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RESEARCH PAPER

Neurosurgical management of brain metastases

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Abstract Brain metastases present a significant public health issue, affecting more than 100,000 patients per year in the U.S. and result in significant morbidity. Brain metastases can occur in a variety of clinical situations ranging from multiple brain metastases with uncontrolled systemic disease to a solitary metastasis in the setting of controlled systemic disease. Additionally, advances in genomics have broadened the opportunities for targeted treatment options and potentially more durable systemic responses. As such, the treatment of brain metastases is now more tailored and multimodal, involving systemic, radiation, and surgical therapies, often in combination. This review discusses the historical and current role of neurosurgical techniques in the treatment of brain metastases.

Keywords Brain metastases · Surgery · Intraoperative mapping · En bloc resection

Introduction

Brain metastases are the most common brain tumors, with an estimated incidence of 100,000–300,000 patients per year in the U.S. [1, 2]. Lung cancer, breast cancer, and melanoma are the most common solid tumors to spread to the central nervous system (CNS) [3]. Overall, approximately 8–10% of patients with cancer will develop symptomatic brain metastases, and approximately half will die within 3–27 months from the initial diagnosis [3–5]. These issues are pressing, as the incidence of brain metastasis may be increasing due to newer targeted therapies and immunotherapies affording patients longer survival times [5, 6]. With advances in radiation technology and systemic therapy, the treatment of brain metastasis has become tailored, and treatment paradigms vary depending on the individual patient. Surgery remains the cornerstone in brain metastasis treatment, and this review will outline its role and the role of radiosurgery in the treatment of brain metastasis.

Single brain metastasis

Surgery

Surgical resection serves an established critical role in the treatment of single brain metastases. This is particularly the case with large (>3 cm in maximal diameter) symptomatic lesions. In the early 1990s, two historic randomized trials confirmed the benefit of surgery for single brain metastases. Patchell and colleagues reported that, compared with patients undergoing whole-brain radiation therapy (WBRT) alone ($n=23$) for a single brain lesion, patients who had surgical resection followed by WBRT ($n=25$) had a lower risk of local recurrence (52 vs. 20%, respectively) [7]. Surgical patients were also afforded a longer duration of functional independence [defined as a Karnofsky Performance Scale (KPS) score of >70] than patients receiving WBRT alone (38 vs. 8 weeks, respectively). Furthermore, undergoing resection resulted in longer survival times than in patients

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treated exclusively with WBRT (40 vs. 15 weeks, respectively). Another prospective randomized trial confirmed the benefit of surgical resection in 63 patients. Patients undergoing surgery experienced improved survival and prolonged functional independence relative to patients undergoing WBRT alone [8].

It is well accepted that surgical resection is ideally followed with adjuvant radiotherapy. Classically, this irradiation has been WBRT. This treatment rationale stems from a multicenter randomized trial that compared the outcome of patients with a single brain metastasis undergoing complete resection followed by observation (n = 46) or postoperative WBRT (n = 49). The authors reported that postoperative irradiation significantly reduced the rate of intracranial tumor recurrence (70 vs. 18%, respectively) and neurological death (44 vs. 14%, respectively) [9]. In a later study, Neider et al. [10] reported the pooled analysis of multiple studies focused on surgical resection of single metastases. A total of 643 patients from 10 studies were included in this analysis. The results of this report demonstrated that postoperative WBRT significantly improved local control at the surgical site. Specifically, the authors reported local recurrence in 40 and 12% of patients treated with surgery alone and surgery followed by postoperative WBRT, respectively [10]. With these supportive data, surgical resection has long been the standard of care for single brain metastases. Of note, recent studies have suggested the potentially negative cognitive effects of WBRT and its impact on patient quality of life [11, 12]. The growing concern regarding the neurotoxicity associated with WBRT has resulted in the use of alternative forms of adjuvant treatment such as stereotactic radiosurgery (SRS). This will be discussed in the "Radiosurgery" below.

In addition to the survival advantage it confers, surgical resection has several indispensable advantages. Upfront resection is the only method to urgently obtain cerebral decompression, relieve mass effect, and rapidly reduce intracranial pressure. Brain metastases induce cerebral edema of varying severity (Fig. 1). Steroid administration is often sufficient to manage edema, but in the circumstance of refractory symptomatic edema, tumor resection is beneficial. Large metastases involving the posterior fossa or ventricular system may cause obstructive hydrocephalus, which can also be addressed with surgical resection to reopen the flow of cerebrospinal fluid (Fig. 2). Additionally, brain metastases can provoke surrounding cortical irritation and seizures, and surgery may help in optimizing seizure control. It should be noted that even though surgical resection is primarily reserved for larger lesions (≥3 cm in maximal diameter), occasionally smaller lesions do require surgical intervention. For example, if a patient's pathological diagnosis is unclear, surgical intervention may be necessary; e.g., a newly discovered brain lesion with a negative systemic workup or in a patient with a history of an unknown primary. Even in the circumstance of a known primary cancer, a biopsy/resection may be necessary if there is no evidence of extracranial metastatic disease and/or if imaging characteristics are suspicious for a primary brain tumor (e.g., glioma). Approximately 11% of patients with a primary cancer outside the brain may have a non-metastatic lesion such as glioma [7]. As the treatment of each of these pathologies is different, confidence in the diagnosis prior to initiating therapy is critical (Fig. 3).

Achieving the full benefit of surgical resection requires good patient selection and surgical technique. Despite the advantages of resection, not all patients are ideal candidates for open surgery. Surgery is most appropriate for patients with good functional performance status (determined by KPS status; Table 1) and controlled systemic cancer. These

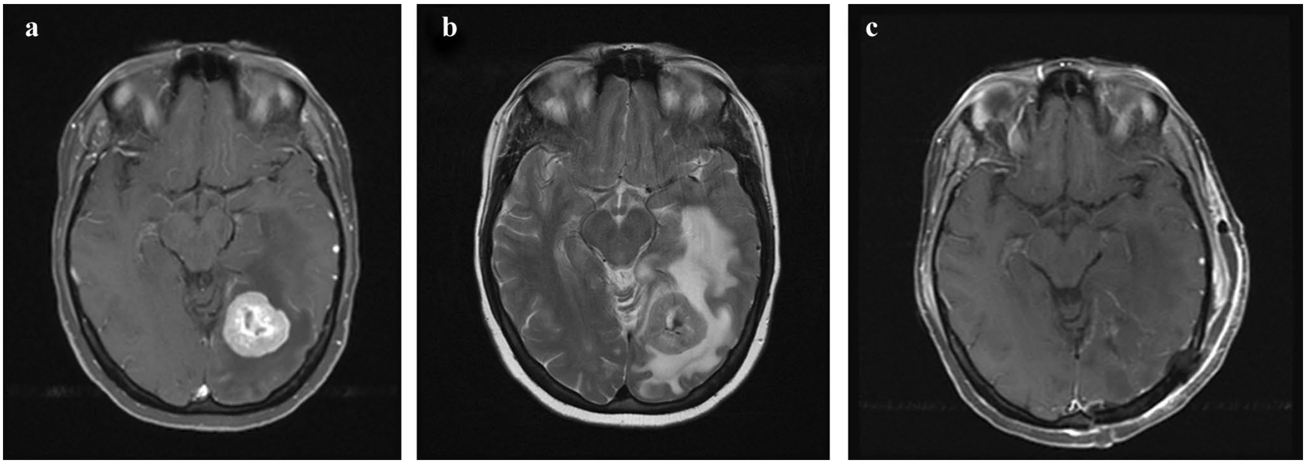

Fig. 1 40-year-old female with a history of breast cancer. **a** T1-weighted gadolinium-enhanced magnetic resonance (MR) images in the axial plane show a heterogeneously enhancing lesion in the left posterior temporal lobe. **b** T2-weighted MR images show the significant edema surrounding lesion. **c** T1-weighted gadolinium-enhanced images post-resection showing gross-total resection

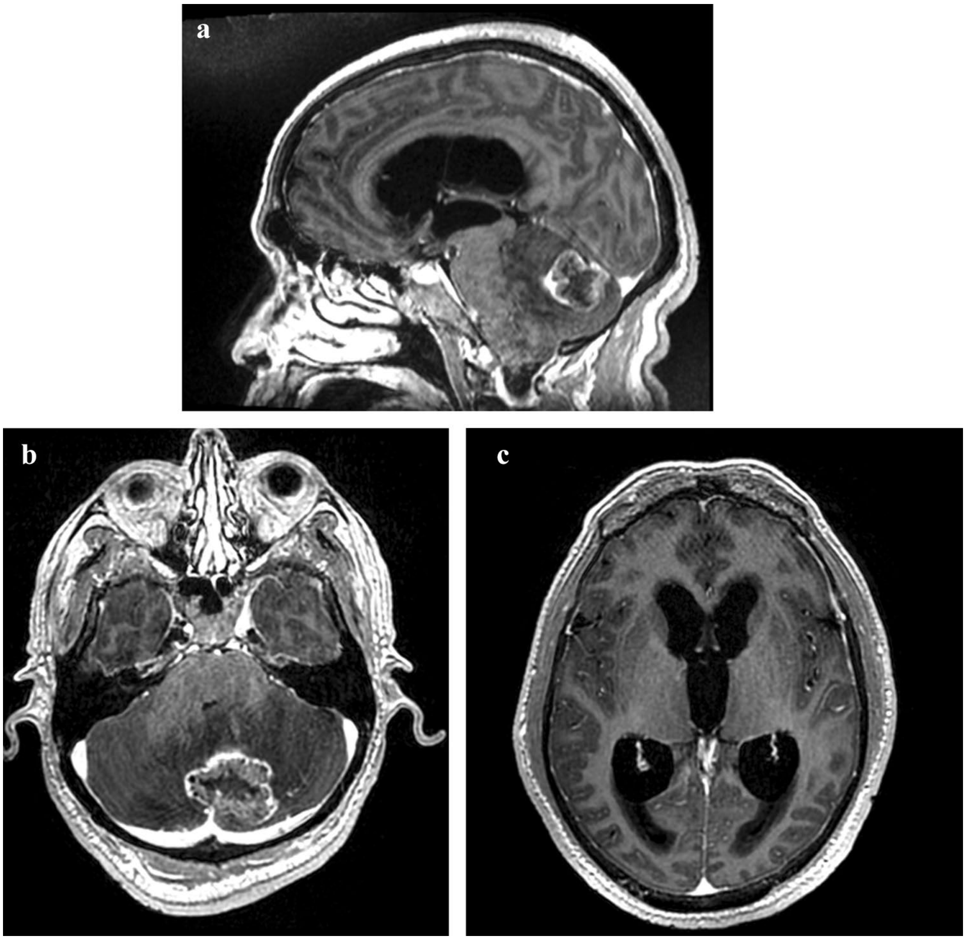

Fig. 2 56-year-old male with a history of non-small cell lung cancer. **a** T1-weighted gadolinium-enhanced MR images in the sagittal plane show a heterogeneously enhancing lesion in the cerebellum. **b, c** T1-weighted gadolinium-enhanced MR images in the axial plane show a heterogeneously enhancing lesion in the cerebellum causing 4th ventricular effacement and obstructive hydrocephalus

factors are collectively captured in the [recursive partitioning analysis (RPA) classification system]. The Radiation Therapy Oncology Group (RTOG) developed this classification, which is graded based on: KPS score, control of systemic disease, patient age, and status of extracranial disease, with RPA class I is associated with the most favorable prognosis, whereas patients with RPA class III have the worst anticipated outcome (Table 2). In a landmark study by Tenduklar et al. [13], the authors analyzed the outcome of 271 patients undergoing resection of a single brain metastasis. In this cohort, patient survival significantly correlated with RPA class, validating the prognostic significance of this scale; the mean survivals of RPA class I, II and II patients post-resection were 21.4, 9, and 8.9 months, respectively. The predictive impact of RPA class has since been validated in multiple surgical series [14, 15]. Overall in RPA class I patients, surgery carries a favorable prognosis, making this patient population most suitable for surgical resection. The Graded Prognostic Assessment (GPA) is a newer prognostic index for patients with brain metastases (Table 3). This prognostic index was originally developed from a database of 1960 patients accrued to four RTOG protocols for patients with brain metastases [16, 17]. The GPA score is based on age, KPS score, number of intracranial lesions, and status of systemic disease. Median overall survival times based on GPA score are: 2.6 months for 0–1 points; 3.8 months for 1.5–2.5 points; 6.9 months for 3 points, and 11 months for 3.5–4 points. This index has been shown to be equally prognostic but more quantitative, and potentially less subjective than the RPA score. Since its conception, the GPA has been refined to include histology-specific prognostic indices based on multi-institutional analysis of 4259 patients with brain metastases from breast carcinoma, small cell and non–small cell lung carcinoma, GI cancers, melanoma, and renal cell carcinoma [17, 18].

The goal of surgical resection is complete removal whenever feasible, while protecting functional cortex, subcortical structures and vascular structures. It is well accepted that gross total resection (GTR) of a tumor improves patient outcome [13, 14]. A recent retrospective review reported the predictors of outcome in 157 patients who underwent surgical resection for brain metastases (96 of which had a single metastasis). Multivariate analysis showed that extent of surgical resection significantly correlated with survival, with GTR and STR (subtotal resection) resulting in median survival of 20.4 and 15.1 months, respectively [14]. Even

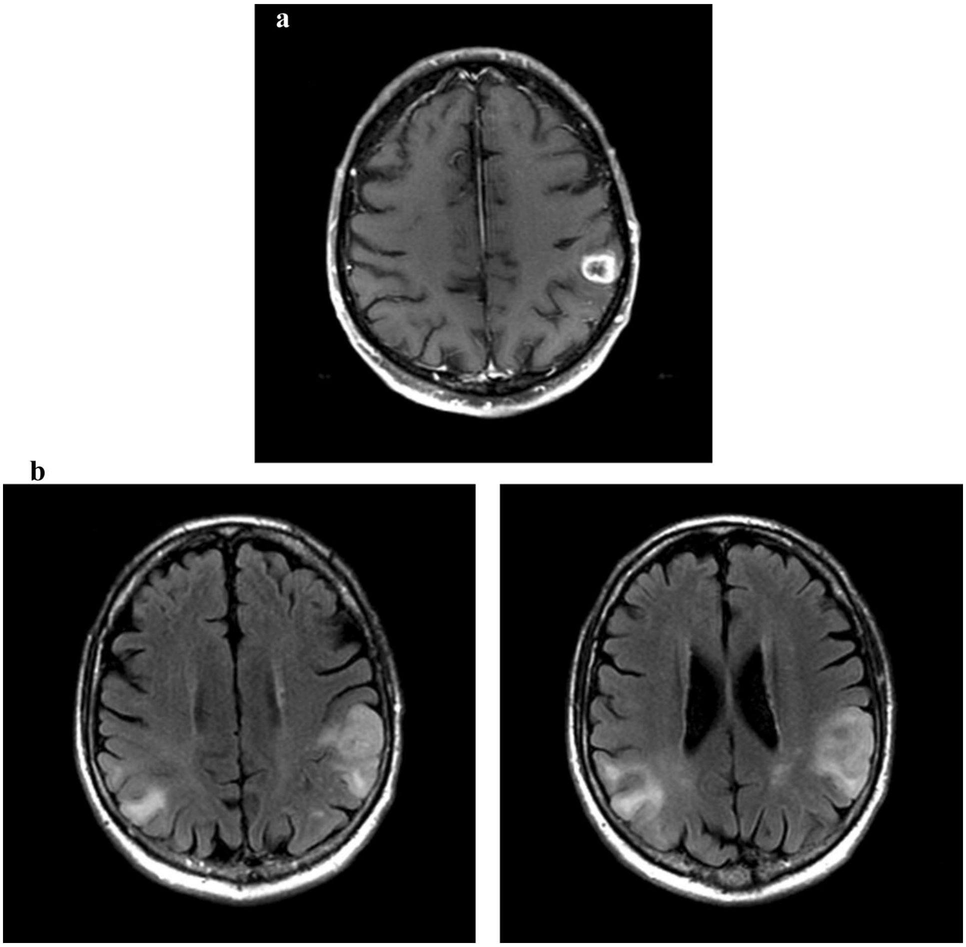

Fig. 3 72-year-old male with a history of squamous cell carcinoma of the base of the tongue. **a** T1-weighted gadolinium-enhanced MR images in the axial plane show an enhancing lesion in the left frontal lobe. **b** T2-weighted/FLAIR images in axial plane show abnormal hyperintensity involving the white matter and cortex, with gyral expansion. There is also abnormal T2 hyperintensity in the right parietal white matter. This was worrisome for bilateral parietal glioma, with the higher grade tumor on the left where there was a focus of necrotic enhancement. The final pathology report in the case was consistent with glioblastoma

Table 1 Karnofsky Performance Scale

Score	
100	Normal, no complaints, no evidence of disease
90	Able to carry out normal activity; mild signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self. Unable to carry out normal activity or do active work
60	Requires occasional assistance, but able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled. Hospitalization indicated though death may not be imminent
20	Very sick. Hospitalization required with active supportive treatment
10	Moribund with fatal processes
0	Death

Modified from Karnofsky et al. [19]

though this is an aggressive approach, surgical resection is generally well tolerated in this patient population. In fact, a large retrospective review of 208 patients undergoing resection for brain metastases (191 with single lesions) reported an overall operative mortality of 1.9% [15].

In addition to the value of obtaining a GTR, there are increasing data suggesting that the method of surgical resection may play a part in clinical outcome. In contrast to primary brain tumors, which are diffusely infiltrating, metastatic lesions are often composed of a dominant mass with generally distinct borders. These lesions tend to displace the surrounding cortex and are surrounded by a gliotic pseudocapsule. Even though tumor infiltration has been reported in the setting of brain metastasis, the depth of infiltration is

Table 2 Recursive partitioning analysis

Class	Characteristics
I	KPS score ≥70 Age <65 Controlled primary disease No extracranial metastases
II	All patients not in class I or class II
III	KPS score <70

Modified from Sperduto et al. [17]

KPS Karnofsky Performance Scale

Table 3 Graded prognostic assessment

Variable	Score		
	0	0.5	1
Age	>60	50–60	<50
KPS	<70	70–80	90–100
No. of central nervous system metastases	>3	2–3	1
Extracranial metastases	Present		Absent

Modified from Sperduto et al. [17]

KPS Karnofsky Performance Scale

reportedly limited to <5 mm [20–22]. Traditionally, tumor resection has been performed in a piecemeal fashion. Specifically, this approached entails entering the lesion and performing intralesional debulking of the mass and subsequent removal of the capsule. While this technique can achieve GTR, it is not an ideal oncological approach because it theoretically exposes surrounding cortex and/or white matter to malignant cells. Additionally, this method of entering the tumor is often bloody, as the center of the lesion can be vascular. Such bleeding can obscure the tumor boundaries making macroscopic determination of complete resection challenging at times. Multiple studies now advocate en bloc resection as an alternative surgical technique to piecemeal resection. En bloc resection involves circumferential dissection of the tumor capsule along the brain-tumor interface. This technique allows continuous visualization of the tumor borders during resection and avoids spillage of tumor contents into the surrounding brain parenchyma. Additionally, the surrounding white matter is typically hypovascular, minimizing blood in the surgical field. Recent data support this technique as both feasible and safe, even when the lesion involves or is adjacent to functional (eloquent) cortex [23]. The clinical value of en bloc resection was demonstrated by a study at The University of Texas M.D. Anderson Cancer Center (M.D. Anderson) that included 570 surgical patients who underwent surgical resection of a single brain metastasis (without postoperative WBRT). The authors aimed to determine predictors of local recurrence (LR) after GTR. In this study, the overall incidence of local recurrence was 15%. Their analysis indicated that larger tumors (>9.7 cm^3) and those undergoing piecemeal resection carried a significantly higher risk of local recurrence. Specifically, patients who underwent piecemeal resection were 1.7 times more likely to develop LR than those with tumors resected in an en bloc fashion [24]. This same group reported the impact of resection technique on posterior fossa metastases. The posterior fossa is of special interest, since metastases to this region have been considered to predispose to the development of leptomeningeal disease (LMD) owing to the proximity of cerebrospinal fluid spaces. Two hundred and sixty surgically treated posterior fossa metastases were included in this study, 123 of which were resected in an en bloc fashion. Overall, GTR was achieved in 96% of patients, and 10% of patients developed LMD (n = 26/260). Multivariate analysis demonstrated that piecemeal resection was significantly associated with increased risk of LMD. Specifically, of the patients undergoing en bloc resection only 5.7% developed LMD compared with 13.9% of piecemeal resection patients [25].

To expand on the role of aggressive surgical resection, the concept of supramarginal resection has emerged in response to the mounting data challenging the classic notion that brain metastases have well-defined borders. An autopsy study involving immunohistochemical analysis of 76 brain metastases reported that only 37% of brain metastases showed sharp demarcation from the surrounding cortex whereas 63% displayed evidence of infiltration of adjacent brain parenchyma [20]. A later autopsy study of 57 cases designated three patterns of invasiveness in brain metastases. Even though “well-demarcated” growth was the most common pattern (51%), one-third of the cases (32%) were categorized as “diffusely infiltrating.” Furthermore, a third group, designated “vascular co-option,” comprised 18% and was characterized by perivascular protrusion of tumor cells into the surrounding cortex [26]. Clinical studies corroborate these autopsy findings. In a prospective study of 39 patients, biopsies were taken from the surgical resection cavity after GTR, and were analyzed. An average of three biopsies were taken per patient, and 64% of patients demonstrated infiltrative tumor cells extending beyond the glial tumor pseudo-capsule in at least one biopsy site [27]. With these data in mind, recent surgical series have investigated the feasibility and efficacy of supramarginal resection. Yoo et al. [22] examined the outcome of supramarginal resection for brain metastases. For this study, the authors made a distinction between conventional GTR and “microscopic total resection” (MTR). MTR was achieved by microscopic removal of the mass followed by suctioning of an additional surrounding cortex to a depth of 5 mm (confirmed by intraoperative navigation and manual measurement). Clean surgical margins were then confirmed with cavity biopsies sent for frozen section. A total of 94 patients were included in this study (43 MTR; 51 GTR), with a mean follow-up of 12.8 months. Multivariate analysis showed that MTR was associated with a statistically significant decrease in risk of local recurrence compared with GTR (23 vs. 43%) [22]. Even though this particular study only included lesions in non-eloquent cortex, supramarginal resection has also been shown to be possible in eloquent cortex [21, 28]. Kamp et al. reported the neurological outcome of 34 patients undergoing supramarginal resection for lesions located in anatomically eloquent cortex. The authors reported that 15% of patients experienced temporary new or worsening neurological deficits; however, all new or worsened post-operative deficits eventually resolved by follow-up evaluation (mean follow-up time 16 months) [28].

The benefit of aggressive surgical resection is diminished if it creates new detrimental neurological deficits postoperatively, which can reduce overall functional status, significantly impair quality of life, and increase the risk of medical complications. To make surgical resection both safe and effective, particularly in eloquent cortex, the use of surgical adjuncts is critical (especially intraoperative mapping). Most data regarding the benefit of intraoperative mapping have been reported for the resection of gliomas; however, the same surgical principles apply for brain metastases located in functional regions (i.e., speech or motor areas). Preoperative evaluation is routinely performed to detect the presence of functional deficits. Furthermore, preoperative functional imaging is highly valued in the evaluation in patients with lesions in precarious locations. Functional MRI, diffusion tensor imaging (DTI), tractography and transcranial magnetic stimulation (TMS) are examples of technologies that use non-invasive methods to define eloquent regions, ascertain their relationship to the lesion of interest, and enhance preoperative planning. Even though the benefit of these imaging modalities is clear, the gold standard for surgery within eloquent cortex remains intraoperative mapping for real-time information regarding proximity to critical structures.

For lesions located close to the motor cortex (posterior frontal lobe/precentral gyrus) or the deep subcortical motor tracts (corticospinal tract), intraoperative mapping is the standard. Intraoperatively, localization of motor cortex can be confirmed by placement of a grid electrode on the cortical surface (Fig. 4). Once its location is confirmed, this region can be protected during resection. Subcortical motor fibers can be localized using direct stimulation with a bipolar or monopolar electrode. Once the positions of these tracts are identified, resection can be alternated with motor stimulation, so the surgeon remains aware of the location of these tracts at all times during resection. The benefit of intraoperative mapping has been reported for the resection of brain metastases. A surgical series consisting of 33 patients with lesions in proximity to the motor cortex described favorable outcomes utilizing mapping techniques. In this report, GTR was achieved in 94% of patients (31/33). Postoperatively, six patients (18%) experienced worsening neurological symptoms, but all patients had recovered by their 3-month follow-up visit [29].

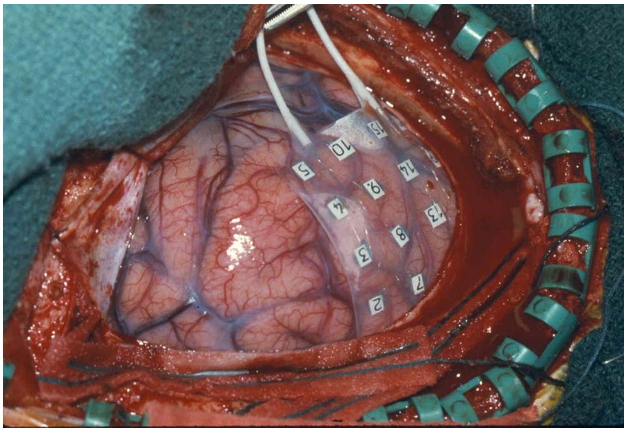

Fig. 4 Intraoperative photograph of motor mapping, with an electrode grid placed on the cortical surface of the brain. This can be used either for recording potentials from peripheral nerve stimulation (somatosensory evoked potentials), or for stimulating the cortex with the resulting electrical activity captured peripherally by electromyography

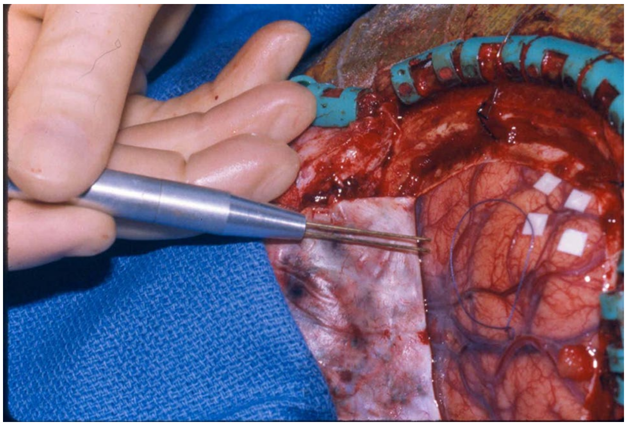

Fig. 5 Intraoperative photograph of speech mapping, with a bipolar electrode being used to stimulate the cortical surface of the brain while the patient is awake and talking

Unlike motor mapping, which can be performed with the patient under general anesthesia, intraoperative language mapping is done with the patient awake. After surgical exposure of the cortex in proximity to or involving the tumor, a current-generating bipolar electrode is used to stimulate the cortex of interest (Fig. 5). Language mapping is performed while the patient is asked to complete a variety of verbal tasks. The cortex is stimulated during these tasks, and areas of speech arrest are marked and carefully avoided during resection. Kamp et al. [21] retrospectively analyzed the outcome of 19 patients who underwent awake craniotomy for resection for metastases in eloquent cortex. In this series, 16% of patients experienced transient deficits after surgery, but none had permanent deficits.

Radiosurgery

Stereotactic radiosurgery (SRS) is a specialized radiation technique in which a targeted dose of radiation is delivered to one or more intracranial lesions with high precision. This treatment can be administered in single or multiple fractions, depending on the system used for delivery. Three types of devices have commonly been used for delivering radiosurgery: the multisource cobalt-60 unit known as the Gamma Knife, specially modified linear accelerators (LINAC-based devices, e.g., CyberKnife, TrueBeam), or charged-particle (e.g., proton beam) irradiators [30]. Multiple studies have confirmed the efficacy of SRS as a sole modality, particularly for the treatment of smaller lesions (<3 cm in maximal diameter). Hasegawa et al. [31] reviewed the outcomes of 172 patients with brain metastases managed with radiosurgery alone. The authors reported an overall median survival time of 8 months. However, the median survival times in patients with no evidence of primary tumor disease or stable disease were 13 and 11 months, respectively. In both univariate and multivariate analyses, only tumor volume was a significant predictor of tumor control. For lesions with tumor volumes <4 cm^3, local control rates were 84 and 77% at 1 and 2 years, respectively. However, in metastases of ≥4 cm^3, the local control rate was 49% at 1 or 2 years [31]. The impact of tumor volume on local control was also shown in a retrospective analysis of 103 melanoma patients who underwent LINAC-based SRS. Sixty-one patients (59%) had a single brain metastasis at presentation. Among the patients treated with SRS alone, the 1-year local control rate for patients with tumors ≤2 cm^3 was 75% compared with tumors >2 cm^3, which had a control rate of 42% [32]. In addition to being effective for appropriately-sized lesions, SRS has the advantage of being minimally invasive, which makes it ideal for patients with multiple medical morbidities or coagulopathy issues. This therapy can be used in lesions are that are not surgically accessible [33, 34], it can be performed on an outpatient basis, and multiple lesions can be treated simultaneously.

Post-resection SRS

In addition to upfront treatment, SRS is also now being considered adjuvant therapy in lieu of WBRT. Post-resection, it is well accepted that irradiation is required to reduce local recurrence, but as mentioned previously, WBRT can be associated with potential toxicities. With the strong evidence of local control after SRS coupled with persistent evidence for the advantages of surgical resection, multiple groups have investigated the utility of administering SRS to the post-resection cavity have emerged, with encouraging results [35–40]. Jensen et al. [37] retrospectively reviewed the outcome of SRS in 112 resection cavities in 106 patients with brain metastases. This series specifically reviewed patients in whom SRS was used an adjuvant to surgical resection in place of WBRT. GTR was obtained in 96% of cases. The median time from surgery to SRS was 24 days. The median overall survival time was 10.9 months, and the local control rate was 80%. On multivariate analysis, lesions >3 cm in maximal diameter was predictive of local treatment failure. These patients had 13.6 times increased risk of treatment failure compared with those patients who had lesions that were ≤3 cm [37]. Robbins et al. [39] reviewed 85 patients over 11 years in whom surgical resection cavities were treated with SRS alone, adding a 2–3 mm-margin to the cavity when planning the treatment volume. Local control was 81% at 1 year and 76% at 2 years, and only 35% of these patients needed salvage WBRT treatment [39]. Brennan et al. [41] published the first prospective study of post-resection SRS, and again showed good local control of lesions treated with SRS after surgery. Risk factors for local failure included tumors ≥3 cm in maximal diameter and lesions with dural involvement. The impact of tumor size on risk of local recurrence has also been demonstrated in additional studies [42]. The timing of post-resection SRS can also affect rate of local recurrence: SRS administered more than 3 weeks after surgery is associated with higher rates of local recurrence [43]. A prospective, randomized trial has recently been completed at M.D. Anderson (NCT00950001) that evaluated the efficacy of post-resection SRS. These authors reported that post-resection SRS significantly lowered the incidence of local recurrence compared to observation alone. This suggests that SRS is valuable potential alterative to adjuvant WBRT [44].

Pre-resection SRS

The novel concept of neoadjuvant (pre-resection SRS) has recently been introduced. One of the reported challenges of postoperative SRS is clear target definition after surgical resection. Neoadjuvant SRS offers the advantage of delivering radiotherapy prior to surgical manipulation and theoretically of reducing intraoperative spread of tumor cells. Additionally, this approach allows for a target with an intact blood supply, which is thought to confer a therapeutic advantage [45]. It has been hypothesized that pre-resection SRS may restrict tumor cell dissemination during surgery by preoperative sterilization of the operative field [46]. Additionally, it is hypothesized that tumors may be more radioresponsive because the target is not a hypoxic tumor bed. Asher et al. [45] presented the first series employing use of SRS prior to surgical resection. They reported this technique to be safe and effective, with rates of local control at 12 and 24 months of 86 and 72%, respectively. Local control was also high even with lesions >3 cm, which had previously consistently been shown to have worse outcomes following SRS. Patel et al. [46] compared 180 patients at two institutions; 66 had SRS to of the lesion followed by resection (pre-resection SRS) within 48 h, and 114 had SRS after resection. These investigators demonstrated similar rates of local control, distal recurrence, and overall survival between the two treatment arms. Interestingly, pre-operative SRS was associated with significantly lower rates of symptomatic radiation necrosis and LMD.

Multiple brain metastases

Surgery

More than 50% of patients with brain metastases present with multiple brain metastases [47]. Whereas the role of surgical resection for single metastasis is well established, the indications for surgery in the setting of multiple brain metastases are less well defined. There are no randomized or prospective studies regarding the survival benefit of surgery in the setting of multiple brain metastases. Regardless, with the improvement of therapeutic options for systemic cancer and more patients surviving with higher functional status, aggressive surgical resection is at times undertaken. In patients with multiple brain metastases, resection may be beneficial for symptomatic relief, especially in patients with a large dominant lesion. Additionally, if technically feasible the best outcome is obtained when all lesions can be resected. Of course, this approach is only be considered in the setting of limited intracranial disease, based on the findings of several retrospective studies. A landmark study by Bindal et al. highlighted the survival benefit for patients with multiple brain metastases when all lesions are successfully removed [48] (Fig. 6). This study included 56 patients, all of whom underwent resection for multiple brain metastases. Thirty patients had one or more lesions left unresected (Group A) and 26 had all lesions resected (Group B). Postoperatively, symptoms improved in 65% of patients in Group A compared with 83% in Group B. Moreover, the survival of patients who had all lesions resected was significantly longer than in patients who had residual lesions (14 vs. 6 months, respectively). Schackert et al., [47] reviewed the surgical outcome of 127 patients with multiple brain metastases. The majority of patients had one lesion resected (49%), while 38, 12, and 1.6% had two, three, and four lesions resected, respectively. Predictors of survival were preoperative KPS and RPA classification, as expected. Patients who had resection of all lesions had prolonged survival compared with patients with residual lesions (10.6 vs. 5.8 months), but this result did not reach statistical significance. Moreover, the survival of patients with four or more metastases was significantly shorter (3.3 months) than in patients with less than four lesions (7.8 months). In summary, some data do support resection in the face of multiple metastases, but prospective studies are needed to better define patient indications for surgery.

Radiosurgery

In patients with multiple smaller brain metastases, radiation treatment options are favored over surgical resection. Historically, patients with more than four metastases have been treated with WBRT. However, the neurocognitive effects of WBRT have become an important issue. Chang et al. [49] highlighted such effects in a study in which patients with 1–3 newly diagnosed brain metastases were randomly assigned to receive SRS with WBRT versus SRS alone. Patients who received WBRT were more likely to show a decline in learning and memory function (with a mean probability of decline of 52% compared with 24% in those not receiving WBRT).

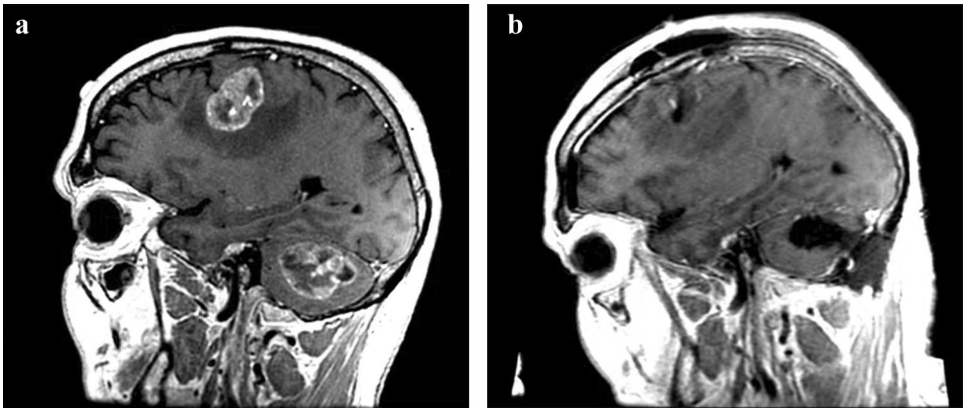

Fig. 6 62-year-old male with a history of non-small cell lung cancer. **a** T1-weighted gadolinium-enhanced magnetic resonance (MR) images in the sagittal plane showed two heterogeneously enhancing lesions, one in the left frontal lobe and one in the cerebellum **b** T1-weighted gadolinium-enhanced images post-resection showing gross total resection of both lesions

Multiple retrospective studies have reported reasonable outcomes in patients treated with SRS for four or more brain lesions [50, 51]. Raldow et al. [52] performed a retrospective analysis of 103 patients treated with SRS for >5 brain metastases, including 61 patients who were previously treated with WBRT (n = 34), SRS (n = 12), or both (n = 15). The median survival time for the whole cohort was 8.3 months. It is important to note that the number of brain metastases (5–9 vs. 10+) was not a significant predictor of survival in this study, and KPS score was the only significant predictor on multivariate analysis [52]. A recent study analyzing 243 patients treated with SRS compared the outcome of patients with 1–4 lesions versus 5+ lesions [53]. Similarly, they reported no statistically significant difference in survival between the two groups of patients. In light of these results, patients with higher numbers of lesions are being treated with SRS alone.

Recurrent brain metastases

Despite maximal therapy, brain metastases often recur locally and distantly, requiring further intervention. As systemic cancer control options increase, such as targeted therapy and immunotherapy improve [54, 55], the subset of patients battling only CNS disease may increase with time. The challenge is that most patients with recurrent lesions have already undergone extensive treatment (i.e., surgery, SRS, and/or WBRT), limiting additional therapeutic options. Moreover, no prospective randomized trials have thus far determined the ideal treatment for this patient population.

Surgery

Surgery can be considered for local or distant recurrences that are large and symptomatic. An earlier study investigated the role of surgery in the treatment of recurrent brain metastasis and analyzed the surgical outcome of 48 patients [56]. All patients had previous surgery for brain metastasis and the majority (65%) had previous adjuvant WBRT. In this patient cohort surgery was well tolerated, with no postoperative mortalities reported. The authors reported that a notable portion of patients (75%) symptomatically improved following re-resection, and the overall median survival time was 11.5 months after reoperation [56]. Factors significantly associated with decreased survival on multivariate analysis were: uncontrolled systemic disease; a preoperative KPS score of <70; and a time to recurrence of <4 months. The authors concluded that patients with good functional status and well-controlled disease should be considered for re-resection. A more recent retrospective analysis [47] reported the outcome of 67 patients with recurrent brain lesions. All patients had surgery as a component of their upfront treatment. GTR was achieved in most patients with single metastases (31/41). The overall median survival time was 7.5 months. Multivariate analysis indicated that RPA class I and time-to-recurrence were significant predictors of patient survival. Regarding the latter, in patients whose recurrence occurred within 200 days of resection, the median survival time was 6 months compared with patients who recurred after 200 days (9.2 months). Hence, surgery is a feasible option in carefully selected patients with intracranial tumor recurrence [47].

Laser interstitial thermal therapy (LITT)

LITT is a relatively new technology that has gained interest for the management of brain metastases that are: (1) refractory to standard-of-care treatment, (2) in surgically inaccessible locations, or (3) in patients who cannot tolerate an open craniotomy. LITT is based on the thermal dose model, wherein there is a relationship between temperature, duration of exposure, and resulting tissue damage. Laser electromagnetic radiation is focused energy that is transformed into thermal energy, which spreads to adjacent tissues to induce coagulation [57]. The goal of LITT is to deliver enough thermal damage to tumor cells to induce necrosis and cell death, while simultaneously avoiding damage to surrounding normal tissues. Energy is transmitted via optic quartz fibers, which are flexible and heat-resistant, allowing efficient transmission to the tissues [57]. The laser is introduced into the lesion of interest via an optical probe, <1 mm in diameter, with approximately 1 cm of laser tip exposed [58]. There are two systems currently used for LITT in the U.S. Both are placed with stereotactic navigation and are compatible with MRI systems and head frames [59].

In this procedure, a small drill is used to penetrate the skull, and the apparatus is secured to the skull to maintain accuracy in triangulation of navigation. The laser probe is advanced to the target while the surgeon monitors its location in real-time on the navigation screen. Once the tip of the probe is at the target, an image is obtained to verify accuracy [58, 60, 61]. The laser is heated, with MR thermography simultaneously used to monitor temperature and heat spread [62]. On a computer workstation, heat maps are presented that display temperature-dependent colors (Fig. 7). The longer the tissues are exposed to thermal energy, the larger the area of damage [60]. This treatment requires close attention by the surgeon to the real-time MR heat map overlaid onto the lesion of interest. It is imperative that no surrounding normal tissue be exposed to enough heat to result in permanent damage. Once the lesion has been sufficiently exposed, the laser is manually shut off. For large or irregular tumors, the probe is repositioned (withdrawn, advanced, or turned) or a side fire probe is used to cover additional

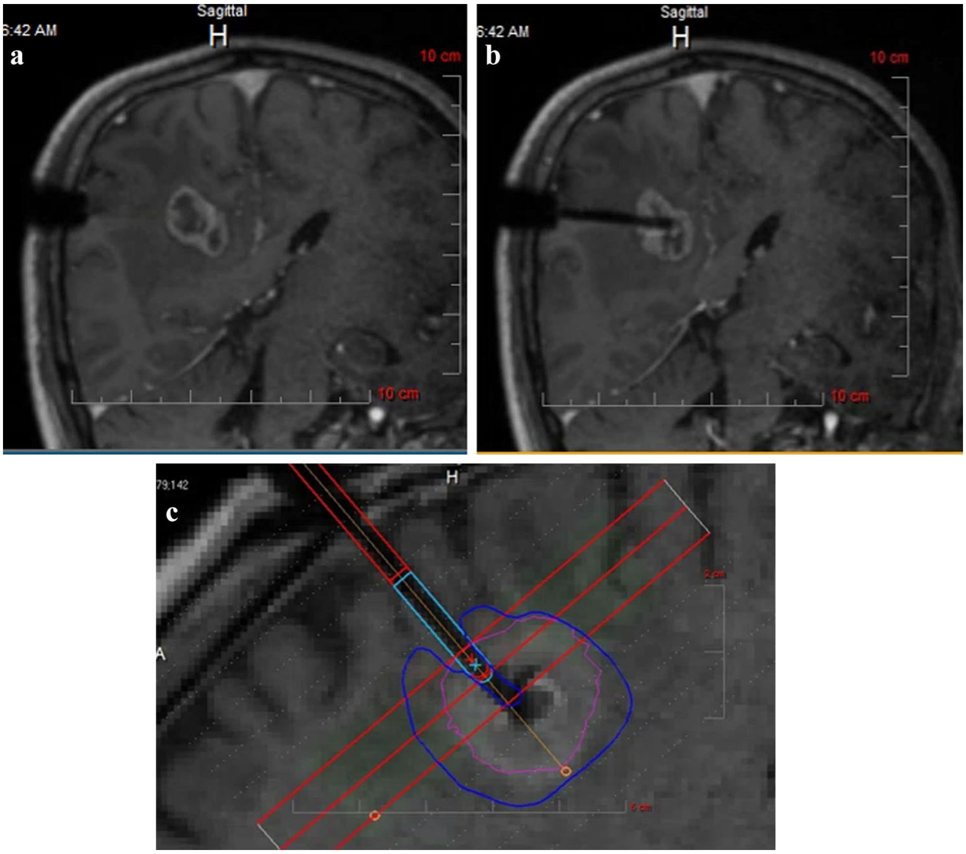

Fig. 7 Laser interstitial thermal therapy (LITT). **a** Intraoperative surveillance of LITT using magnetic resonance (MR) imaging. **b** MR image after placement of the laser electrode. **c** Representative heat maps during treatment

volume. The process is repeated until a maximal safe volume of the lesion has been exposed to fatal thermal energy [63].

Most clinical data for LITT come from treating patients with glioblastoma, and the technique has been demonstrated to be safe when surgical resection is not possible and radiation options have been exhausted [64–67]. Carpentier et al. performed the first pilot study evaluating the safety and feasibility of LITT in focal metastatic brain tumors at a single treatment center. Six patients underwent LITT and, with the exception of one patient who was hospitalized prior to treatment, all patients left within 24 h and experienced no adverse effects [68]. This study was intended as a feasibility study and did not report long-term tumor control. However, a follow-up study reported the long-term results in 2011 [69]. Fifteen treatments were performed on seven patients, with follow-up intervals up to 2 years. The median survival time was 17 months, which exceeded the prognosis at the time of patient enrollment. Lesions initially increased but subsequently demonstrated a steady decrease in size, with the treated metastases eventually becoming undetectable [69]. Although formal studies of the efficacy of LITT are ongoing, case reports and case series are promising [70]. Rao et al. monitored 15 patients after LITT for lesions that had progressed on imaging after SRS [71]. These lesions were presumed to have originated from either from recurrence or from radiation necrosis. At a median follow-up time of 6 months, local control was achieved in 75% of patients. The overall survival rate was 57%, and the progression-free survival time was 37.8 weeks. One drawback of this study is that tissue diagnosis was not obtained in all patients, and radiation necrosis was not distinguished from recurrence. This conundrum is often encountered in clinical practice and underscores that the decision to operate on a recurrent lesion remains a difficult one. This study is significant in that it showed a decrease in lesion size regardless of pathology, i.e., tumor recurrence or necrosis [71]. Torres-Reveron et al. treated six patients with metastatic lesions that had recurred after SRS [72]. They employed PET or MRI spectroscopy to select patients with findings suggestive of disease recurrence rather than radiation necrosis. All patients had uncomplicated procedures and were discharged within 48 h. All patients in this analysis demonstrated a decrease in size of the lesion at 2 weeks. Ali et al. reviewed 26 metastases across four institutions [73]. Although there was significant heterogeneity in the primary cancer pathology, degree of lesion covered by the laser, and subsequent treatment (i.e., adjuvant hypofractionated SRS), this review suggested that ablation of >80% of the metastatic tumor volume is associated with decreased risk of disease progression. Overall, many studies have shown LITT to be feasible and safe. Though not statistically powered to evaluate efficacy, preliminary data suggest that LITT is effective in treating tumors that are resistant to current therapies, that recur despite aggressive therapies, or that are not accessible by current surgical options. It remains to be seen whether LITT is as effective as the current standard of first-line interventions. Further prospective studies are continuing to determine the efficacy and indications for this evolving therapy [74].

Radiosurgery

In the circumstance of recurrent disease, where surgical options are not advisable or feasible, patients can be treated with WBRT. However, the use of this treatment is controversial due to concerns of neurotoxicity and cognitive side effects in patients whose metastatic intracranial burden may already predispose them to cognitive decline. Additionally, the median survival time after re-irradiation is reported to be very modest (3–5 months) [75–77]. In light of this, the efficacy of salvage SRS in the setting of recurrent metastasis has been reported in the literature [78–80]. A retrospective study including 111 patients treated with salvage SRS after previous WBRT reported a favorable outcome. Specifically, the median survival time was 9.9 months, and the 1-year local control rate was 68%. Interestingly, in patients who had recurrence <6 months after the initial treatment, the median survival time was 6.8 months relative to 12.3 months in patients who had recurrence more than 6 months after treatment. This treatment was well tolerated, with limited reported toxicity [78]. Overall, use of salvage SRS in the setting of previous WBRT seems reasonable in patients with limited treatment options.

Conclusion

In the contemporary management of metastatic cancer, brain metastasis is a challenging issue and carries a poor prognosis. Despite these factors, concepts in the management of this clinical problem are advancing, and tailored, multimodal therapy has become standard of care. The role of surgery in managing brain metastases is well accepted, particularly for single metastses, and it is likely to continue as a cornerstone of therapy. Further prospective studies are needed to define better the role of surgery for multiple metastases and the role of LITT for recurrent metastases and potentially as an upfront treatment modality.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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