

## When Less is More – the Value of Stereotactic Biopsy for Diagnosis in the Era of Cytoreductive Neuro-Oncology

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### ABSTRACT

Compelling reasons for offering patients maximal cytoreductive surgery of brain neoplasms include improvement in survival, improvement in neurological function, and better histopathological tissue representation. Despite these benefits, stereotactic brain biopsy may be a better option in certain circumstances, including consideration of highly chemo- and/or radiation responsive lesions in the differential diagnosis, expected inability to perform adequate cytoreductive surgery due to anatomic relationships, poor pre-operative performance status not expected to improve with cytoreductive surgery, and poor life expectancy regardless of aggressive surgical resection. We discuss the pros and cons of stereotactic brain biopsy in the “Era of Cytoreductive Surgery.”

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**Key words:** Stereotactic biopsy; Brain tumor; Cytoreductive surgery; Benefits; Risks

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### EDITORIAL

For the vast majority of intracranial masses, the initial and preferred therapeutic response is “take it out.” That generally means for the neurosurgeon to attempt gross total resection. We could therefore consider that we are in the “Era of Cytoreductive Surgery.” But are some patients better served by a more conservative approach consisting of a stereotactic biopsy instead of cytoreductive surgery?

Recent studies have shown that patients with increased extent of brain tumor resection (> 78% to > 90% depending on pathology) have increased survival benefits when compared to patients with none to incomplete resections<sup>[1,2,3]</sup>. Maximal resection can also lead to improved neurological functioning<sup>[4]</sup>. Patients are able to participate more fully in their activities of daily living and have better quality of life<sup>[4]</sup>. Maximal resection decreases rates of incorrect diagnosis due to poor sampling or sampling bias because the pathologist has more tissue to review<sup>[5]</sup>. And perhaps most importantly, the decrease in disease burden resulting from maximal resection can allow patients to respond more effectively to adjuvant therapies to improve survival<sup>[3]</sup>.

Maximal cytoreductive resection must obviously be balanced against its potential negative of associated complications. Overall, the rate of major complications, such as stroke, worsening neurological functions, or death associated with aggressive intracranial tumor removal is approximately 13%<sup>[6]</sup>, which increases to 27.5% if the tumor is located in an eloquent or less accessible location<sup>[7]</sup>. Furthermore, certain groups of patients have poor neurological outcomes after maximal resection of their brain tumor. For instance, Park, et al<sup>[8]</sup>, showed that patients with tumor volume greater than 50 cm<sup>3</sup> as well as tumors located in an eloquent cortex and dominant hemispheres have poor neurological function and survival after maximal resection of their lesions. Patients with Karnofsky scores less than 70 have also been shown to have worse neurological and survival benefits after maximal resection<sup>[8,9]</sup>. This poor outcome in relation to Karnofsky scores and cytoreductive surgery has been shown to persist regardless of the location of the mass to be resected<sup>[10]</sup>, although some low Karnofsky score patients may derive some benefit from surgical decompression<sup>[11,12]</sup>; further

characterization of those low Karnofsky score patients who would benefit is necessary. Maximal cytoreductive therapy may delay adjuvant therapy because patients need to recover from surgery and wounds need to heal. Ideally, multi-modality therapies (radiation and/or chemotherapy) should start within 6 weeks for surgery<sup>[13,14]</sup>. Initiation of radiation therapy longer than 37 days following glioma resection decreases survival rates, especially in patients older than 40 years<sup>[15]</sup>. Maximal resection can also be associated with increased hospitalization and cost of stay. When compared with non-invasive surgical therapies, patients undergoing resection for brain tumor stay in the hospital average 15 days longer and cost about \$3000 more per day<sup>[16,17]</sup>. Finally, failed gross total resection (i.e. subtotal resection) leads to poor outcome in patients. Patients with subtotal resection have poor survival and poor quality of life due to worsening of functional status after surgery<sup>[18]</sup>. This deterioration of functional status has been attributed to worsening of peritumoral edema after surgery<sup>[18]</sup>.

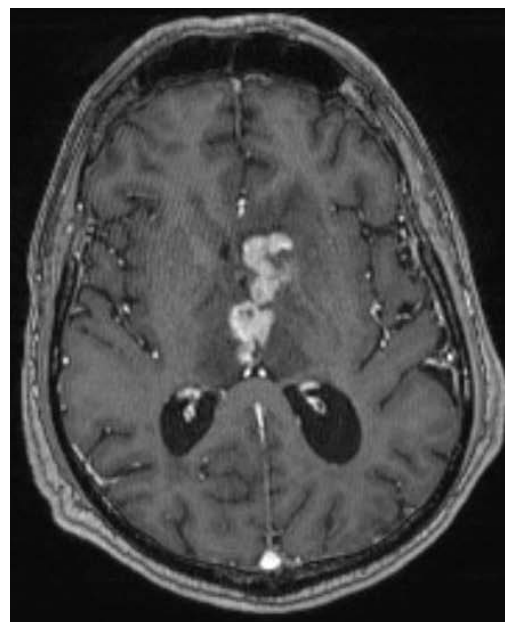
As an alternative, stereotactic biopsy provides a means of obtaining a tissue diagnosis without dealing with the potential negative consequences of maximal resection<sup>[19]</sup>. This procedure can be performed with minimal damage to the surrounding brain using a small probe navigated with computer guidance to a specifically targeted point (or points) from where the biopsy can be taken<sup>[19]</sup>. Options for stereotactic biopsy include frame-based or neuro-navigational guidance techniques. Frame-based biopsy technologies, such as the CRW frame (Integra Lifesciences Corporation, Plainsboro, New Jersey), use Cartesian geometrical coordinates to link the biopsy probe to the precise location of the lesion identified on head CT or MRI<sup>[19]</sup>. For neuro-navigational guided needle biopsy, the biopsy probe is directed to a target selected while following the trajectory on the navigational screen in real time on a pre-operative obtained CT or MRI<sup>[20]</sup>, a device such as Navigus (Medtronic Inc., Minneapolis, MN) can stabilize the probe<sup>[21]</sup>. Both of these methods aid in specific targeting of the lesion, even those that are less accessible, with limited injury to the surrounding tissue.

However, stereotactic biopsy in of itself does not allow for improvement of symptoms since it only removes a minimal portion of the lesion; it does not decrease disease burden. Stereotactic biopsy can lead to sampling bias. This sampling bias occurs because the tissue selected at the target may not be representative of the entire heterogeneous lesion. Marginal tissue may be non-diagnostic because it shows only inflammation or gliosis; more central tissue could show necrosis. Insufficient volume of tissue may be acquired to make the correct diagnosis<sup>[22]</sup>. While a diagnostic accuracy of 95% has been reported for neoplastic processes with stereotactic biopsy<sup>[23,24,25]</sup>, multiple biopsy sites may be required to achieve this goal<sup>[25,26]</sup>, particularly for deep-seated or cerebellar lesions. Biopsy results can direct subsequent clinical care in these patients, but the absolutely correct diagnosis on stereotactic biopsy compared to resected samples in the same population may only be 63%<sup>[5]</sup>. Some patients may require subsequent cytoreductive surgery if adjuvant therapies fail; about 26% of patients treated in such manner have minor to no response to adjuvant chemo-radiotherapy and require further surgical treatment<sup>[27]</sup>. Some lesions are poorly located for safe stereotactic biopsy. Cortical lesions, those within the ventricles, and those demonstrating hemorrhage might be better approached with an open procedure<sup>[23, 28]</sup>.

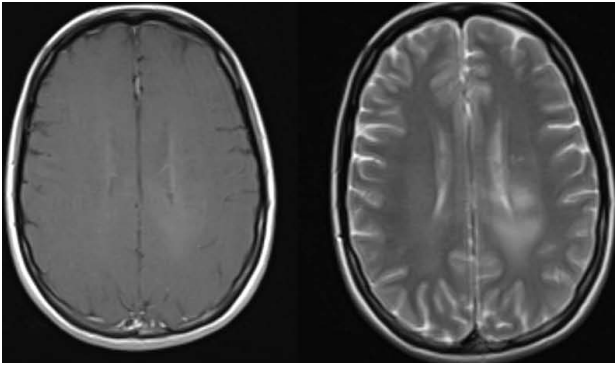
On balance, the arguments favor cytoreductive surgery for the majority of cases because of its ability to decrease disease burden and symptoms, and increase chance of survival. However, certain classes of patients presenting with brain tumors will likely not benefit

from maximal surgical resections. Tumor location can limit extent of surgical resection. Tumors located in eloquent brain such as deep nuclei, brain stem, motor cortex, or subcortical structures may not be able to be maximally resected without causing significant harm to the patient<sup>[18]</sup>. Some intracranial pathologies are highly responsive to chemotherapy or radiation therapy. These pathologies include lymphoma, germinoma, small cell lung cancer<sup>[30]</sup>; they should be treated primarily with chemotherapy and/or radiation therapy, as some studies have shown that radiation therapy for these lesions is as efficacious as or better than cytoreductive therapy<sup>[31,32]</sup>. For primary CNS lymphoma, outcome is superior when treated with chemo-radiotherapy compared to cytoreductive therapy<sup>[33,34]</sup>. Smaller brain metastases (less than 3 cm) can be effectively treated with stereotactic radiosurgery as with cytoreductive surgery<sup>[35]</sup>. In these cases, stereotactic biopsy can confirm a tissue diagnosis and direct clinicians to using effective modes of therapy other than cytoreductive surgery. Occasionally, non-neoplastic diseases are diagnosed. Patients who turn out to have cerebral abscess instead of neoplasm may be able to be managed with antibiotics instead of surgery<sup>[36]</sup>. Resection would almost never be required for tumorifactive multiple sclerosis<sup>[37]</sup>. Low Karnofsky score patients (< 50) may also be best managed with stereotactic biopsy, particularly since the parameters for those likely to benefit from cytoreductive surgery are not well defined. When performance is diminished by significant mass effect within the frontal or temporal lobe or by displacement of eloquent structures rather than by invasion<sup>[38]</sup>, or by an extra-axial mass, cytoreductive surgery makes sense. In other low performers, where normal brain is invaded by tumor stereotactic biopsy may be in order.

We can consider the above analysis to place our decision-making for managing patients with brain masses in appropriate context. Once we determine that a brain tissue diagnosis is necessary for treatment decisions, we can consider the various surgical options for obtaining that diagnosis. We can start with the differential diagnosis based on history, physical examination, and imaging. If we suspect that the lesion is one that may be highly responsive to radiation/



**Figure 1** T1 gadolinium-enhanced axial MRI of the brain showing a mass in the corpus callosum extending into bilateral frontal lobes of a 60 year-old woman presenting with headache, confusion, and seizure. Stereotactic biopsy showed anaplastic astrocytoma.



**Figure 2** A. T1gadolinium-enhanced axial MRI of the brain showing a left parietal corona radiata/peri-ventricular lesion in a 47 year-old woman presenting with right leg weakness. B. T2 weighted axial MRI of the same patient showing the adjacent edema. Stereotactic biopsy showed infiltrating astrocytoma.

and or chemotherapy, we should consider stereotactic biopsy for establishing that diagnosis (Figure 1). Anatomic relationships of the lesion(s) are the next consideration. Those lesions within or adjacent to eloquent structures without a satisfactory corridor for access and expected post-operative neurological deficit may best be served with stereotactic biopsy (Figure 2). Similarly, lesions in which anatomic relationships will constrain aggressive extent of resection such as a suspected glioblastoma of the anterior corpus callosum involving bifrontal corona radiation (Figure 3) may also be a better candidate for stereotactic biopsy. Another example better served with stereotactic biopsy is the patient with multiple, widely spaced brain lesions without a diagnosis of metastatic cancer. We should then consider the patient's neurological condition. If signs and symptoms are well controlled with glucocorticoid steroids and a metastatic process is suspected, stereotactic biopsy can be used to establish the diagnosis prior to proceeding with radiosurgery (Figure 2) and avoid cytoreductive surgery. If the patient has a low Karnofsky performance index and is unlikely to benefit significantly from resection, stereotactic biopsy should be considered. Lastly, we should consider the patient's life expectancy to the best of our ability. Those patients with disease burden suggesting no more than 3 to 6 months life expectancy who require brain tissue for diagnosis would probably benefit more from stereotactic biopsy to minimize any recovery time. This algorithm is outlined in Figure 4.

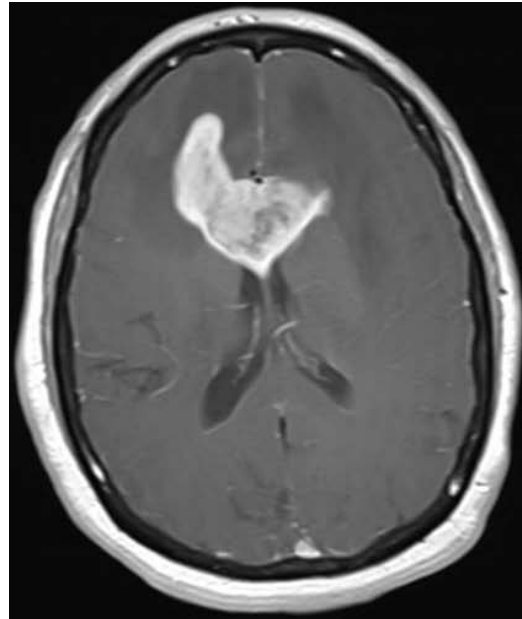
Cytoreductive surgery may be our initial consideration when addressing neoplasms in the brain. It may be the best option for most patients. But we should remember that some patients are better managed with a less invasive procedure – stereotactic brain biopsy.

## CONFLICT OF INTERESTS

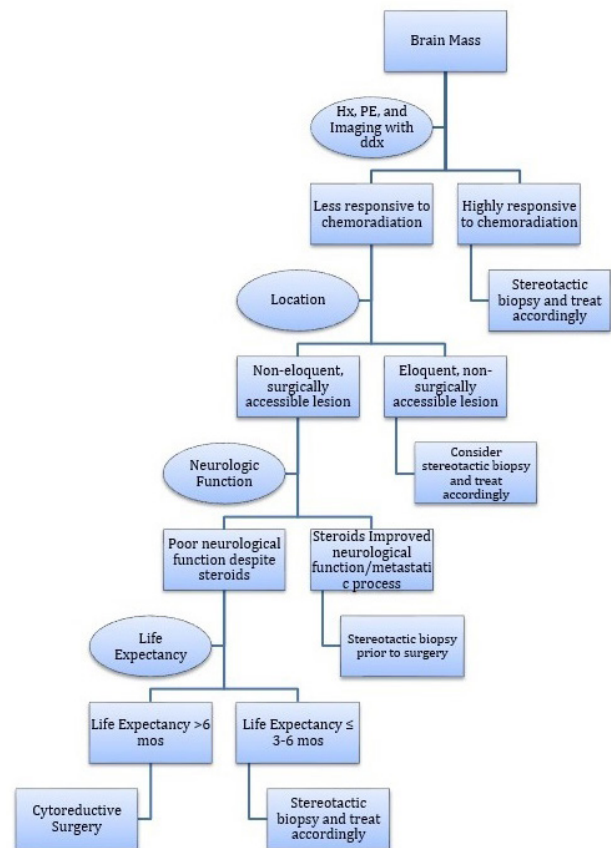
There are no conflicts of interest with regard to the present study.

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**Figure 3** T1 gadolinium enhanced axial MRI of the brain showing a peri-ventricular enhancing mass in a 63 year man presenting with confusion, ataxia, and cognitive deficits. Stereotactic biopsy showed B-cell lymphoma.



**Figure 4** Algorithm addressing factors involved in deciding cytoreductive surgery versus stereotactic biopsy.

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