

Surgical advances in the management of brain metastases

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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.¹ Population-based studies estimate that 8.5–9.6% of cancer patients will develop a BM,^{2,3} while autopsy studies suggest that approximately 25% of people who die of cancer had developed metastatic disease to the brain.^{4,5} 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.⁶ As cancer treatment, diagnosis, and surveillance improve, incidence rates will continue to rise.^{1,6} Neurosurgery is an essential tool in the therapeutic arsenal against brain metastases and has been shown to improve

survival and quality of life.^{7,8} 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

Table 1. Surgical Innovations for Brain Metastases

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

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 2. 2019 Congress of Neurological Surgeons (CNS) Guidelines on the Role of Surgery in the Management of Adults with Metastatic Brain Tumors

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)?	<i>Level 1:</i> 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. <i>Level 3:</i> Surgery + SRS is recommended to provide survival benefit in patients with metastatic brain tumors <i>Level 3:</i> 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.
	Should patients with newly diagnosed metastatic brain tumors undergo surgical resection followed by WBRT, SRS, or another combination of these modalities?	<i>Level 1:</i> Surgery + WBRT is recommended as superior treatment to WBRT alone in patients with single brain metastases. <i>Level 3:</i> Surgery + SRS is recommended as an alternative to treatment with SRS alone to benefit overall survival. <i>Level 3:</i> 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?	<i>Level 3:</i> 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

literature, and compared to controls in the same cohort, patients who underwent minimally invasive keyhole surgeries experienced shorter mean length of stay.³¹ Lastly, Baker 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

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.³⁷ 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

Tubular retractors have been implemented for the resection of deep-seated metastases. Depending on the surgeon's experience, operative microscopes (OMs),⁴⁵ exoscopes,^{44,46,47} endoscopes,^{41,45} intraoperative MRI,⁴⁸ and intraoperative ultrasound⁴⁹ may be used with tubular retractor-assisted resection of BMs. Though most commonly utilized for subcortical and periventricular lesions, tubular retractors can also facilitate high-efficacy, low-morbidity resection of brain metastases in the posterior fossa.^{47,49} Furthermore, the physical characteristics of the BM determine the efficacy of tubular retractors. Softer metastases, such as breast and melanoma, are favored, allowing depth cannulation into the tumor and inside-out resection.^{41,45,46} Firmer lesions, such as metastatic sarcoma, require surface cannulation to avoid displacement of the tumor, while hemorrhage-prone BMs, such as renal cell carcinoma, are less amenable to the piecemeal resection executed with tubular retractors.^{41,45} In retrospective clinical studies, high rates of GTR (73% to 100%) of deep-seated brain metastases have been achieved with BrainPath, VBAS, and METRx.^{40,41,45-47} Tubular-retractor-assisted biopsy has also been studied as an alternative to stereotactic needle biopsy and has demonstrated superior tissue yield without the need for reoperation.⁵⁰

Supramarginal Resection

Though brain metastases are often sharply demarcated on neuroimaging and grossly delimited by glial pseudocapsules, histopathological studies have identified distinct invasion patterns of BMs,^{51,52} and the presence of infiltrating metastatic cells beyond the glial pseudocapsule 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.⁵⁶ 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 ¹²⁵I and shrinkage of the tumor cavity shifting the position 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 a 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.⁷⁰ 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 1986,⁷⁵ 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

ceUS utilizes contrast agents containing microparticles and air bubbles to enable enhanced real-time visualization of the cerebral vasculature.⁹⁰ In Kanno et al.,⁹⁰ the first study to evaluate ceUS in tumor resections, most metastatic tumors demonstrated strong signals on ceUS. Moreover, there was a more significant correlation between ceUS and digital subtraction (DS) angiograms than between ceUS and contrast-enhanced CT and MRI, highlighting that US contrast enhancement is more closely related to vascularity while CT or MR contrast enhancement is related to destruction of the blood-brain barrier.⁹⁰ As such, ceUS can aid BM resection by identifying feeding arteries, draining veins, and tumor vasculature and by confirming total resection through the disappearance of Doppler signal.⁹⁰ The utility of intraoperative ceUS was confirmed in Engelhardt et al.,⁹¹ a prospective study in which metastatic visualization was enhanced with contrast and hyperechoic tumors were distinguished from hypoechoic peritumoral edema. Similarly, in Prada et al.,⁹² all brain metastases appeared markedly hyperechoic on ceUS, and contrast enhancement clearly defined the tumor borders.

US elastography measures the elastic properties of tissue either through controlled low-frequency vibrations generated by the probe (vibrography) or through observations of arterial pulsations.^{93,94} In Scholz et al.,⁹³ vibrography measurements of metastatic carcinoma demonstrated a range of strain: lower strain than brain tissue, identical strain to brain tissue, or inhomogeneous strain. In Chauvet et al.,⁹⁵ intraoperative shear wave elastography significantly differentiated metastases from meningiomas based on elasticity. In Prada et al.,⁹⁶ intraoperative strain elastography (SE) based on brain pulsatility measured BMs as either stiffer (kidney, colon) or softer (endometrial, lung) than normal brain. In 64% of the study's 64 cases, including gliomas, meningiomas, metastases, and other tumor types, SE differentiated lesion margins more sharply than 2D B-mode US.

3D iUS reconstructs 2D slices into volumetric images that may be reviewed in any plane and can accurately pinpoint tumors and vessels in a more intuitive way than 2D techniques.^{97,98} In Unsgaard et al.,⁹⁹ there was 100% concordance between 3D iUS and histopathologic biopsy in differentiating BMs from non-BM tissue, while T1- and T2-weighted MRI yielded 90% and 86% concordance with histopathology, respectively. In Rygh et al.,¹⁰⁰ 3D-iUS angiography with power Doppler was a useful intraoperative neuronavigational tool, enabling identification of hidden vessels in 3 out of 5 BM cases and therefore improving spatial perception of risk structures. Of note, power Doppler is less angle-dependent than color flow Doppler, allowing better reconstruction of vessel continuity.¹⁰⁰ In Tronnier et al.,¹⁰¹ 3D-navigated US offered a primary visualization of metastases that was comparable to intraoperative MRI.

iUS modalities are being combined with preexisting imaging techniques, such as MRI-based neuronavigation,¹⁰² MRI tractography,¹⁰³ and augmented reality,¹⁰⁴ to improve real-time visualization of the brain parenchyma and to monitor and compensate for brain shift. Most of these applications depend on an algorithmic registration process that enables parenchymal shifts detected intraoperatively by iUS to update preoperative MRI images.⁸⁴ Registration is technically challenging since US and MR images highlight different anatomic details and generate unique artifacts and noise patterns.¹⁰⁵ Development

of brain-shift-monitoring technologies is still in a relatively early stage, but preliminary results are promising.¹⁰⁵

Intraoperative Brain Mapping

Complete resection of brain metastases in patients with well-controlled systemic disease can improve survival.^{59,60} 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.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).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.¹⁰⁸ The central sulcus is the location of "phase reversal."¹⁰⁸ Subcortical structures, including white matter, can also be stimulated and assessed with MEPs or other functional readouts.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.¹¹⁰ Though brain mapping has been more extensively studied in gliomas,^{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.,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,¹¹⁴ which has been previously recommended for glioma surgery.¹¹⁵ Surgery improved the strength of 21% of patients.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 3.¹¹⁴ In another retrospective study including 56 BMs, Obermueller *et al.*, confirmed that > 80% reduction in MEP amplitude was a more appropriate BM-specific alarm threshold than > 50% reduction.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.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 transfalci 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.¹²⁵ 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.¹²⁹ 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 HDXO-scope, BrightMatter, ORBEYE, and KINEVO 900.

First implemented by Mamelak 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 retrosigmoid 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,¹³² 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.^{41,46,47} In Marenco-Hillebrand *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.¹³³ Lastly, exoscopes have enabled new intraoperative fluorescent imaging techniques, such as second-window indocyanine green (SWIG), discussed in the subsequent section.^{134,135} In conclusion, several reports have demonstrated safe and effective exoscope-based resection of metastatic lesions.

Fluorescence-Guided Surgery

Since the 1940s,¹³⁶ 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,¹³⁷ yet similar benefits have not been found with BMs.^{138–140} 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,¹³⁶ 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,^{141–144} though visualization is limited in cases of pigmented melanoma, hemorrhagic metastases, or previously irradiated tissue.¹⁴⁵ Across several retrospective cohorts, fluorescein visualization facilitated GTR in 83.3–100% of cases.^{142,143,146} 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.^{144,147} 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.¹⁴⁸ 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.¹³⁴ 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.¹⁴⁹ 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.¹⁵⁰ In another prospective study by Muto *et al.*¹³⁴ 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.*,¹³⁵ 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.

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