How Do I Treat…
…Patients with Surgically Resectable Brain Cancers?

BY ARNOLD B. ETAME, MD, PHD

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"Awake-brain surgery permits safe resection of tumors in brain areas that are eloquent to motor and speech functions."

It is estimated that more than 70,000 primary brain tumors will be diagnosed in the United States in 2013 based on the Central Brain Tumor Registry of the United States data. Metastatic brain tumors are more common than primary brain tumors. In addition, metastases can often present as multiple lesions in contrast to primary brain tumors.

Management strategies for brain tumors often entail some combination of surgery, chemotherapy, and radiotherapy. Benign symptomatic primary brain tumors might require only surgery, whereas malignant primary brain tumors often require surgery, chemotherapy, and radiotherapy. In addition, surgery followed by radiotherapy is sometimes desired for large symptomatic metastatic lesions.

Furthermore, given the volume constraints of the intracranial compartment, an expanding tumor mass with associated edema will invariably result to neurological symptoms. These include headache, nausea, vertigo, motor, sensory, visual, gait, cognitive, and most commonly seizure-related symptoms.

In such instances, surgical resection has the added advantage of quickly ameliorating tumor-related mass-effect and hence improves quality of life. Surgery therefore remains a cornerstone in the management of brain tumors.

Defining the goals of surgery is a critical component in the surgery decision-making process, because such goals ultimately have to be balanced with any potential neurological morbidity.

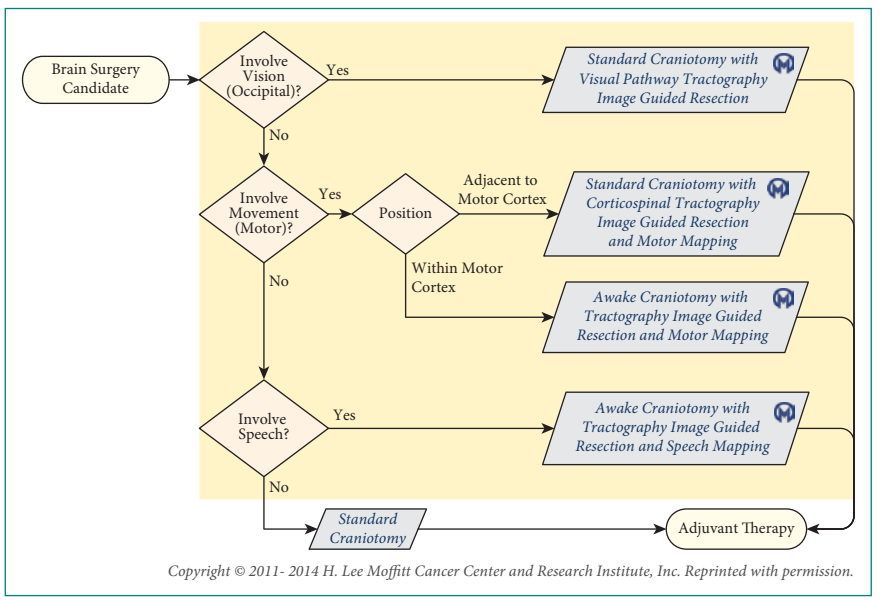
Tumor location is another important factor to consider, because language and motor areas could provide significant limitations towards the goal of safe maximum resection. In such instances functional preservation is paramount, which implies that a subtotal resection would be acceptable.

In other instances, surgery is intended strictly for the purpose of tissue diagnosis as opposed to resection. Such patients would be subjected to either a stereotactic needle biopsy or an open craniotomy biopsy depending on tumor location and risk, as well as the pretest probability of a successful diagnostic yield based on the radiographic characteristics of the tumor.

Open biopsies are ideal for superficial tumors and provide the advantage of larger sample size coupled with the ability to easily sample various regions of the tumor. For deeper lesions, stereotactic needle biopsy is preferred.

"The goals of surgery should always prioritize neurological functional preservation."

At our comprehensive cancer center, we encounter brain tumors at a higher frequency. I am involved mostly with the surgical, as well as the stereotactic radiosurgery, management of brain tumors. Patients are discussed at our weekly interdisciplinary tumor board, whereby surgical candidates are identified on a consensus basis. In recommending brain surgery, the overall functional status and disease burden of the patient are taken into account, especially for patients with systemic metastatic disease.



Algorithmic Representation of Craniotomy Options for Patients with Tumors in Eloquent Brain Regions for Speech, Motor, and Vision

A major priority of my surgical approach with brain tumors is to enhance neurological outcomes for brain tumor patients. In order to accomplish this objective, I have incorporated MRI-guided imaging approaches that permit intraoperative interrogation of both tumor and critical white matter fiber tracts in patients undergoing brain surgery.

I employ diffusion tractography imaging (DTI), which uses diffusion of water molecules within white matter fibers in the brain as a surrogate for the orientation and localization of those fibers. Hence DTI permits delineation of critical white matter fiber tracts that are closely associated with the tumor.

The ability to localize and spare critical fibers during tumor resection undoubtedly enhances neurological outcomes. In addition, I employ awake-brain tumor surgeries strategies for functional interrogation during tumor resection. All of these are accomplished through stereotactic techniques that permit navigation during tumor resection.

I take brain eloquence into consideration when deciding stereotactic craniotomy options for brain tumors. Tumors in areas that are eloquent for speech, motor, and visual pathways (temporal/occipital) are surgically treated distinctly from tumors in non-eloquent regions.

The risk of neurological deficits is quite profound in eloquent regions, and the deficits themselves can be very disabling for patients. Tumors in non-eloquent brain regions are treated using a standard stereotactic craniotomy. The stereotactic component permits a safe and reliable approach to the tumor for resection using trajectories that minimize cortical damage.

When patients harbor tumors in eloquent regions of the brain, DTI is often incorporated into the stereotactic craniotomy technique, thereby permitting simultaneous interrogation of tumor and closely associated critical white matter fibers. For tumors close to the visual pathways within the temporal and occipital lobes, I often delineate Meyer's visual fibers (temporal) and optic radiations (occipital), and stereotactically ascertain their positional relationship to the tumor.

A surgical trajectory to the tumor that spares the visual fibers is then planned. This is particularly important for occipital lobe lesions whereby compromise of visual fibers could result to dense visual field defects. Similarly, for tumors that are close to the motor cortex but do not actually involve motor fibers, I would often incorporate DTI for corticospinal motor fibers into the stereotactic craniotomy technique, thereby permitting

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CDK-4/6 Inhibitor Palbociclib Doubles Time to Progression in Advanced Breast Cancer

BY ROBERT H. CARLSON

SAN DIEGO, Calif.—The drug palbociclib (PD-0332991), an inhibitor of cyclin-dependent kinases (CDK) 4 and 6, significantly improved progression-free survival when administered as a first-line treatment along with the aromatase inhibitor letrozole, in patients with ER-positive HER2-negative metastatic breast cancer. These results from the Phase II PALOMA-1 study were presented here at the American Association for Cancer Research Annual Meeting (***Abstract CT101***).

Median progression-free survival was 20.2 months for the 84 patients receiving the palbociclib-letrozole combination versus 10.2 months for 81 patients receiving letrozole alone, reported Richard S. Finn, MD, Associate Professor of Medicine at UCLA.

AACR/Todd Buchanan

RICHARD S. FINN, MD: "Survival events in ER-positive breast-cancer take time to evolve, but we are very encouraged by the overall survival."

The progression-free survival hazard ratio for women taking the combination was 0.49 compared with women receiving letrozole alone. Overall survival was trending in favor of palbociclib-letrozole, Finn said, but the difference was not statistically significant.

The study's senior author is Dennis Slamon, MD, PhD, Professor of Medicine at UCLA's Jonsson Comprehensive Cancer Center and Director of the Revlon/UCLA Women's Cancer Research Program, where the preclinical work was performed. The study was sponsored by Pfizer Oncology.

Cyclin-dependent kinases have been around for some time. The Nobel Prize in 2001 was awarded to scientists responsible for the discovery and identification of cyclin, CDKs, and cell cycle checkpoints—Leland H. Hartwell, PhD; Sir Tim Hunt, FRCS; and Sir Paul M. Nurse, PhD.

Palbociclib blocks the transition from G1 to S phase in the cell cycle where CDK-4 and -6 play a critical role in regulating cell metabolism.

Finn said that palbociclib is unlike earlier CDK inhibitors which were "pan CDK inhibitors," while this second-generation CDK-4/6 inhibitor is very specific in blocking CDK-4/6, leading to less toxicity.

PALOMA-1 comprised two parts, based on biomarkers: Part 1 included ER-positive patients; women in Part 2 also had ER-positive disease and their tumors also showed changes in cyclin D1 and/or loss of p16. This was intended to test whether or not biomarkers could further define appropriate candidates for treatment.

Patients in both parts were randomly assigned to receive letrozole at 2.5 mg daily continuously with or without palbociclib at 125 mg on a three-weeks-on/one-week-off treatment course. About one-third of patients had prior hormonal therapy and chemotherapy in the adjuvant setting.

ER-Negative Status Best Biomarker

Flinn said that ER-negative status was the best biomarker for selecting patients, and changes in cyclin D1 and/or loss of p16 were not as predictive.

But interestingly, while progression-free survival was superior for all patients on the combination arms,

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"The results are very positive, and if confirmed by the ongoing Phase III study, palbociclib in combination with hormonal therapy would be a new standard of care in the therapy of patients with advanced ER-positive disease."

—José Baselga, MD

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simultaneous interrogation of the relation of tumor with motor fibers. In addition, a motor functional MRI (fMRI) is also incorporated to delineate the motor cortex.

Awake-Surgery

When patients present with tumors that involve the motor cortex or speech areas of the dominant frontal and temporal lobes, intra-operative correlation with function is critical. I would always therefore perform an awake-craniotomy that stereotactically incorporates DTI tractography and fMRI.

The awake-surgery permits intraoperative mapping or direct correlation of function to brain anatomy, thereby delineating what can be safely resected. In addition, potential neurological deficits can be identified early since the patient is awake, thereby minimizing the chances of irreversible damage.

The synergy of image-guided co-localization and interrogation of tumor and critical white matter fibers, coupled with the functional advantage of the awake-patient during surgery, significantly improves the outcomes of surgeries in eloquent areas, as has been realized in our brain tumor program.

In summary, surgery has a central role in the management of patients with brain tumors. The goals of surgery should always prioritize neurological functional preservation. Tumor location is critical, and can correlate with surgical morbidity. Stereotactic techniques that permit co-localization of critical eloquent fibers in relation to tumor can minimize neurological deficits. Awake-brain surgery permits safe resection of tumors in brain areas that are eloquent to motor and speech functions.

Comments, Questions?

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