Surgical advances in the management of brain metastases

Patrick R. Ng*, Bryan D. Choi, Manish K. Aghi, and Brian V. Nahed*

Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA (P.R.N., B.D.C., B.V.N.); Department of Neurosurgery, University of California San Francisco, San Francisco, CA, USA (M.K.A.)

Corresponding Author: Brian V. Nahed, MD, MSc, Department of Neurosurgery, Brain Tumor Center/Pappas Center for Neurooncology, Massachusetts General Hospital, Harvard Medical School, 15 Parkman Street, Wang 745, Boston, MA 02114, USA (bnahed@mgh.harvard.edu).

Abstract
As the epidemiological and clinical burden of brain metastases continues to grow, advances in neurosurgical care are imperative. From standard magnetic resonance imaging (MRI) sequences to functional neuroimaging, preoperative workups for metastatic disease allow high-resolution detection of lesions and at-risk structures, facilitating safe and effective surgical planning. Minimally invasive neurosurgical approaches, including keyhole craniotomies and tubular retractors, optimize the preservation of normal parenchyma without compromising extent of resection. Supramarginal surgery has pushed the boundaries of achieving complete removal of metastases without recurrence, especially in eloquent regions when paired with intraoperative neuromonitoring. Brachytherapy has highlighted the potential of locally delivering therapeutic agents to the resection cavity with high rates of local control. Neuronavigation has become a cornerstone of operative workflow, while intraoperative ultrasound (iUS) and intraoperative brain mapping generate real-time renderings of the brain unaffected by brain shift. Endoscopes, exoscopes, and fluorescent-guided surgery enable increasingly high-definition visualizations of metastatic lesions that were previously difficult to achieve. Pushed forward by these multidisciplinary innovations, neurosurgery has never been a safer, more effective treatment for patients with brain metastases.

Keywords
brachytherapy | intraoperative neuroimaging and neuromonitoring | fluorescent-guided neurosurgery | minimally invasive neurosurgery | supramarginal surgery

Brain metastases (BMs) are the most common type of intracranial tumor in adults, occurring about 10 times more frequently than primary malignant brain tumors. Population-based studies estimate that 8.5–9.6% of cancer patients will develop a BM, while autopsy studies suggest that approximately 25% of people who die of cancer had developed metastatic disease to the brain. Incidence rates of BMs are difficult to assess since no national registries exist specifically for patients with brain metastases, and current estimates likely underestimate the true burden of disease. As cancer treatment, diagnosis, and surveillance improve, incidence rates will continue to rise. Neurosurgery is an essential tool in the therapeutic arsenal against brain metastases and has been shown to improve survival and quality of life. Given the growing epidemiological and clinical burden of brain metastases, advancements in surgical management are imperative. This review will cover recent innovations in neurosurgical techniques and intraoperative considerations for the treatment of brain metastases (Table 1).

Preoperative Considerations
The preoperative workup of lesions suggestive of brain metastases centers on neuroimaging. Computed tomography (CT) rules out neurosurgical emergencies, provides superior...
visualization of bony details, particularly if metastases involve the calvarium, and is used for patients with MRI contraindications.9 Contrast-enhanced magnetic resonance imaging (MRI) offers superior sensitivity in detecting metastases, especially when the lesions are small or located in the posterior fossa, frontotemporal region, and cortex.9,11 BMs do not have any pathognomonic features on CT or MRI, but post-contrast T1 enhancement, ring-enhancement, spherical shape, and multiple lesions are suggestive of metastatic disease.9 Other imaging modalities, such as diffusion-weighted imaging (DWI), susceptibility-weighted imaging (SWI), diffusion tensor imaging (DTI), MR perfusion imaging, 18F-2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET), amino acid PET, and MR spectroscopy, are actively under investigation for diagnosing metastases, differentiating metastases from similar-appearing lesions, and identifying the primary tumor type.9 For lesions located in eloquent areas of the brain, preoperative imaging may include functional MRI (fMRI), transcranial magnetic stimulation (TMS), and/or DTI. All of which have been shown to improve surgical outcomes.12–14

If a diagnosis is required and surgical resection would not be safe, a suspected lesion should be biopsied.15 Routine hematoxylin-eosin (H&E) staining of surgical specimens differentiates metastases from other lesions, while immunohistochemical markers are utilized if H&E findings are equivocal.16 Molecular analysis of samples can identify the tissue of origin in cases where whole-body imaging and H&E staining fail to do so, or lineage markers and biomarkers, both of which can impact treatment strategies such as selection of targeted agents and eligibility for clinical trials.17 Given recent findings that BMs harbor molecular differences compared to their respective primary tumors,18 securing BM tissue samples through biopsies or surgery for molecular analysis will become more common to assist in clinical decision-making.

The main objectives of surgery are to acquire tissue for diagnosis, reduce symptomatic mass effect and vasogenic edema, definitively treat local lesions with improved quality of life, and prolong overall survival when combined with adjuvant radiation therapy.19 Two randomized controlled trials from the early 1990s established the overall survival and functional benefits of surgery with adjuvant radiotherapy over radiotherapy alone.20,21 For patients with multiple brain metastases, retrospective studies have shown that resecting up to three metastases offers survival rates comparable to those of patients who underwent resection of a single BM.22–24 Surgery alone is not sufficient for local control of BMs and therefore must be complemented with either whole-brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS), though SRS is preferred when safe and especially for low tumor volumes.15 The 2019 Congress of Neurological Surgeons (CNS) guidelines for the treatment of adults with metastatic brain tumors can be found in Table 2.25

### Surgical Approach

#### Minimally Invasive Craniotomy

Improvements in preoperative diagnostic imaging and intraoperative illumination devices have facilitated the miniaturization of cranial approaches, from Dandy’s “macrosurgical” craniotomies to Yasargil’s microneurosurgery to today’s minimally invasive techniques.26 While standard craniotomy approaches can effectively access various intracranial lesions, minimally invasive approaches can also be tailored uniquely to the target lesion.27 Conventional craniotomies typically produce openings that are larger than the target, whereas keyhole craniotomies can create openings (~2–5 cm in diameter) smaller than the target with complete exposure achieved by subtending the angles of approach.26–28 Keyhole approaches limit brain exploration and retraction and embody the operative philosophy of preserving as much normal tissue as possible while achieving sufficient exposure and maximal resection. Studies have shown that keyhole approaches minimize soft tissue and bone trauma, decrease postoperative complications, and improve cosmetic results.29 Due to a more restricted surgical corridor and limited visual control, keyhole approaches are typically augmented with endoscopic devices, special tube-shaft microinstruments, and intraoperative imaging, monitoring, and mapping.26 Since the surgical pathway cannot be changed during surgery, meticulous preoperative planning is paramount.26

Keyhole approaches can enable safe and effective resection of brain metastases. In Tobler and Stanley,30 stereotactic-guided keyhole craniotomies enabled gross total resection (GTR) in 100% of 14 patients with metastatic tumors located in eloquent cortical regions. Moreover, 88% of patients experienced significant alleviation or elimination of their preoperative neurologic deficits.30 Phang et al.31 achieved complete resection in 85% of 35 patients with brain metastases with a range of tumor volumes and locations, including the posterior fossa, all cortical lobes, intraventricular regions, and the basal ganglia. Median survival of these patients was comparable to that of the

---

#### Table 1. Surgical Innovations for Brain Metastases

| Preoperative Workup | Neuroimaging (CT, MRI, functional imaging) |
|---------------------|------------------------------------------|
| Surgical Approach | Minimally invasive craniotomies |
| Tubular retractors | * |
| Supramarginal resection | * |
| Brachytherapy | * |
| Intraoperative Augmentation | Neuronavigation |
| Intraoperative ultrasound | * |
| Intraoperative brain mapping | * |
| Endoscope | * |
| Exoscope | * |
| Fluorescence-guided surgery | * |

---

Ng et al. Surgical advances in the management of brain metastases

---

Neuro-Oncology Advances
et al.32 showed that patients with multiple (2 to 10+) brain metastases in diverse locations (ie, the cortical lobes, the posterior fossa, and the thalamus) may undergo 2 to 4 simultaneous keyhole craniotomies and resections with survival outcomes and surgical risks comparable to patients undergoing resection of single brain metastases. These patients also experienced improvements in Karnofsky Performance Scale (KPS) scores during the early postoperative period and were successfully weaned from steroids.32

Performance Scale (KPS) scores during the early postoperative period and were successfully weaned from steroids.32

Lastly, Baker et al.35 showed that patients with multiple (2 to 10+) brain metastases in diverse locations (ie, the cortical lobes, the posterior fossa, and the thalamus) may undergo 2 to 4 simultaneous keyhole craniotomies and resections with survival outcomes and surgical risks comparable to patients undergoing resection of single brain metastases. These patients also experienced improvements in Karnofsky Performance Scale (KPS) scores during the early postoperative period and were successfully weaned from steroids.32

The supraorbital (SO) “eyebrow” craniotomy is a keyhole modification of the standard pterional approach and is especially useful for metastases located in the orbitofrontal surface and frontal pole.33 Similar to other minimally invasive techniques, the SO approach minimizes soft tissue/bone trauma and brain exposure to non-physiologic surroundings, minimizes brain retraction, decreases the time between skin incision to dural opening (~10 min), decreases approach-related morbidity, improves cosmetic results, and shortens hospitalization.34 In Reisch et al.,35 77% of 375 patients who underwent a SO craniotomy experienced no follow-up pain, and 84% were very pleased with the cosmetic outcome. In Eroglu et al.,36 84.6% of 13 BM cases achieved GTR with the SO approach, and 92.3% of these patients were highly satisfied with the cosmetic result.

Minimally invasive techniques can be applied to any standard craniotomy.28 For example, Bonney et al. showed that the supracerebellar-infratentorial (SCIT) approach, once thought to require a large craniotomy extending inferiorly to the rim of the foramen magnum, can be achieved with a 2.5 cm keyhole opening.27 This approach enabled near-total resection of a pontine lung metastasis in the pineal region.37

As data on the safety and efficacy of minimally invasive methods continues to emerge and as surgeons gain experience with these techniques, keyhole craniotomies will become a preferred approach for select BM patients.

**Tubular Retractors**

Resection of deep intracranial lesions depends on proper visualization and access along the surgical corridor, which requires retraction of surrounding structures. Though handheld blade retractors and mounted devices are commonly used, these techniques can exert prolonged, focal pressure on the brain parenchyma, which has been shown to compromise vascular flow, induce local ischemia, and cause direct tissue injury.38 First introduced by Kelly et al.,39 tubular retractors establish surgical corridors by displacing the parenchyma with blunt tips and evenly distributing radial force to the surrounding tissue. Initially designed to attach to a stereotaxic frame, tubular retractors are now typically positioned with frameless neuronavigational systems.40 Preoperative imaging, including DTI, identifies pathways that minimize the disruption of white matter tracts.41 Though postoperative DWI/ADC imaging has shown that tubular retraction can still cause cytotoxic edema and cellular damage,42 complication rates with tubular retractors have been shown to be lower than with traditional paddle retractors.43 The three main tubular retractors that have been studied for the resection of deep intracranial lesions are the ViewSite Brain Access System (VBAS), the BrainPath tubular retraction system, and the Minimal Exposure Tubular Retractor system (METRx), though the METRx was originally designed for minimally invasive spinal surgery and is not approved for intracranial use.43 There is no difference in patient outcomes between BrainPath and VBAS.44

| Target Population | Question | Recommendations |
|-------------------|----------|-----------------|
| Adult patients with newly diagnosed metastatic brain tumors, excluding radiosensitive tumor histologies. | Should patients with newly diagnosed metastatic brain tumors undergo surgery, stereotactic radiosurgery (SRS), or whole brain radiation therapy (WBRT)? | **Level 1:** Surgery + WBRT is recommended as first-line treatment in patients with single brain metastases with favorable performance status and limited extracranial disease to extend overall survival, median survival, and local control. **Level 3:** Multimodal treatments including either surgery + WBRT + SRS boost or surgery + WBRT are recommended as alternatives to WBRT + SRS in terms of providing overall survival and local control benefits. |
| Adult patients with newly diagnosed metastatic brain tumors undergoing resection followed by WBRT, SRS, or another combination of these modalities? | | **Level 2:** Surgery + WBRT is recommended as superior treatment to WBRT alone in patients with single brain metastases. **Level 3:** Surgery + SRS is recommended as an alternative to treatment with SRS alone to benefit overall survival. **Level 3:** It is recommended that SRS alone be considered equivalent to surgery + WBRT. |
| Adult patients diagnosed with recurrent, non-radiosensitive metastatic brain tumors. | Should patients with recurrent metastatic brain tumors undergo surgical resection? | **Level 3:** Craniotomy is recommended as a treatment for intracranial recurrence after initial surgery or SRS. |

Key clinical questions and levels of each recommendation, which are directly linked to Class I, II, or III evidence, are included in the table. Class I evidence is extrapolated to Level 1 recommendations or lower. Class II evidence is extrapolated to Level 2 recommendations or lower. Class III evidence only yields Level 3 recommendations. The table is adapted from Nahed et al. 2019 with permission.25
Supramarginal Resection

Though brain metastases are often sharply demarcated on neuroimaging and grossly delimited by glial pseudo-capsules, histopathological studies have identified distinct invasion patterns of BMs,51,52 and the presence of infiltrating metastatic cells beyond the glial pseudo-capsule has been shown to significantly impact overall survival.53 Often determined by the surgeon’s subjective visual evaluation or a postoperative MRI, GTR may not detect microscopic infiltrating metastatic cells, which may partly account for the 46–57% of patients who experience local recurrence without subsequent radiotherapy.54,55 Supramarginal or microscopic total resection (MTR), in which the GTR margin is extended by 5 mm and the new margin is confirmed to be tumor-free by intraoperative frozen sectioning, has been studied as a technique to improve local control and progression of metastatic disease. In a retrospective study by Yoo et al.,56 94 patients with a single brain metastasis underwent either MTR (n = 43) if the tumor was located in non-eloquent areas or GTR (n = 51) if the tumor was located in eloquent regions, followed by systemic chemotherapy with or without radiotherapy. The 2-year local recurrence rates (29.1% for MTR vs. 63.2% for GTR) and 2-year survival rates (27.3% for MTR and 3.8% for GTR) were significantly different, though median survival time between the two groups was not significantly different.58 In a retrospective study by Kamp et al.,57 complete supramarginal resection with electrophysiological monitoring was successfully implemented in 19 cases of eloquent BMs. No patients suffered new permanent neurologic deficits, and 15.7% experienced temporary deficits. Neurologic symptoms improved in five patients.57 In Pessina et al.,58 a retrospective study of 69 patients with single large (> 2.1 cm) BMs, supramarginal resection with adjuvant SRS enabled a 1- to 2-year local control of 100% and a median survival of 24 months. Of note, the association between supramarginal resection and increased median survival may be influenced by the study’s inclusion criteria of patients with controlled extracranial disease. Some studies have shown that greater extent of surgical resection prolongs survival only in cohorts with controlled extracranial disease.59,60 Overall, studies of supramarginal resection suggest that maximizing the extent of resection can improve the recurrence rates and survival of patients with BMs. These preliminary results could be further investigated with prospective and randomized studies.

Brachytherapy

Brachytherapy involves implantation of radioactive isotopes into a tumor cavity and has been investigated as both a primary and adjuvant therapy for BMs. Two modalities have been primarily studied for the treatment of brain metastases: iodine-125 (125I) and cesium-131 (131Cs) brachytherapy.61 Though 125I brachytherapy is the more widely studied and has been associated with local control and overall survival rates comparable to SRS,62,63 clinical adoption has been limited by high rates of radiation necrosis (up to 30%).64 High rates of radiation necrosis in 125I brachytherapy trials have been attributed to the long half-life of radioactive seeds.65

Compared to 125I, 131Cs brachytherapy is a more promising modality with similarly high local control rates and a more favorable side effect profile. In a phase I/II study of surgical resection with 131Cs brachytherapy for newly diagnosed brain metastases, Wernicke et al.66 demonstrated 100% local control, median overall survival of 9.9 months, and no cases of radiation necrosis. In a follow-up prospective study of surgical resection with 131Cs brachytherapy for large BMs (≥ 2.0 cm), 100% local control was achieved, as well as median overall survival of 15.1 months and no cases of radiation necrosis.67 Of note, 39% of the lesions were > 3.0 cm.67 The excellent local control rates of adjuvant 131Cs brachytherapy for large BMs is significant given the comparatively poor local control rates of adjuvant SRS for large BMs (60.9% for BMs ≥ 3.0 cm vs. 92.5% for BMs < 3.0 cm).68 In a retrospective study, Wernicke et al. investigated surgical resection with 131Cs brachytherapy as a salvage treatment for patients with recurrent brain metastases post-radiation (SRS and/or WBRT) and reported a 1-year actuarial local freedom from progression (FFP) of 83.3%, median overall survival of 7 months, and 1 case of asymptomatic radiation necrosis out of 15 patients.69 Though radiotherapy, such as SRS, is the definitive adjuvant for surgical resection, Julie et al. conducted a retrospective matched-pair analysis of surgery with adjuvant 131Cs brachytherapy (n = 30) vs. surgery with adjuvant SRS (n = 60) and demonstrated a significantly lower local recurrence, significantly increased local-recurrence-free survival, and significantly increased distant-recurrence-free survival (DRFS) with 131Cs brachytherapy. The local benefits of 131Cs brachytherapy were thought to reflect radiobiological advantages, improved action against larger tumors, and a shorter delay between...
resection and delivery of adjuvant therapy. The significantly improved DRFS was not anticipated and was speculated to be due to either delays in initiating or continuing systemic treatments for SRS patients or unaccounted differences between the two cohorts.75 Lastly, a prospective study by Pham et al. suggests that 131Cs brachytherapy may support stable or improved functional recovery as measured by FACT-Br and MMSE scores.71 These results are favorable given that prior studies have associated radiotherapy with post-operative neurocognitive decline.72,73

The relative improvements in efficacy and safety, particularly the dramatic decrease in radiation necrosis, of 131Cs brachytherapy compared to 125I are related to differences in radiobiological properties and improved methodology in delivering the isotopes.131Cs has a shorter half-life, which limits radiation exposure to the patient, and a higher dose rate, which delivers a greater proportion of the dose in a shorter time.66 Furthermore, in the studies conducted by Wernicke et al.,131Cs was delivered at lower doses, with lower seed activity, and through a “seeds-on-a-string” technique that prevented cavity shrinkage, which increases the proximity of surrounding tissue and the risk of necrosis.74 In conclusion, adjuvant 131Cs brachytherapy has demonstrated promising benefits, especially with larger lesions, as well as significantly lower rates of radiation necrosis than 125I brachytherapy. A randomized controlled trial comparing post-surgical 131Cs brachytherapy vs. SRS for newly diagnosed brain metastases is currently underway and will provide crucial data on the appropriate use-cases of brachytherapy (NCT 04365374, Clinicaltrials.gov).

Intraoperative Augmentation
Neuronavigation
First introduced by Roberts et al. in 1986,76 frameless stereotactic navigation systems, or neuronavigation, have become an essential intraoperative tool in predicting the location of target lesions and neighboring regions at risk during surgery. Neuronavigation is established through four steps.76 First, preoperative images are acquired. MRI allows high-resolution visualization of the parenchyma and soft tissue, while fMRI and DTI localize eloquent cortex and white matter fiber tracks. Second, the images are uploaded into the neuronavigation system. Third, the images are registered or mapped onto the physical patient via homologous landmark/fiducial matching or surface matching. Lastly, a tracked tool in the physical space allows identification of the corresponding anatomy in the images, typically displayed on a monitor in the operating room (OR). Patient-to-image registration has a paired point matching accuracy between 1.6 and 6.2 mm.76–78

In clinical practice, neuronavigation is ubiquitous, facilitating the surgical resection of brain metastases.79 In Schackert et al.,80 neuronavigation prolonged median survival time in patients with single (16 months vs. 10 months) and multiple (11 months vs. 5 months) metastases, though these results were not statistically significant. The lack of statistical significance was partially explained by brain shift and a biased selection criteria for neuronavigation, which was used for patients with deep-seated or near-eloquent lesions and not for patients with uncomplicated lesions. In Tan and Black, image-guided resection of BMs decreased length of hospital stay, improved functional status, and prolonged survival.81 A primary limitation of conventional neuronavigational systems is a lack of accommodation for brain shift—movements in the patient’s anatomy during surgery from parenchymal swelling, resection, gravity, CSF drainage, and other factors.76 Lesion size affects the degree of brain shift with smaller tumors (< 30 cm³) not significantly altering the success of neuronavigation-guided resection.82 Intraoperative imaging, which is discussed in a subsequent section, may facilitate more accurate real-time visualization of a shifting brain parenchyma.

Intraoperative Ultrasound
First applied to adult neurosurgery in the 1980s,83 intraoperative ultrasound (iUS) has become an essential neurosurgical tool. Current modalities include 2D US, 3D US, contrast-enhanced US (ceUS), high-frequency US (hfUS), and US elastography.84 In general, iUS has been studied for three main applications: intraoperative navigation, assessing the extent of resection, and measuring/compensating for brain shift.84 The benefits of iUS include its low cost, minimal disruption of intraoperative workflows, and a lack of radiation exposure. While brain parenchyma is largely uniform in echogenicity on iUS with gray matter slightly more hyperechoic than white matter, tumors are relatively hyperechoic due to high mass density.84

2D US is the most basic modality that has been applied to BMs. In Di Lorenzo et al.,85 2D iUS-guided tumor biopsies were faster and less costly than CT-guided biopsies and yielded comparable rates of histological diagnosis on first biopsy procedure. In a prospective study by Hammoud et al.,86 2D iUS reliably localized 100% of 34 BMs and accurately determined the extent of resection in all cases, as confirmed by a mean difference of zero between postexcision tumor volumes measured by iUS and postoperative MRI. However, iUS was less precise for recurrent tumors with prior surgery or radiation, possibly due to postintervention changes complicating the tissue echogenicity.86 In a case series including three patients with BMs, LeRoux et al. showed that 2D iUS improved identification of tumor margins compared to both contrast and non-contrast T1-weighted MRI and helped distinguish tumor and normal brain from edema visualized on T2-weighted MRI.87 In a retrospective series by Serra et al.,88 hfUS facilitated GTR in all 8 BM cases. iUS can improve not only the localization and resection of BMs, but also postoperative performance. In a retrospective study by de Lima Oliveira et al.,89 78 BM patients underwent surgery either with iUS (n = 35) or without (n = 43) iUS. Compared to the control group, the iUS group had significantly higher postoperative KPS scores and a significantly higher proportion of patients who improved their KPS scores, especially with moderately difficult tumor resections, eloquent tumors, tumors not associated with vessels or nerve, and solitary lesions.89 Furthermore, the residual tumor volume, as assessed by postoperative MRI, was significantly lower in the iUS group than in the control group.89
Intraoperative Brain Mapping

Complete resection of brain metastases in patients with well-controlled systemic disease can improve survival.\textsuperscript{19,60} Tumors located in eloquent brain regions are particularly challenging to resect completely. Preoperative imaging, such as fMRI, DTI, and TMS, and intraoperative neuronavigation can aid surgical planning, but these techniques are susceptible to brain shift and limited in resolution. Intraoperative brain mapping refers to neurophysiological methods that precisely identify brain areas associated with motor, sensory, language, and other neurological functions and therefore enable maximal resection of eloquent lesions.

Direct cortical and subcortical stimulation has been the gold standard for intraoperative brain mapping since the 1930s.\textsuperscript{106} The motor cortex can be identified by stimulating the pre- and postcentral gyri, premotor area, and supplementary motor area and either observing the extremities for contralateral movement or measuring action potentials recorded by peripheral electrodes, also referred to as motor-evoked potentials (MEPs).\textsuperscript{107} Alternatively, the central sulcus, primary motor cortex, and primary somatosensory cortex can be identified by stimulating the contralateral median, ulnar, or posterior tibial nerves and measuring sensory evoked potentials (SEPs) on the cortical surface.\textsuperscript{108} The central sulcus is the location of “phase reversal.”\textsuperscript{108} Subcortical structures, including white matter, can also be stimulated and assessed with MEPs or other functional readouts.\textsuperscript{109} Awake craniotomies, in which electrical stimulation is applied to cortical or subcortical structures while patients perform intraoperative tasks, can also identify brain regions involved in language, calculation, motor, somatosensory, and visual functions.\textsuperscript{110} Though brain mapping has been more extensively studied in gliomas,\textsuperscript{111–113} these techniques have been safely and effectively applied to BMs.

Intraoperative neurophysiological monitoring with MEPs has facilitated safe, efficacious, and neurologically beneficial resection of BMs. In a retrospective study by Krieg et al.,\textsuperscript{114} 56 eloquent metastases were resected with intraoperative MEPs monitoring. A threshold of > 80% reduction in MEP amplitude yielded a lower false-positive rate and correlated better with postoperative outcomes than > 50% reduction,\textsuperscript{114} which has been previously recommended for glioma surgery.\textsuperscript{115} Surgery improved the strength of 21% of patients.\textsuperscript{114} New permanent motor deficits (12.5% of cases) were associated with location of the tumor (precentral gyrus > corticospinal tract > insula), preoperative motor deficits, preoperative radiotherapy, and recursive partitioning analysis (RPA) class 3.\textsuperscript{114} In another retrospective study including 56 BMs, Obermueller et al.,\textsuperscript{116} confirmed that > 80% reduction in MEP amplitude was a more appropriate BM-specific alarm threshold than > 50% reduction.\textsuperscript{116} In this cohort, compared to gliomas, the BM group had more stable MEPs, a significantly higher proportion of patients with improved postoperative neurological status, and less subtotal resection.\textsuperscript{116} These two...
studies support the use of intraoperative MEP monitoring in the resection of motor-eloquent BMs.

Awake craniotomies for BMs have also been studied. In Chua et al.,117 data from 7 studies and 104 patients with eloquent BMs who underwent awake craniotomies were aggregated. Gross total or supramarginal resection was achieved in 93% of patients,117 which is higher than the mean GTR of glioma patients who underwent intraoperative mapping.113 The overall local recurrence rate of 3 studies (70 patients) was 9%, and the median survival of 2 studies (36 patients) was 12–16.2 months.117 These findings are comparable to historical rates in the literature.54 Furthermore, 73% of patients had no change or improvement in neurologic outcomes, and only one out of 104 patients developed late neurologic deficits after awake craniotomies.117 Thus, awake craniotomies can safely and effectively treat BMs.

Intraoperative brain mapping has been combined with other surgical innovations to optimize the resection of BMs. In a prospective study by Krieg et al., 250 patients with peri-Rolandic metastatic lesions were preoperatively evaluated with (n = 120) or without (n = 130) navigated TMS (nTMS). The nTMS group had lower rates of intraoperative MEPs monitoring, shorter surgical times, lower rates of residual tumor, decreased surgery-related paresis, and smaller craniotomies. These results demonstrate how preoperative TMS can improve the implementation of intraoperative brain mapping and ensure that the technique is only used for cases in which functional regions are truly at-risk.118 Lastly, intraoperative neurophysiological monitoring has been augmented with 3D US to optimize the resection of BMs.119,120

Endoscope

First developed by Dandy to visualize and treat intraventricular pathologies, the endoscope has become an essential intraoperative tool for facilitating minimally invasive approaches and for resecting intraventricular, paraventricular, sellar, pineal, and other deep-seated lesions.121 Though initially limited by poor lighting and magnification, advances in lens development, fiberoptics, and device design have enabled high-definition, 3D, angled visualization.121 Compared to OMs, endoscopes provide wider fields of view in small spaces and are typically paired with less invasive approaches.27 Limitations include a constrained surgical working space, short focal/field depths, and technical difficulties with larger lesions.121 When applied to tumor surgery, an endoscope can serve either as the primary mode of visualization, or as an adjunct to access views not possible with the OM and to evaluate the extent of resection.27

Several studies have evaluated the endoscopic resection of BMs located in various intracranial regions. In a prospective series by Plaha et al.,122 endoscope-assisted bimanual microsurgery achieved total resection in 92% of 12 metastases located in the temporal and frontal lobes, parafalcine region, cerebellum, and other areas. Ma et al.123 applied endoscope-assisted bimanual microsurgery to temporal lobe metastases and reported GTR in 63.6%, a median overall survival of 12.9 months, and shorter hospital stays.

Barkhoudarian et al.124 developed an endoscope-assisted transfalcine approach for eleven contralateral deep medial cortical metastases and demonstrated how endoscopes can visualize residual tumor missed by OMs, allowing additional resection in 91% of cases. In a retrospective study by Zacharia et al.,125 endoscopic endonasal resection of twelve anterior skull base metastases led to an overall survival of 16 months and median progression-free survival of 18 months. These survival outcomes were better than prior studies of skull base metastases.126 Endoscopes have also supplemented other minimally invasive approaches, such as the SO craniotomy, enabling more direct illumination in deep operative fields and visualization of regions previously hidden from view.126 Ports or tubular retractors can further facilitate endoscopic resection of intraparenchymal, deep-seated, and intraventricular metastases.127 Ports are typically large enough to accommodate a rigid endoscope and at least two instruments, allowing bimanual microsurgical dissection.127 Despite these benefits, a retrospective study by Hong et al. suggested that endoscopes may be more useful as an adjunct for inspection of the tumor bed, rather than a primary visualization tool.45 Lastly, devices designed for narrow surgical corridors, such as a side-cutting variable aspiration instrument (NICO Myriad, Indianapolis, IN), can augment the safety and efficacy of endoscopic BM resection.128

Exoscope

Exoscopes are telescope-based video systems with long optical working distances and wide fields of view that provide high-definition 2D or 3D views of the surgical field. Developed over the past decade, the exoscope combines the manageability and high-definition monitor-based views of endoscopes and the magnification, lighting, stereopsis, and dissection quality of OMs.129 In a systematic review of 29 studies and 574 patients, Ricciardi et al. showed that exoscopes are superior or equivalent to OMs in ergonomic comfort, image quality, magnification, lighting, costs, quality of microsurgical dissection, and educational opportunities for surgeons, trainees, and OR staff.128 Limitations include a lack of stereopsis in 2D exoscopes, though this has been resolved with 3D models, physical discomfort from prolonged usage of 3D glasses, and difficult repositioning, though this has also been addressed with models that include a foot-pedal controller and a sterile pilot unit.129 Current exoscopes include the VITOM 2D or 3D and HDX0-scope, BrightMatter, ORBHEYE, and KINEVO 900.

First implemented by Mamalak et al.,130 exoscopes have been applied to the surgical management of BMs. In Roethe et al., an exoscopic visualization system was used to resect 3 cases of metastatic lesions out of a total 20 randomized supratentorial tumors. The study found that frontoparietal and pterional approaches were better suited for exoscopic visualization than retrosigmoidal or suboccipital approaches. Furthermore, there were limitations in visualizing deep lesions and small bleeding vessels, and participants concluded that the exoscope was not sufficient to replace the OM.131 In Oertel and Burkhardt the VITOM-3D exoscope enabled the resection of three frontal or temporal metastatic lesions, though the authors...
also reported limitations with deep-seated tumors and tissue identification during bleeding. When paired with other surgical innovations, such as tubular retractors, the exoscope can enable the resection of more complex lesions. For example, studies have reported 64–95% GTR rates, stable or improved postoperative neurological function, and shorter hospital stays for subcortical and posterior fossa BMs using exoscopes and tubular retractors. In Marenco-Hillenbrand et al., exoscopic visualization of burr hole-based resections achieved GTR and stable or improved KPS scores in all 8 BM cases. This study proved that exoscopes can be used at the extreme limit of keyhole surgeries without compromising surgical outcomes. Lastly, exoscopes have enabled new intraoperative fluorescent imaging techniques, such as second-window indocyanine green (SWIG), discussed in the subsequent section. In conclusion, several reports have demonstrated safe and effective exoscope-based resection of metastatic lesions.

**Fluorescence-Guided Surgery**

Since the 1940s, fluorescent dyes have been studied to improve intraoperative delineation of tumor from normal parenchyma and optimize the extent of resection. 5-aminolevulinic acid (5-ALA), a precursor of the heme synthesis pathway that is converted to fluorescent protoporphyrin IX (PpIX), has been shown to significantly increase the rate of complete resection and progression-free survival in gliomas, yet similar benefits have not been found with BMs. Two other FDA-approved fluorophores—fluorescein and indocyanine green (ICG)—have demonstrated more promising results for BMs. Applied to brain tumor surgery since the 1940s, fluorescein is a yellow–green xanthine fluorophore that passively extravagates into brain tissues with disrupted blood–brain barrier. Most studies employ a YELLOW 560 nm filter directly integrated into the OM to visualize the fluorescent signal. With fluorescein labeling, 90–100% of BMs demonstrate strong signal, though visualization is limited in cases of pigmented melanoma, hemorrhagic metastases, or previously irradiated tissue. Across several retrospective cohorts, fluorescein visualization facilitated GTR in 83.3–100% of cases. Retrospective studies comparing fluorescein-guided surgery and white light-guided surgery suggest that fluorescein may be associated with better GTR rates, postoperative KPS, and survival. In conclusion, fluorescein can safely and consistently localize BMs, though its clinical value is yet to be definitively determined.

Indocyanine green (ICG) is a hydrophobic cyanine dye that binds to intravascular plasma proteins and is visualized with near-infrared (NIR) cameras. Since NIR light has a longer wavelength than visible light, signal from the tumor can be viewed through the dura and up to 20 mm through normal parenchyma, which can facilitate precise dural incisions and neuronavigation unaffected by brain shift. Recently, Lee and colleagues developed a technique called second window indocyanine green (SWIG), in which a high dose of ICG is administered 24 hours prior to surgery and accumulates in tumor tissue via increased permeability and retention effect. In a prospective study by Lee et al., the sensitivity, specificity, positive predictive value, and negative predictive value of SWIG was 96.4%, 27.3%, 77.1%, and 75.0%, respectively, compared to 82.1%, 90.9%, 95.8%, and 66.7% for white light; therefore, SWIG improved the sensitivity of tumor detection at the expense of specificity. GTR was achieved in 77% of 13 BMs and in 100% of lesions not previously treated. In another prospective study by Muto et al., SWIG enabled GTR in 90% of 10 BMs with complete resection corresponding with an absence of NIR signal. Lastly, in a prospective study by Teng et al., compared to postoperative MRI, absence of NIR signal was a better predictor of GTR, reduced recurrence rate, and improved progression-free survival. In conclusion, SWIG-guided surgery is a promising approach for the treatment of BMs still under investigation.

**Conclusion**

From sophisticated preoperative imaging to new techniques in operative approach and intraoperative augmentation, neurosurgical advances have dramatically altered the treatment of patients with brain metastases, the most common intracranial adult tumor. Keyhole craniotomies and tubular retractors represent a movement toward more minimally invasive neurosurgical approaches, ensuring that patients receive optimal care while minimizing morbidity. Supramarginal surgery has pushed the boundaries of achieving extent of resection. Brachytherapy has highlighted the potential of locally delivering therapeutic agents to the resection cavity. Innovations in neuronavigation, iUS, brain mapping, endoscopes, exoscopes, and fluorescent stains have enabled increasingly effective high-definition, real-time visualizations of the brain. Pushed forward by these multidisciplinary innovations, neurosurgery has never been a safer, more effective treatment for patients with brain metastases.

**Funding**

None.

**Conflict of interest statement.** Brian V. Nahed: Consulting fee/advisory board for Robeaute. Other authors have nothing to disclose.

**References**

1. Ostrom QT, Wright CH, Barnholtz-Sloan JS. Brain metastases: epidemiology. *Handb Clin Neurol*. 2018;149:27–42.
2. Schouten LJ, Rutten J, Haveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer*. 2002;94(10):2698–2705.
3. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973–2013) with breast cancer and melanoma. *Cancer*. 2016;122(15):2427–2437.
to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol.* 2004;22(14):2865–2872.

4. Posner JB, Chernik NL. Intracranial metastases from systemic cancer. *Adv Neurol.* 1978;19:579–592.

5. Takakura K, ed. *Metastatic Tumors of the Central Nervous System.* 1st ed. Tokyo: Igaku-Shoin; 1982.

6. Fox BD, Cheung VJ, Patel AJ, Suki D, Rao G. Epidemiology of metastatic brain tumors. *Neurosurg Clin N Am.* 2011;22(1):1–6, v.

7. Bindal RK, Sawaya R, Leavens ME, Hess KR, Taylor SH. Reoperation for recurrent metastatic brain tumors. *J Neurosurg.* 1995;83(4):600–604.

8. Bindal AK, Bindal RK, Hess KR, et al. Surgery versus radiosurgery in the treatment of brain metastases. *J Neurosurg.* 1996;84(5):748–754.

9. Pope WB. Brain metastases: neuroimaging. *Handb Clin Neurol.* 2018;149:89–112.

10. Sze G, Milano E, Johnson C, Heier L. Detection of brain metastases: comparison of contrast-enhanced MR with unenhanced MR and enhanced CT. *AJNR Am J Neuroradiol.* 1990;11(4):785–791.

11. Schellinger PD, Meineck HM, Thron A. Diagnostic accuracy of MRI compared to CCT in patients with brain metastases. *J Neurooncol.* 1999;44(3):275–281.

12. Luna LP, Sherbaf FG, Sair HJ, Mukherjee D, Oliveira IB, Köhler CA. Can preoperative mapping with functional MRI reduce morbidity in brain tumor resection? A systematic review and meta-analysis of 68 observational studies. *Radiology.* 2021;300(2):338–349.

13. Raffa G, Scibilia A, Conti A, et al. The role of navigated transcranial magnetic stimulation for surgery of motor-eloquent brain tumors: a systematic review and meta-analysis. *Clin Neurol Neurosurg.* 2019;180:7–17.

14. Potgiesser AR, Wagemakers M, van Huizen AL, de Jong BM, Hoving EW, Groen RJ. The role of diffusion tensor imaging in brain tumor surgery: a review of the literature. *Clin Neurol Neurosurg.* 2014;124:51–58.

15. National Comprehensive Cancer Network. NCCN Guidelines. Published online 2021. https://www.nccn.org/guidelines/category_1. Accessed June 1, 2021.

16. Achrol AS, Rennert RC, Anders C, et al. Brain metastases. *Nat Rev Dis Primers.* 2019;5(15).

17. Berghoff AS, Bartsch R, Wöhrer A, et al. Predictive molecular markers to the central nervous system: recent advances and future avenues. *Acta Neurochir.* 2014;128(6):879–891.

18. Brastianos PK, Carter SL, Santagata S, et al. Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. *Cancer Discov.* 2015;5(11):1164–1177.

19. Evwem MD, Morris DE, Carey LA, Ladha AM, Brem S. Guidelines for the initial management of metastatic brain tumors: role of surgery, radiosurgery, and radiation therapy. *J Neurol Surg B Skull Base.* 2020;149(1):35–44.

20. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med.* 1990;322(8):494–500.

21. Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol.* 1993;33(6):583–590.

22. Bindal RK, Sawaya R, Leavens ME, Lee JJ. Surgical treatment of multiple brain metastases. *J Neurosurg.* 1993;79(2):210–216.

23. Paek SH, Audu FB, Sperling MR, Cho J, Andrews DW. Reevaluation of surgery for the treatment of brain metastases: review of 208 patients with single or multiple brain metastases treated at one institution with modern neurosurgical techniques. *Neurosurgery.* 2005;56(5):1021–34; discussion 1021.

24. Salvati M, Tropeano MP, Maiola V, et al. Multiple brain metastases: a surgical series and neurosurgical perspective. *Neural Sci.* 2018;39(4):671–677.

25. Nahed BV, Alvarez-Breckenridge C, Brastianos PK, et al. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the role of surgery in the management of adults with metastatic brain tumors. *Neurosurgery.* 2019;84(3):E152–E156.

26. Pernecke A, Reisch R. Keyhole Approaches in Neurosurgery: Volume I Concept and Surgical Technique. Vienna, Austria: Springer-Verlag Wien; 2008.

27. Garrett M, Consiglieri G, Nakaji P. Transcranial minimally invasive neurosurgery for tumors. *Neurosurg Clin N Am.* 2010;21(4):595–605, v.

28. Teo C. *Principles and Practice of Keyhole Brain Surgery.* Stuttgart, Germany: Georg Thieme Verlag; 2019.

29. Reisch R, Stadie A, Kockro RA, Hopf N. The keyhole concept in neurosurgery. *World Neurosurg.* 2013;79(2 Suppl):S17.e9–S17.13.

30. Tobler WD, Stanley M. Stereotactic resection of brain metastases in eloquent brain. *Stereotact Funct Neurosurg.* 1994;53(1–4):38–44.

31. Phang I, Leach J, Leggate JRS, Karabatsou K, Coope D, D’Urso PI. Minimally invasive resection of brain metastases. *World Neurosurg.* 2019;130:e362–e367.

32. Baker CM, Glenn CA, Briggs RG, et al. Simultaneous resection of multiple metastatic brain tumors with multiple keyhole craniotomies. *World Neurosurg.* 2017;106:359–367.

33. Ditzel Filho LF, McLaughlin N, Bresson D, Solari D, Kassam AB, Kelly DF. Supraorbital eyebrow craniotomy for removal of intraaxial frontal brain tumors: a technical note. *World Neurosurg.* 2014;81(2):348–356.

34. Reisch R, Pernecke A, Filippi R. Surgical technique of the supraorbital key-hole craniotomy. *Surg Neurol.* 2003;59(3):223–227.

35. Reisch R, Marcus HJ, Hugelshofer M, Kochlin NO, Stadie A, Kockro RA. Patients’ cosmetic satisfaction, pain, and functional outcomes after supraorbital craniotomy through an eyebrow incision. *J Neurosurg.* 2014;121(3):730–734.

36. Ergolu U, Shah K, Bozkurt M, et al. Supraorbital keyhole approach: lessons learned from 106 operative cases. *World Neurosurg.* 2019;124:e667–e674.

37. Bonney PA, Boettcher LB, Cheema AA, Maurer AJ, Sughrue ME. Operative results of keyhole supracerebellar-infratentorial approach to the pons: region. *J Clin Neurosci.* 2015;22(7):1105–1110.

38. Andrews RJ, Bringas JR. A review of brain retraction and recommendations for minimizing intraoperative brain injury. *Neurosurgery.* 1993;33(6):1052–63; discussion 1063.

39. Kelly PJ, Goerss SJ, Kall BA. The stereotactic retractor in computer-assisted stereotactic microsurgery. Technical note. *J Neurosurg.* 1988;69(2):301–306.

40. Greenfield JP, Cobb WS, Tsouris AJ, Schwartz TH. Stereotactic minimally invasive tubular retractor system for deep brain lesions. *Neurosurgery.* 2008;63(4 Suppl 2):334–9; discussion 339.

41. Day JD. Transsulcal parafascicular surgery using Brain Path® for subcortical lesions. *Neurosurgery.* 2017;64:134–146.

42. Bander ED, Jones SH, Kovarikayla I, Schwartz TH. Utility of tubular retractors to minimize surgical brain injury in the removal of deep intraparenchymal lesions: a quantitative analysis of FLAIR hyperintensity and apparent diffusion coefficient maps. *J Neurosurg.* 2016;124(4):1053–1060.

43. Echeverry N, Mansour S, MacKinnon G, Jaraki J, Shapiro S, Snelling B. Intracranial tubular retractor systems: a comparison and review of the literature of the BrainPath, Vycor, and METRx tubular retractors in the management of deep brain lesions. *World Neurosurg.* 2020;143:134–146.

44. Eichberg DG, Di L, Shah AH, et al. Minimally invasive resection of intracranial lesions using tubular retractors: a large, multi-surgeon, multi-institutional series. *J Neurooncol.* 2020;149(1):35–44.

45. Hong CS, Prevedello DM, Elder JB. Comparison of endoscope versus microscope-assisted resection of deep-seated intracranial
lesions using a minimally invasive port retractor system. J Neurosurg. 2016;124(3):799–810.

46. Bakhsheshian J, Strickland BA, Jackson C, et al. Multicenter investigation of channel-based Subcortical trans-Sulcal Exoscopic resection of metastatic brain tumors: a retrospective case series. Oper Neurosurg (Hagerstown). 2019;16(2):159–166.

47. Mampre D, Bechtie A, Chaichana KL. Minimally invasive resection of intra-axial posterior Fossa tumors using tubular retractors. World Neurosurg. 2018;119:e1016–e1020.

48. Akbari SHA, Sylvester PT, Kulwin C, et al. Initial experience using intraoperative magnetic resonance imaging during a trans-sulcal tubular retractor approach for the resection of deep-seated brain tumors: a case series. Oper Neurosurg (Hagerstown). 2019;16(3):292–301.

49. Zammar SG, Cappelli J, Zacharia BE. Utility of tubular retractors augmented with Intraoperative ultrasound in the resection of deep-seated brain lesions: technical note. Cureus. 2019;11(3):e4272.

50. Bander ED, Jones SH, Pisapia D, et al. Tubular brain tumor biopsy improves diagnostic yield for subcortical lesions. J Neurooncol. 2019;141(1):121–129.

51. Berghoff AS, Rajky O, Winkler F, et al. Invasion patterns in brain metastases of solid cancers. Neuro Oncol. 2013;15(12):1664–1672.

52. Baumert BG, Rutten I, Dehing-Oberij C, et al. A pathology-based substrate for target definition in radiosurgery of brain metastases. Int J Radiat Oncol Biol Phys. 2006;66(1):187–194.

53. Siam L, Bleckmann A, Chaung HN, et al. The metastatic infiltration at the metastasis/brain parenchyma-interface is very heterogeneous and has a significant impact on survival in a prospective study. Oncotarget. 2015;6(30):29254–29267.

54. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA. 1998;280(17):1485–1489.

55. Mahajan A, Ahmed S, McAuley MF, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. Lancet Oncol. 2017;18(8):1040–1048.

56. Yoo H, Kim YZ, Nam BH, et al. Reduced local recurrence of a single brain metastasis through microscopic total resection. J Neurosurg. 2009;110(4):730–736.

57. Kamp MA, Dib ô É, Niemann L, et al. Proof of principle: supramarginal resection of cerebral metastases in eloquent brain areas. Acta Neurochir (Wien). 2012;154(11):1981–1996.

58. Pessina F, Navarria P, Cozzi L, et al. Role of surgical resection in patients with single large brain metastases: feasibility, morbidity, and local control evaluation. World Neurosurg. 2016;94:6–12.

59. Agboula O, Benoit B, Cross P, et al. Prognostic factors derived from recursive partition analysis (RPA) of Radiation Therapy Oncology Group (RTOG) brain metastases trials applied to surgically resected and irradiated brain metastatic cases. Int J Radiat Oncol Biol Phys. 1998;42(1):155–159.

60. Lee CH, Kim DG, Kim JW, et al. The role of surgical resection in the management of brain metastasis: a 17-year longitudinal study. Acta Neurochir (Wien). 2013;155(3):389–397.

61. Chitti B, Goyal S, Sherman JH, et al. The role of brachytherapy in the management of brain metastases: a systematic review. J Contemp Brachytherapy. 2020;12(1):67–83.

62. Ruge MI, Kocher M, Maarouf M, et al. Comparison of stereotactic brachytherapy (125 iodine seeds) with stereotactic radiosurgery (LINAC) for the treatment of singular cerebral metastases. Strahlenther Onkol. 2011;187(1):7–14.

63. Rogers LR, Rock JP, Sills AK, et al.; Brain Metastasis Study Group. Results of a phase II trial of the GliaSite radiation therapy system for the treatment of newly diagnosed, resected single brain metastases. J Neurosurg. 2006;105(3):375–384.

64. Bernstein M, Cabantog A, Laperriere N, Leung P, Thomason C. Brachytherapy for recurrent single brain metastasis. Can J Neurol Sci. 1995;22(1):13–16.

65. Mahase SS, Navazhina K, Schwartz TH, Parashar B, Wernicke AG. Intraoperative brachytherapy for resected brain metastases. Brachytherapy. 2019;18(3):258–270.

66. Wernicke AG, Yondorf MZ, Peng L, et al. Phase I/II study of resection and intraoperative cesium-131 radiisotope brachytherapy in patients with newly diagnosed brain metastases. J Neurosurg. 2014;121(2):338–348.

67. Wernicke AG, Hirschfeld CB, Smith AW, et al. Clinical Outcomes of Large Brain Metastases Treated With Neurosurgical Resection and Intraoperative Cesium-131 Brachytherapy: Results of a Prospective Trial. Int J Radiat Oncol Biol Phys. 2017;98(5):1059–1088.

68. Brennan C, Yang TJ, Hiltunen P, et al. A phase 2 trial of stereotactic radiosurgery boost after surgical resection for brain metastases. Int J Radiat Oncol Biol Phys. 2014;88(1):130–136.

69. Wernicke AG, Smith AW, Taube S, et al. Cesium-131 brachytherapy for recurrent brain metastases: durable salvage treatment for previously irradiated metastatic disease. J Neurosurg. 2017;126(4):1212–1219.

70. Julie DA, Lazov SP, Vanderbilt DB, et al. A matched-pair analysis of clinical outcomes after intracavitary cesium-131 brachytherapy versus stereotactic radiosurgery for resected brain metastases. J Neurosurg. 2020;134(5):1447–1454.

71. Pham A, Yondorf MZ, Parashar B, et al. Neurocognitive function and quality of life in patients with newly diagnosed brain metastasis after treatment with intra-operative cesium-131 brachytherapy: a prospective trial. J Neurooncol. 2016;127(1):63–71.

72. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 2009;10(11):1037–1044.

73. Murray KJ, Scott C, Zachariah B, et al. Importance of the mini-mental status examination in the treatment of patients with brain metastases: a report from the Radiation Therapy Oncology Group protocol 91-04. Int J Radiat Oncol Biol Phys. 2000;48(1):59–64.

74. Wernicke AG, Lazow SP, Taube S, et al. Surgical technique and clinically relevant resection cavity dynamics following implantation of cesium-131 (Cs-131) brachytherapy in patients with brain metastases. Oper Neurosurg (Hagerstown). 2016;12(1):49–60.

75. Roberts DW, Strohbehn JW, Hatch JF, Murray W, Kettenberger H. A frameless stereotactic integration of computerized tomographic imaging and the operating microscope. J Neurosurg. 1986;65(4):545–549.

76. Gerard LJ, Kersten-Oertel M, Petrecca K, Sirhan D, Hall JA, Collins DL. Brain shift in neuronavigation of brain tumors: a review. Med Image Anal. 2017;35:403–420.

77. Cao A, Thompson RC, Dumpty P, et al. Laser range scanning for image-guided neurosurgery: Investigation of image-to-physical space registrations: laser range scanning: image-to-physical space registrations. Med Phys. 2006;35(4):1593–1605.

78. Golfinos JG, Fitzpatrick BC, Smith LR, Spetzler RF. Clinical use of a frameless stereotactic arm: results of 325 cases. J Neurosurg. 1995;83(2):197–205.

79. Garber ST, Jensen RL. Image guidance for brain metastases resection. Surg Neurol Int. 2012;3(Suppl 2):S111–S117.

80. Schackert G, Steinmetz A, Meier U, Sobottka SB. Surgical management of single and multiple brain metastases: results of a retrospective study. Onkologie. 2001;24(3):246–255.

81. Tan TC, Black PM. Image-guided craniotomy for cerebral metastases: techniques and outcomes. Neurosurgery. 2007;61(1 Suppl):349–56; discussion 356.
82. Benveniste RJ, Germano IM. Correlation of factors predicting intraoperative shift with successful resection of malignant brain tumors using image-guided techniques. Surg Neurol. 2005;63(6):542–8; discussion 548.
83. Chandler WF, Knake JE, McGillicuddy JE, Lillehei KO, Silver TM. Intraoperative use of real-time ultrasonography in neurosurgery. J Neurosurg. 1982;57(2):157–163.
84. Sastry R, Bi WL, Pfeffer S, et al. Applications of ultrasound in the resection of brain tumors. J Neuroimaging. 2017;27(1):1–5.
85. Di Lorenzo N, Esposito V, Lunardi P, Delfini R, Fortuna A, Cangore T. A comparison of computerized tomography-guided stereotactic and ultrasound-guided techniques for brain biopsy. J Neurosurg. 1991;75(5):763–765.
86. Hammoud MA, Ligon BL, elSouki R, Shi WM, Schomer DF, Sawaya R. Applications of ultrasound in the resection of brain metastases: effect on Karnofsky Index scores and tumor volume. World Neurosurg. 2017;103:557–565.
87. Kanno H, Ozawa Y, Sakata K, et al. Intraoperative power Doppler ultrasonography with a contrast-enhancing agent for intracranial tumors. J Neurosurg. 2005;102(2):295–301.
88. Engelhardt M, Hansen C, Eyding J, et al. Feasibility of contrast-enhanced sonography during resection of cerebral tumors: initial results of a prospective study. Ultrasound Med Biol. 2007;33(4):571–575.
89. Prada F, Perin A, Martegani A, et al. Intraoperative contrast-enhanced ultrasound for brain tumor surgery. Neurosurgery. 2014;74(5):542–52; discussion 552.
90. Scholz M, Noack V, Pechlivanis I, et al. Vibrography during tumor neurosurgery. J Ultrasound Med. 2005;24(7):985–992.
91. Selbekk T, Bang J, Unsgaard G. Strain processing of intraoperative ultrasound images of brain tumors: initial results. Ultrasound Med Biol. 2005;31(1):45–51.
92. Chauvet D, Imbault M, Capella L, et al. In vivo measurement of brain tumor elasticity using intraoperative shear wave elastography. Ultraschall Med. 2016;37(6):584–590.
93. Prada F, Del Bene M, Rampini A, et al. Intraoperative strain elastography in brain tumor surgery. Oper Neurosurg (Hagerstown). 2019;17(2):227–236.
94. Riccabona M, Nelson TR, Weitzer C, Resch B, Pretorius DP. Potential of three-dimensional ultrasound in neonatal and paediatric neurosonography. Eur Radiol. 2003;13(9):2082–2093.
95. Unsgaard G, Ommedal S, Muller T, Grönningaeter A, Nagelhus Hernes TA. Neuronavigation by intraoperative three-dimensional ultrasound: initial experience during brain tumor resection. Neurosurgery. 2002;50(4):804–12; discussion 812.
96. Unsgaard G, Selbekk T, Brostrøp Müller T, et al. Ability of navigated 3D ultrasound to delineate gliomas and metastases–comparison of image interpretations with histopathology. Acta Neurochir (Wien). 2005;147(12):1259–69; discussion 1269.
97. Rygh OM, Nagelhus Hernes TA, Lindseth F, Selbekk T, Brostrøp Müller T, Unsgaard G. Intraoperative navigated 3-dimensional ultrasound angiography in tumor surgery. Surg Neurol. 2006;66(6):581–92; discussion 592.
98. Prada F, Del Bene M, Mattei L, et al. Preoperative magnetic resonance and intraoperative ultrasound fusion imaging for real-time neuronavigation in brain tumor surgery. Ultrason Imag. 2015;36(2):174–186.
99. Xiao Y, Elkonies L, Reinertsen I, Rivaz H. Nonlinear deformation of tractography in ultrasound-guided low-grade gliomas resection. Int J Comput Assist Radiol Surg. 2018;13(3):457–467.
100. Gerard IJ, Kersten-Oertel M, Drouin S, et al. Combining intraoperative ultrasound brain shift correction and augmented reality visualizations: a pilot study of eight cases. J Med Imaging (Bellingham). 2018;5(2):021210.
101. Tornier VM, Bonsanto MM, Staubert A, Knauth M, Kunze S, Wirtz CR. Comparison of intraoperative MR imaging and 3D-navigated ultrasonography in the detection and resection control of lesions. Neurosurg Focus. 2001;10(2):E3.
102. Prada F, Del Bene M, Mattei L, et al. Preoperative neuronavigation and intraoperative ultrasound fusion imaging for real-time neuronavigation in brain tumor surgery. Ultrason Imag. 2015;36(2):174–186.
103. Tharin S, Golby A. Functional brain mapping and its applications to neurosurgery. Neurosurgery. 2007;60(4 Suppl 2):185–201; discussion 201.
104. Kombos T, Soess O, Kern BC, et al. Comparison between monopolar and bipolar electrical stimulation of the motor cortex. Acta Neurochir (Wien). 1999;141(12):1295–1301.
105. Wood CC, Spencer DD, Allison T, McCarthy G, Williamson PD, Goff WR. Localization of human sensorimotor cortex during surgery by cortical surface recording of somatosensory evoked potentials. J Neurosurg. 1988;69(1):99–111.
106. Skirboll SS, Ojemann GA, Berger MS, Lettich E, Winn HR. Functional cortex and subcortical white matter located within gliomas. Neurosurgery. 1996;38(4):678–84, discussion 684.
107. Gogos AJ, Young JS, Morshed RA, Henvey-Jumper SL, Berger MS. Awake glioma surgery: technical evolution and nuances. J Neurooncol. 2020;147(3):515–524.
108. De Witt Hamer PC, Robles SG, Zwierdemann AH, Duffau H, Berger MS. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol. 2012;30(20):2559–2565.
109. Suarez-Meade P, Marenco-Hillembrand L, Prevatt C, et al. Awake vs. asleep motor mapping for glioma resection: a systematic review and meta-analysis. Acta Neurochir (Wien). 2020;162(7):1709–1720.
110. Gerritsen JKW, Arends L, Klimek M, Dirven CMF, Vincent AJE. Impact of intraoperative stimulation mapping on high-grade glioma surgery outcome: a meta-analysis. Acta Neurochir (Wien). 2019;161(1):99–107.
111. Krieg SM, Schaffner M, Shibani E, et al. Reliability of intraoperative neurophysiological monitoring using motor evoked potentials during resection of metastases in motor-eloquent brain regions: clinical article. J Neurosurg. 2013;118(6):1269–1278.
112. Krieg SM, Shibani E, Droese D, et al. Predictive value and safety of intraoperative neurophysiological monitoring with motor evoked potentials in glioma surgery. Neurosurgery. 2012;70(5):1069–70; discussion 1070.
113. Obermueller T, Schaeffner M, Shibani E, et al. Intraoperative neuromonitoring for function-guided resection differs for supratentorial motor eloquent gliomas and metastases. BMC Neurol. 2015;15:211.
114. Chua TH, See AAQ, Ang BT, King NKK. Awake craniotomy for resection of brain metastases: a systematic review. World Neurosurg. 2018;120:e1128–e1135.
115. Krieg SM, Picht T, Sohlmann N, et al. Resection of motor eloquent metastases aided by preoperative nTMS-based motor maps-comparison of two observational cohorts. Front Oncol. 2016;6:261.
116. Nossek E, Korn A, Shahar T, et al. Intraoperative mapping and monitoring of the corticospinal tracts with neurophysiological assessment
and 3-dimensional ultrasonography-based navigation. Clinical article. J Neurosurg. 2011;114(3):738–746.

120. Policicchio D, Ticca S, Dipellegrini G, Doda A, Muggianu G, Boccaletti R. Multimodal surgical management of cerebral lesions in motor-eloquent areas combining Intraoperative 3D Ultrasound with Neurophysiological mapping. J Neurol Surg Part C Eur Neurosurg. 2021;82(4):344–356.

121. Cappabianca P, Cinalli G, Gangemi M, et al. Application of neuroendoscopy to intraventricular lesions. Neurosurgery. 2008;62(Suppl 2):575–597; discussion 597-598.

122. Plaha P, Livermore LJ, Voets N, Pereira E, Cudlip S. Minimally invasive endoscopic resection of intraparenchymal brain tumors. World Neurosurg. 2014;82(6):1198–1208.

123. Ma R, Coulter CA, Livermore LJ, Voets NL, Al Awar O, Plaha P. Endoscopy in temporal lobe Glioma and metastasis resection: is there a role? World Neurosurg. 2018;117:e238–e251.

124. Barkhoudarian G, Farahmand D, Louis RG, et al. Microsurgical endoscope-assisted gravity-aided transfalcine approach for contralateral metastatic deep medial cortical tumors. Oper Neurosurg (Hagerstown). 2017;13(6):724–731.

125. Zacharia BE, Romero FR, Rapoport SK, Raza SM, Anand VK, Schwartz TH. Endoscopic endonasal management of metastatic lesions of the anterior skull base: case series and literature review. World Neurosurg. 2015;84(5):1267–1277.

126. Wilson DA, Duong H, Teo C, Kelly DF. The supraorbital endoscopic approach for tumors. World Neurosurg. 2014;82(6 Suppl):S72–S80.

127. McLaughlin N, Prevedello DM, Engh J, Kelly DF, Kassam AB. Endoneurosurgical resection of intraventricular and intraparenchymal lesions using the port technique. World Neurosurg. 2013;79(2 Suppl):S18.e1–S18.e8.

128. McLaughlin N, Filho I, Prevedello D, Kelly D, Carrau R, Kassam A. Side-cutting aspiration device for endoscopic and microscopic tumor removal. Skull Base. 2011;21(5):229–232.

129. Ricciardi L, Chaichana KL, Cardia A, et al. The exoscope in neurosurgery: an innovative “point of view”. A systematic review of the technical, surgical, and educational aspects. World Neurosurg. 2019;124:136–144.

130. Mamelak AN, Nobuto T, Berci G. Initial clinical experience with a high-definition exoscope system for microneurosurgery. Neurosurgery. 2010;67(2):476–483.

131. Roethe AL, Landgraf P, Schröder T, Misch M, Vajkoczy P, Picht T. Monitor-based exoscopic 3D4k neurosurgical interventions: a two-phase prospective-randomized clinical evaluation of a novel hybrid device. Acta Neurochir (Wien). 2020;162(12):2949–2961.

132. Oertel JM, Burkhardt BW. Vitoron-3D for exoscopic neurosurgery: initial experience in cranial and spinal procedures. World Neurosurg. 2017;105:153–162.

133. Marenco-Hillembraad L, Suarez-Meade P, Chaichana KL. Bur hole-based resections of intrinsic brain tumors with exoscopic visualization. J Neurol Surg Part C Eur Neurosurg. 2021;82(2):105–111.

134. Muto J, Mine Y, Nakagawa Y, et al. Intraoperative real-time near-infrared optical imaging for the identification of metastatic brain tumors via microscope and exoscope. Neurosurg Focus. 2021;50(1):E11.

135. Teng CW, Cho SS, Singh Y, et al. Second window ICG predicts gross-total resection and progression-free survival during brain metastasis surgery [Published online ahead of print February 2021]. J Neurosurg. 2021;135:1026–1035. doi: 10.3171/2020.8.JNS201810.

136. Moore GE, Peyton WT. The clinical use of fluorescein in neurosurgery: the localization of brain tumors. J Neurosurg. 1958;5(4):392–398.

137. Stummer W, Pichlmayer U, Meintl T, Wiestler OD, Zanella F, Reulen HJ; ALA-Glioma Study Group. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase Ill trial. Lancet Oncol. 2006;7(5):392–401.

138. Coburger J, Engelke J, Scheuerle A, et al. Tumor detection with 5-aminolevulinic acid fluorescence and Gd-DTPA-enhanced intraoperative MRI at the border of contrast-enhancing lesions: a prospective study based on histopathological assessment. Neurosurg Focus. 2014;36(2):E3.

139. Kamp MA, Munoz-Bendix C, Mijdervijk HJ, et al. Is 5-ALA fluorescence of cerebral metastases a prognostic factor for local recurrence and overall survival? J Neurooncol. 2019;141(3):547–553.

140. Hussein A, Rohde V, Wolfert C, et al. Survival after resection of brain metastases with white light microscopy versus fluorescence-guidance: A matched cohort analysis of the Metastasys study data. Oncotarget. 2020;11(32):3026–3034.

141. Schobesker KM, Proescholdt M, Hohne J, et al. Sodium fluorescein-guided resection under the YELLOW 560 nm surgical microscope filter in malignant brain tumor surgery—a feasibility study. Acta Neurochir (Wien). 2013;155(4):693–698.

142. Schobesker KM, Hoejene H, Hohenberger C, et al. Fluorescein sodium-guided resection of cerebral metastases—experience with the first 30 patients. Acta Neurochir (Wien). 2015;157(6):899–904.

143. Hohene J, Hohenberger C, Proescholdt M, et al. Fluorescein sodium-guided resection of cerebral metastases—an update. Acta Neurochir (Wien). 2017;159(2):363–367.

144. Xiao SY, Zhang J, Zhu ZQ, et al. Application of fluorescein sodium in breast cancer brain-metastasis surgery. Cancer Manag Res. 2018;10:4325–4331.

145. Falco J, Cavallò C, Vetrano IG, et al. Fluorescein application in cranial and spinal tumors enhancing at preoperative MRI and operated with a dedicated filter on the surgical microscope: preliminary results in 279 patients enrolled in the FLUOCERTUM prospective study. Front Surg. 2019;6:49.

146. Hamamc@uk MK, AÇakayakay MÖ, Gökber B, Kasmanc MÖ, KınıC T. The use of the YELLOW 560 nm surgical microscope filter for sodium fluorescein-guided resection of brain tumors: Our preliminary results in a series of 28 patients. Clin Neural Neurosurg. 2016;143:39–45.

147. Kofoid MS, Pedersen CB, Schulz MK, et al. Fluorescein-guided resection of cerebral metastases is associated with greater tumor resection [Published online March 15 2021]. Acta Neurochir (Wien). 2021. doi:10.1007/s00701-021-04796.

148. Zhang DY, Singhal S, Lee JYK. Optical principles of fluorescence-guided surgery in brain tumors. Acta Neurochir (Wien). 2017;159(32):3026–3034.

149. Wester RC, Hunink MG, et al. Clinical guidelines for the application of 5-fluorouracil-based resections of intrinsic brain tumors with exoscopic visualization. J Neurol Surg Part C. 2014;75(2):124–132.

150. Kodama S, Suzuki S, Koike M, et al. Intraoperative near-infrared optical imaging can localize gadolinium-enhancing gliomas during surgery. Neurosurgery. 2016;79(6):856–871.