

Figure 3:

(A) Axial T1 weighted post-contrast MRI of the brain displaying a right medial occipital enhancing mass. (B) Axial T1 weighted post-contrast MRI of the brain demonstrates a multicystic peripherally enhancing mass in the right parietal lobe. (C) Axial T1 weighted post-contrast MRI of the brain demonstrates a ring enhancing mass in the right posterior frontal lobe.