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Review

Surgical treatment of brain metastasis: A review

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ABSTRACT

Brain metastasis is the most common intracranial tumor in adults. Currently, treatment of brain metastasis requires multidisciplinary approach tailored for each individual patient. Surgery has an indispensible role in relieving intracranial mass effect, improving neurological status and survival while providing or confirming neuropathological diagnosis with low mortality and morbidity rates. Besides the resection of a single brain metastasis in patients with accessible lesions, good functional status, and absent/controlled extracranial disease; surgery is proven to play a role in management of multiple metastases. Surgical technique has an impact on the outcome since piecemeal resection rather than *en bloc* resection and leaving infiltrative zone behind around resection cavity may have a negative influence on local control. Best local control of brain metastasis can be accomplished with optimal surgical resection involving current armamentarium of preoperative structural and functional imaging, intraoperative neuromonitoring, and advanced microneurosurgical techniques; followed by adjunct therapies like stereotactic radiosurgery, whole brain radiotherapy, or intracavitary therapies. Here, treatment options for brain metastasis are discussed with controversies about surgery.

Contents

1. Introduction

Brain metastasis is the most common intracranial tumor in adults and the incidence of brain metastasis is believed to be increasing due to improved imaging techniques with an increased ability to detect smaller tumors, and improvement in the treatment of many tumors leading to prolonged survival [1,2]. In adults, lung cancer is the main cause of brain metastasis (50–60%), followed by breast cancer (15–20%) and melanoma (5–10%) respectively [3]. The treatment algorithm for brain metastasis is changing depending on factors such as primary histology and other clinical characteristics of patients as well as available therapeutics options in each clinic. However, surgery continues to play a significant role in management of patients with brain metastasis and here, the controversies regarding surgical management for brain metastasis are discussed with the review of the current literature.

1.1. Indications

The resection of a single brain metastasis is considered to be a standard option in patients with accessible lesions, good functional status, and absent/controlled extracranial disease [4–6]. According to evidence based medicine data, level I evidence supports the use of surgical resection plus post-operative WBRT (whole brain radiation therapy), as compared to WBRT alone in patients with good performance status (functionally independent and spending less than 50% of time in bed) and limited extra-cranial disease [7]. The hallmark study conducted by Patchell and colleagues [8]

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randomized 48 patients with single brain metastases to surgery and WBRT (25 patients) compared with WBRT alone (23 patients) and evaluated local recurrence and survival rates. In this study, the addition of surgery reduced the local recurrence in these patients from 52 to 20% and improved median survival from 15 to 40 weeks, and lengthened functional independence (8 weeks to 38 weeks); all results were significantly different. Similar results for 63 patients with a Karnofsky Performance Score (KPS) score of $\geq$50 were reported by Vecht et al. [9] who noted that the improvement in median survival (12 months vs. 7 months) applied only to patients with stable extracranial disease. These studies showed that surgery improved the survival, local control and functional status compared to the WBRT alone.

Recent technical advances in stereotactic radiosurgery (SRS) have outnumbered patients treated with SRS compared to surgery. However, surgical resection continues to play a crucial role in the multidisciplinary management of single brain metastases. Only surgical extirpation allows the rapid debulking of a large, immediately life-threatening tumor, making it beneficial to patients with neurological signs and symptoms related to metastatic disease [10–13]. Surgery relieves mass effect and symptomatic intracranial hypertension, restores CSF flow, and lower steroid dependence through a reduction in peritumoral edema [14]. Medically uncontrollable seizures due to brain metastasis are an indication for resection, as surgery can provide seizure relief [15]. Surgical extirpation is sometimes viewed as a salvage treatment for patients with brain metastases [16–18]. Additionally, patients with improved functional status after surgery may get better outcomes with adjunct treatments. Surgical extirpation has an indispensible benefit of providing or confirming a pathological diagnosis [19,20]. Palliative surgical procedures may also be utilized in the multidisciplinary management of brain metastases. Patients who have large cystic lesions in the eloquent area with poor performance status may undergo palliative insertion of an Ommaya reservoir for cystic tumor management. Moreover, patients diagnosed with leptomeningeal metastases may get benefit from insertion of Ommaya reservoir and intrathecal/intraventricular drug delivery. Other palliative surgical interventions are for endoscopic third ventriculostomy or ventriculoperitoneal shunt procedures for patients suffering from acute hydrocephalus due to metastasis to the mesencephalic aqueduct, brainstem, or cerebellum, and those with obstructed cerebrospinal fluid (CSF) absorption resulting from carcinomatous meningitis. Those palliative procedures may ameliorate impaired consciousness and improve neurological status of patients [21,22].

Surgical decision is first made depending on patients' clinical situation. Surgery is often used in patients with Recursive Partitioning Analysis (RPA) class I/II, a single metastasis, and a minimal or controlled systemic tumor. These patients are also good candidates for SRS, too. The patient must be medically suitable for both surgery and recovery before proceeding with resection, and the disease prognosis should be amenable to benefit from local CNS tumor control. Since the cause of death in cancer patients with brain metastases has been reported to be exacerbation of the primary lesion in 50%, and neural death due to brain metastases or leptomeningeal metastases in 30% [23], surgical candidates are expected to have at least 6 months of survival [21]. However patients having expected survival less than 6 months may not necessarily lose the possibility of getting surgical benefits. By and large, surgical mortality is around 0.7–1.9% and neurological morbidity is 3.9–6%. Systemic complications, including pneumonia, urinary infection, and venous thrombosis, occur in 13.9% of the patients [21,24,25].

Patients with brain metastases often have rapidly progressing neurologic symptoms, necessitating rapid determination of optimal therapeutic strategies. Surgical treatment is highly helpful for patients with a single metastasis measuring 3 cm or more, with cerebellar neoplasms, with tumors associated with severe cerebral edema, or those with multiple tumors with advanced neurologic symptoms [21]. Cerebellar metastases represent a special group of brain metastases because they may cause obstructive hydrocephalus and brain stem compression, and survival of patients with cerebellar metastases has been reported as more disappointing than that reported for cerebral hemispheric metastases. However, surgical resection provides a significant benefit in cerebellar metastases. In Yoshida and Takahashi's study, 38 patients with cerebellar metastases underwent surgical resection alone; their median survival was 20.5 months. In the 27 patients who underwent surgical resection plus radiation, the median survival was 35.5 months. For 21 patients who underwent WBRT without surgical resection, the median survival was 6.5 months and for those who were treated with SRS alone, 9.1 months [26].

The level I evidence supports the role of surgery in patients with single brain metastasis, particularly for RPA class I patients. In most patients with single metastasis, surgical resection improves neurological status and provides survival benefit, with acceptable morbidity and mortality rates.

1.2. Technique of surgery and significance of tumor infiltration

The aim of surgery in treating brain metastasis is to lengthen the survival time of patients while improving neurological conditions and performance status [21]. Surgical planning commonly involves detailed preoperative structural and functional imaging. Utilization of intraoperative image guidance, microsurgical techniques, perioperative neurologic monitoring reduces possibility of surgery related mortality and morbidity. Advances in current applications in surgery allow for accurate localization of the tumor before surgery to reduce the required craniotomy size, to avert injury to normal brain tissue, and to minimize searching for the tumor during surgery [25,27–30]. In most cases, the primary goal of surgery is gross-total resection of the tumor with minimal disruption of, or injury to, the brain. In some cases, the additional goals of debulking and relief of mass effect are considered. Data from a retrospective review performed by Korinth et al. [31] showed that the early postoperative KPS score was improved in 59% of patients, unchanged in 32%, and worse in 9% in patients who had undergone microsurgical tumor removal between 1989 and 1996; even before the current improvements in surgical armamentarium have taken place.

Control of local disease is crucial in management of brain metastasis. Patel et al. [32] found that two variables significantly associated with the incidence of local recurrence; namely the preoperative tumor volume and the method of resection. Larger tumors (with a volume of at least 9.71 cm^3) were associated with a significantly higher incidence of local recurrence. Resection of the tumor in a piecemeal fashion significantly increased the incidence of local recurrence in comparison with *en bloc* resection. However, they underscored that in certain situations piecemeal resection was inevitable, such as densely adherent or infiltrating tumors or extremely friable tumors. Tumor location in eloquent brain is an obstacle for *en bloc* resection. For tumors located within or near eloquent cortex, partial resection can easily be justified rather than risking the deterioration of neurological and performance status due to total resection, and radiotherapy should be used to address possible residual tumor [32]. *En bloc* resection is particularly instrumental during resection of posterior fossa metastases. A recent retrospective study from MD Anderson Cancer Center [33] on 379 patients with posterior fossa metastases, who underwent either surgery or radiosurgery, revealed a significant increase of leptomeningeal in patients in whom the tumor was removed via a piecemeal approach (13.8%) compared with an *en-bloc* resection (5.6%).

Notwithstanding, complete removal has been confirmed on immediate postoperative MR imaging, a local recurrence frequently has been observed in the surgical bed. The reported local recurrence rate in the surgical bed following complete resection together with postoperative radiotherapy is 10–34% at 1 year after treatment [34–39]. Neuropathological studies have shown that infiltration may produce clinically undetectable cancer cell islands and that the capacity for this infiltration may vary with different histological tumor types, with aggressive tumors showing a maximum infiltration depth of 1–3 mm [40,41]. Considering significance of tumor infiltration on local recurrence, Yoo et al. [42] evaluated the role of "microscopic total resection", which was the removal of the tumor mass and also the infiltrating microscopic tumor cells within apparently normal-looking surrounding brain tissue within ~5 mm area by using an ultrasonic aspirator; and compared the results with radiologically gross total resections. The microscopic total resection group had better local control of the tumor than did the gross total resection group (The 1- and 2-year respective local recurrence rates were 29.1 and 29.1% in the microscopic total resection group and 58.6 and 63.2% in the gross total resection group). Interestingly, there was no significant difference in the local recurrence rate between the microscopic total resection group without radiotherapy (30.3%) and the gross total resection group with postoperative radiotherapy (26.3%). This study suggests that microscopic total resection can be performed to remove infiltrating cells around tumor mass to reduce local recurrence where achievable.

1.3. Local control after resection

The majority of patients with brain metastasis die of extracranial disease progression, whereas those with uncontrolled brain metastases more often die of neurological causes. Death due to a neurological cause alone is around 15% in the surgically treated patients. Therefore, achieving local control is of primary importance when considering treatment options in patients with brain metastases [5,43–45].

In 1998, Patchell et al. [36] investigated the benefit of using WBRT as an adjunctive therapy following surgical tumor removal in these patients. The study randomized 95 patients to surgery alone or surgery plus WBRT. Progression of intracranial disease was fourfold greater in the surgery-alone group (70% compared with 18%), and local recurrence was also higher in this group (46% compared with 10%). Median survival time was not found to be significantly different in this study with an overall time of 10.8 months for surgery alone compared with 12.0 months for WBRT plus surgery although this study was not powered to detect a significant difference in survival. These data support the use of WBRT with surgery for improvement in local control and prevention of recurrence/progression.

Despite WBRT, local progression/recurrence may occur. The use of SRS to the resection cavity as an alternative to WBRT has also been investigated for improving local control. A study by Kim et al. [46] retrospectively evaluated 79 patients who received gamma knife surgery to the resection cavity after progression of brain metastasis with WBRT. Although no survival benefit was shown, 94.9% of patients receiving SRS achieved local disease control. Solty et al. [47] evaluated the role of SRS to the tumor bed, deferring WBRT after resection of a brain metastasis. Actuarial local control rates were 88% and 79% at 6 and 12 months, respectively with an overall 14% local failure rate. This value compares favorably with historic results with observation alone (54%) and postoperative WBRT (80–90%). In this study, the authors recommended inclusion of a 2 mm margin around the resection cavity. However when the inclusion of a 2-mm margin was retrospectively evaluated for 93 patients with a single metastasis undergoing SRS for an unresected metastasis in another study, higher rates of severe complications were reported and the authors emphasized the significance of resection before SRS [48]. Quigley and Karlovits [49] reported their results on patients with up to four intracranial metastases treated with resection followed by SRS to the resection cavity or SRS alone. The lesions were <3 cm and the median dose was 16 Gy. The mean survival was better for the patients who had undergone resection plus SRS at 19.6 months than for those treated with SRS alone at 10.3 months. Lesions treated with surgery and SRS had a local failure rate of 5.8%. Karlovits et al. [50] later showed that 7.7% local recurrence rate in patients receiving SRS to the resection cavity and concluded that controlled extracranial disease and solitary metastasis were associated with a better survival. Do et al. [51] showed 12% overall local recurrence after SRS or stereotactic radiotherapy. Jagannathan et al. [20] demonstrated local tumor control at the site of the surgical cavity as 94%. The authors noted that tumor recurrence at the surgical site was statistically related to the volume of the surgical cavity as larger resection cavities tended to have a higher treatment failure rate. They recommended preferring WBRT for extremely large resection cavity volume or indistinct cavity margins. Iwai et al. [52] emphasized the significance of radiosurgical dose which should be higher than 18 Gy to be effective. Mathieu et al.'s study [53] disclosed similar results with 27% local failure at a median follow-up period of 13 months and the median survival was 13 months after radiosurgery. The use of adjuvant SRS to the operative bed following resection of intracranial metastases results in a local intracranial recurrence rate equivalent to that achieved with adjuvant WBRT. Roberge et al. [54] administered SRS to resection cavity after WBRT to decrease the local recurrence rates. In addition to the 30 Gy in 10 daily fractions, 10 Gy radiosurgery dose was delivered to the resection cavity margins. They achieved a 94% local control at 2 years. Above mentioned studies were summarized in Table 1.

Main purpose of SRS administration to resection cavity is to prevent potential long-term neurotoxicity caused by WBRT. However, proponents of WBRT claimed that neurocognitive deterioration is linked to late tumor progression rather than to the adverse effects of WBRT [36,55,56]. On the other hand, Aoyama et al. showed no difference in deaths from neurological causes at 1 year in a phase III randomized trial comparing the combination of SRS and upfront WBRT to SRS alone but later a greater decline in neurocognitive function at 3 years was recognized in patients receiving WBRT with SRS vs. those receiving SRS alone [57,58]. The EORTC 22952-26001 study assessing the role of adjuvant WBRT vs. observation after SRS or resection of 1–3 brain metastases showed that intracranial progression was significantly more frequent in the observation arm (78%) than in the WBRT arm (48%). After surgery, at 2 years, WBRT reduced the probability of relapse at initial sites from 59% to 27%. After radiosurgery, at 2 years, WBRT reduced the probability of relapse at initial sites from 31% to 19%. At 2 years, 22.3% and 22.6% of the patients were alive and functionally independent in the observation and WBRT arms, respectively, there was no significant difference. Neurologic death was more frequent in the observation arm. Median progression-free survival was slightly longer in patients receiving WBRT (4.6 months) compared with those on observation alone (3.4 months) but overall survival did not differ (a median survival of 10.9 months in the observation arm and 10.7 months in the WBRT arm). The authors concluded that after SRS or resection of a limited number of brain metastases, standard adjuvant WBRT reduces the probability of intracranial relapses and neurological death with no difference in a survival time with functional independence or in a prolonged overall survival time [59].

To improve local tumor control, intraoperative local chemotherapy and radiotherapy adjuncts have been utilized. Patients with

Table 1
Retrospective studies for SRS applied to tumor resection cavities.

Author (year)	Type of study	Number of patients	Method	Dose isodose	Local recurrence	Time to progression/ recurrence	Survival
Kim et al. (2006) [46]	Retrospective	79	Failed WBRT-progression-resection-SRS to resection cavity	18 Gy 50% isodose	5.1%	6.1 mo	69.9 weeks
Karlovits et al. (2009) [50]	Retrospective	52	1–4 metastasis Solitary lesion resected	15 Gy 80–90% isodose	7.7%	Not reached	15 mo
Solty et al. (2008) [47]	Retrospective	65	1–4 metastasis 69 resection cavity	18.5 Gy	14% 0% when 2 mm margin included	NR	
Do et al. (2009) [51]	Retrospective	30	1–4 metastases 33 resection cavity	SRS 5–18 Gy SRT22–27.5 Gy in 4–6 fractions	12%	NR	12 mo
Jagannathan et al. (2009) [20]	Retrospective	106	112 resection cavity	17 Gy 50% isodose	13% at 1 year 80.3% overall	Not reached	10.9 mo
Iwai et al. (2008) [52]	Retrospective	21	Surgery + boost SRS	17 Gy 50% isodose	24%	NR	20 mo
Roberge et al. (2009) [54]	Retrospective	27	Resection + WBRT + SRS	10 Gy	2 years control 94%	NR	17.6 mo
Mathieu et al. (2008) [53]	Retrospective	40	80% complete resection 20% partial resection	16 Gy	27%	NR	13 mo

WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; NR, not reported; mo, months.

single brain metastasis underwent craniotomy and carmustine polymer wafers were placed in the tumor resection cavity; subsequently, the patients received conventional WBRT. The local recurrence rate was 0%, with 16% of patients relapsing elsewhere in the brain and 8% in the spinal cord. Median survival was 33 weeks, with 33% of patients surviving at 1 year and 25% at 2 years. The adverse events were modest. These data suggest a potential usefulness of local chemotherapy after surgical resection in reducing the risk of local relapse [60]. The Gliasite® Radiation Therapy System is an intracavitary high-activity ^{125}I brachytherapy, performed with a balloon placed in the resection cavity and filled with a radioactive solution. It delivers highly localized doses of radiation to the resection margins (60 Gy to 1 cm depth). A phase II trial in resected single brain metastases [61] has reported an overall and 1-year local control rate of 83 and 79%, respectively, with 17% of local failures. Radiation necrosis was found in 17% of patients. The median survival for patients with radiation necrosis was significantly longer than for patients without necrosis. Another retrospective study [62] has reported the results of ^{125}I brachytherapy using low-activity permanent seeds placed in the resection cavity. Local tumor control was achieved in 96% of patients, with 4% of local failures.

Local control is essential after resecting brain metastasis. All modalities show similar control rates but their evidence level has not been established yet. Surgical resection followed by WBRT represents a superior treatment modality, in terms of improving tumor control at the original site of the metastasis and in the brain overall, when compared to surgical resection alone as the only level I evidence [7].

1.4. SRS vs. surgery

SRS has been broadly applied in initial treatment, recurrence and adjuvant regiments combined with surgery or WBRT. Stereotactic radiosurgery may be justified as a first choice as its non-invasiveness, single out-patient visit, high local control rate, and low morbidity. It can be used in patients who are not surgical candidates due to medical comorbidity or advanced systemic disease and is easily applied to multiple brain metastases. However, there are some limitations and disadvantages to the use of radiosurgery for brain metastases. Stereotactic radiosurgery does not relieve the symptoms and signs of the disease caused by mass effect of tumor, edema or hydrocephalus. Moreover, there is no histopathological diagnosis of the lesion without resection. Large tumors (typically those >3 cm in diameter) may not be appropriate for radiosurgery. Stereotactic radiosurgery itself may increase the peritumoral edema [15]. Besides the advantages of the ability to confirm the diagnosis, eliminate mass effect; surgery improve tolerance to adjuvant therapy.

The effectiveness of stereotactic radiosurgery (SRS) compared to that of surgical resection has not been evaluated within a phase III randomized trial for patients with single brain metastasis. Bindal et al. [63] showed improved median (16.4 months for resection with or without WBRT vs. 7.5 months for SRS with or without WBRT; $P < 0.001$). The difference in survival was due to a higher rate of mortality from brain metastasis in the radiosurgery group than in the surgery group and the higher mortality rate found in the radiosurgery group was due to a greater progression rate of the radiosurgically treated lesions. Some authors argued later that inappropriate SRS doses as low as 12 Gy have been used in this study (median dose, 20 Gy; range, 12 Gy–22 Gy). Several studies have suggested that the results of SRS and WBRT are equivalent to surgery and WBRT in selected subsets of patients, like RPA class I, single metastasis and favorable histological status [23,64–67]. The study by Schoggl et al. [66] compared patients who underwent resection + WBRT with patients receiving WBRT + SRS for single brain metastasis. The median size of the treated lesions SRS patients was 7800 mm^3, and 12 500 mm^3 for resection group. The 1-year local control rates were 95% in the SRS group and 83% in the resection group. The 1-year survival rates were not significantly different (52% and 44%, respectively). Radioresistant tumors responded better to SRS and the authors advocated the use of SRS especially for radioresistant tumors and reserving the surgery for the larger tumors with mass effect. In another study for single brain metastasis, O'Neill et al. [64] compared 74 patients treated with resection with or without WBRT with 23 patients treated with SRS with or without WBRT. A local recurrence was observed in 58% of patients in the resection group and in none of the patients in the SRS group. The 1-year survival rates were not different. These groups differed in terms of WBRT that 18% of patients in the resection group and 4% of patients in the SRS group had not received additional WBRT. A recent study by Rades et al. [68] retrospectively compared neurosurgical resection followed by WBRT with WBRT

Table 2
Summary of studies comparing surgery with SRS in the treatment of brain metastases.

Author (year)	Method	Complete resection %	Tumor size	Median survival	Local control	Median time to local failure
Bindal et al. (1996) [63]	SRS ± WBRT	NR	1.96 cm^3	16.4	61%	
	Surgery ± WBRT	NR	NR	7.2	87%	
Schoggl et al. (2000) [66]	SRS ± WBRT	NR	7800 mm^3	52% at 1 year	95%	
	Surgery ± WBRT	NR	12 500 mm^3	44% at 1 year	83%	
O'Neill et al. (2003) [64]	SRS ± WBRT		NR	NR	100%	
	Surgery ± WBRT		NR	NR	42%	
Rades et al. (2009) [68]	SRS + WBRT		NR	61%	87%	
	Surgery + WBRT	84%	NR	53%	56%	
Roos et al. (2011) [69]	SRS + WBRT			6.2 mo	NR	3.1
	Surgery + WBRT		Tumor larger	2.8 mo	NR	1.7
Kocher et al. (2011) [59]	SRS + WBRT	100%		NR	81%	
	Surgery + WBRT		Tumor larger	NR	73%	

NR, not reported; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; mo, months.

followed by SRS in patients with a single brain metastasis. Eighty-four percent of patients in the resection + WBRT group underwent complete resection. The 1-year local control rates were 87% after WBRT + SRS group and 56% after resection + WBRT group. However, there was no significant difference in survival rates (the 1-year survival rates were 61% after WBRT + SRS and 53% after resection + WBRT). Roos et al. [69] conducted a randomized controlled study on patients harboring solitary brain metastasis and randomized into surgery + WBRT and SRS + WBRT groups. Mean survival rates were 6.2 and 2.8 months for SRS + WBRT and resection + WBRT patients, respectively. Corresponding median failure-free survival times were 3.1 and 1.7 months. This trial was closed early due to slow accrual and therefore suffered from low statistical power. The tumor sizes were larger in the surgery group and there was no mention about percentage of complete resection. In Kocher's study [59], local recurrence was more frequent in resection group. After resection, at 2 years, WBRT reduced the probability of local recurrence from 59% to 27% and after radiosurgery, at 2 years; WBRT reduced the probability of relapse at initial sites from 31% to 19%. However, it is worth to mention that patients who entered after surgery more often had a single metastasis with a larger diameter (up to 70 mm), and lesions were more frequently located in the posterior fossa that may affect the local control rates. The studies comparing surgery with SRS are summarized in Table 2.

1.5. *Tumor histopathology*

Tumor histopathology may be important in developing a treatment plan for an individual with brain metastasis given that different histological types have different chemotherapeutic and radiation management options [70,71]. Tumors such as sarcoma, renal cell carcinoma, and melanoma are considered resistant to WBRT. It has been shown that these tumors may respond to radiosurgery [72–74]. Staging of the tumor with size, location, and metastases and grading of the tumor according to histological findings both allow one to estimate prognosis; a reasonable life expectancy allows surgery to afford a survival benefit considering surgical burden and postoperative recovery. With the advent of new therapies for systemic disease, the long-term survival in patients with cancer, such as those with breast cancer, has improved. Data from several studies have shown that, with surgery plus postsurgical radiotherapy, breast cancer has the best prognosis, whereas melanoma and renal cell cancer have the worst [74–76]. A Japanese study revealed that patients with brain metastasis who underwent craniotomy for tumor resection combined with radiotherapy had mean survival of 12.3 months. In this study, in patients with pulmonary adenocarcinoma, mean survival time was 15.1 months, and the 5-year survival rate was 15.0%. Mean survival time and the 5-year survival rate in patients with squamous cell carcinoma of the lung were 14.9 months and 23.2%, respectively, while the corresponding figures were 13.8 months and 32.5%, respectively, in patients with breast cancer [21]. Sarcoma metastasis is radioresistant and surgery has been shown to be more effective in treating selected patients with sarcoma metastatic to the brain. The complete removal of sarcoma metastases ("*en bloc*" and a good performance status) are associated with the best prognosis even if they are multiple [77]. Another radioresistant tumor, intracranial melanoma metastasis shows frequent intratumoral bleeding. In such cases, surgery should be selected as a first choice in management because presence of pretreatment bleeding in patients treated with SRS may adversely affect the survival (6.8 vs. 2.1 months) [78].

Brain metastases are a heterogeneous population. A recent study by Sperduto et al. [79] analyzed diagnosis specific prognostic factors on retrospective analysis of 4259 patients from 11 institutions. For non-small-cell lung cancer and small-cell lung cancer, the significant prognostic factors were Karnofsky performance status, age, presence of extracranial metastases, and number of brain metastases. For melanoma and renal cell cancer, the significant prognostic factors were Karnofsky performance status and the number of brain metastases. For breast and gastrointestinal cancer, the only significant prognostic factor was the Karnofsky performance status. The diagnosis specific-graded prognostic assessment (DS-GPA) scores correlated well with the outcome stratified by diagnosis for newly diagnosed brain metastases patients and might have merits for optimal disease specific treatment of patients with brain metastases in the future. In non-small cell lung carcinoma (NSCLC) and breast cancer, multiple treatment options showed improved survival compared with WBRT alone with slightly better tendency with surgical treatments included (risk of death: in NSCLC group; 1.0 for WBRT, 0.62 for SRS, 0.53 for WBRT + SRS, 0.42 for resection + SRS, 0.46 for resection + WBRT, 0.39 for resection + SRS + WBRT; in breast cancer group, 1.0 for WBRT, 0.75 for SRS, 0.72 for WBRT + SRS, 0.42 for resection + SRS, 0.61 for resection + WBRT, 0.36 for resection + SRS + WBRT). For SCLC, WBRT remains the mainstay of therapy; however, surgery or SRS might be useful for the occasional patient with persistent brain metastases after WBRT. In melanoma, SRS alone was not significantly better than WBRT alone; however, the relatively small subsets treated with surgery plus WBRT or surgery plus WBRT plus SRS did better than either WBRT alone or SRS alone (risk of death; 1.0 for WBRT, 0.74 for SRS, 0.83 for WBRT + SRS, 0.76 for resection + SRS, 0.61 for resection + WBRT, 0.49 for resection + SRS + WBRT). In renal cell carcinoma, no treatment was significantly better than WBRT alone. In gastrointestinal cancer, the relatively small subset treated with surgery plus WBRT was the only group to do significantly better than those treated with WBRT alone (risk of death; 1.0 for WBRT, 0.89 for SRS, 0.77 for WBRT + SRS, 1.85 for resection + SRS, 0.37 for resection + WBRT, 0.45 for resection + SRS + WBRT). The authors concluded that the patient had a single brain metastasis with a symptomatic mass effect in an operable location, surgery is appropriate. Otherwise, each case should be considered according to the DS-GPA scores and the risk of death for a given therapeutic modality for getting the optimal treatment.

1.6. Multiple metastases

The presence of multiple brain metastases has long been accepted as a partial contraindication for surgery because of the beliefs regarding inefficiency of surgery to improve short expected survival and surgical technical difficulties. Primary tumor control is more important for survival time than the number of brain lesions; although, patients with uncontrolled primary disease are more likely to harbor a larger number of brain lesions than patients in whom the primary tumor is controlled [80].

Pollock et al. [77] reviewed data from 52 patients harboring multiple brain metastases, who had undergone radiosurgery, tumor resection, or both after WBRT. The median survival was 15.5 months. The RPA class I correlated with improved survival, with patients surviving a median of 19 months. In contrast, patients in class III survived a mean of 8 months and those in class II survived a mean of 13 months. Aggressive treatment may prolong the survival in RPA class I and II patients with controlled primary disease and a limited number of metastases.

A retrospective, single-institutional cohort study demonstrated that patients who underwent imaging-complete resection of 2–4 brain metastases had the same median survival (14 months) as patients undergoing imaging-complete resection of a single lesion, though patients who had some but not all lesions resected had a median survival of 6 months and did not appear to have any benefit [16]. These studies suggest that a highly selected subset of patients with a limited number of multiple brain metastases may benefit from resection of all lesions [16] or the dominant lesion [24,81].

Patients with four or more brain tumors are usually not treated surgically, given the poor prognosis in this situation. No level I evidence defines optimal treatment of patients with more than 5 brain metastases. Whole brain radiation therapy remains the standard of care in most patients with life expectancy greater than 3 months based on systemic disease. Level II evidence suggests that SRS may be effective in up to 10 brain metastases if they are smaller than 3 cm and are not associated with mass effect or edema [82].

1.7. Recurrent disease

Treatment of recurrent brain metastasis is highly controversial. In patients with recurrence after initial resection or SRS, mean survival time after the second surgery is reported between 8.3 and 11.1 months in selected patients [83–85]. Bindal et al. [83] reported that reoperation for recurrent brain metastases after the initial resection prolonged survival and improved quality of life. The median time from first craniotomy to diagnosis of recurrence (time to recurrence) was 6.7 months (range 1.2–28.8 months). The time to recurrence after initial resection was significantly associated with overall survival in a multivariate analysis. The patients who underwent a second reoperation survived a median of 8.6 additional months vs. 2.8 months for those who did not undergo a second operation. Prognostic factors were the presence of active systemic disease, KPS score ≤70, time to recurrence <4 months, age ≥40 years, and primary tumor type of breast or melanoma. Another study conducted for recurrent brain metastasis from lung cancer showed median overall survival of 8.3 months after the second brain surgery. Moreover, 66.6% of all patients presenting with neurological impairment improved, and 50% regained normal

Table 3
The randomized, controlled studies involving surgical treatment in the treatment of brain metastases.

Author year	Type of study	Groups	Survival	Local recurrence/progression	Distant recurrence	Progression free survival	Functional independence	Death from neurological causes
Patchell et al. (1990) [8]	RCT	Surgery + WBRT-25	40 weeks*	52%**			38 weeks***	29%
		WBRT-23	15 weeks	20%			8 weeks	50%
Vecht et al. (1993) [9]	RCT	Surgery + WBRT	43 weeks				33 weeks	35%
		WBRT	26 weeks				15 weeks	33%
Patchell et al. (1998) [36]	RCT	Surgery	43 weeks	46%		27 weeks	35 weeks	44%
		Surgery + WBRT	48 weeks	10%		50 weeks	37 weeks	14%
Muacevic et al. (2008) [89]	RCT	SRS	10.3 mo	3% at 1 year	26%# at 1 year			11% at 1 year
		Surgery + WBRT	G2: 9.5 months (Log-rank; P = NS)	18% at 1 year	3% at 1 year			29% at 1 year
Kocher et al. (2011) [59]	Phase III	Surgery + WBRT	10.9	27% at 2 years	23%	4.6 mo	9.5 mo	28%
		SRS + WBRT		19% at 2 years	33%			
		Surgery + observation	10.7	59% at 2 years	42%	3.4 mo	10 mo	44%
		SRS + observation		31% at 2 years	48%			
Roos et al. (2011) [69]	RCT	SRS + WBRT	6.2 mo			3.1 mo		
		Surgery + WBRT	2.8 mo			1.7 mo		

SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy; mo, months; RCT, randomized controlled trial.
* $P \leq 0.01$
** $P \leq 0.02$
*** $P \leq 0.05$
\# $P = 0.04$

function. The interval until first brain metastasis and between first and recurrent metastases was significantly predictive of survival [86].

Surgical resection is an option for recurrence after SRS. In patients with symptomatic mass effect, progressive neurological signs or symptoms, imaging evidence of tumor progression, or intractable seizures after radiosurgery, resection may be warranted. Truong et al. [87] reported that patients who underwent SRS and required resection had a better prognosis than patients who did not undergo subsequent resection, most likely with a selection bias as patients in better condition or those who had lived longer underwent resection. Kano et al. [88] evaluated the prognostic factors that correlate with the survival of patients who require a resection of a brain metastasis after stereotactic radiosurgery (SRS). The median survival after resection as 7.7 months and the local tumor control rates after resection were 71, 62, and 43% at 6, 12, and 24 months, respectively. The mortality and morbidity rates of resections after failed SRS (1.7 and 6.9%, respectively) were similar to those of first surgical resections reported in the literature. One month after resection, the median KPS score improved to 90. Histological examinations of resected tumors confirmed residual tumor in 55% and mixed tumor and radiation effect in 45%. They found that the most important factor influencing duration of survival was the delayed local progression after SRS (>3 months).

Vecil et al. [84] reported that the median time from SRS surgery was 5.2 months. They found that patient's RPA classification (11.1 months for RPA II vs. 2.4 months for RPAIII) was the most important factor on survival.

These studies suggest that surgery at recurrence may improve local control and overall survival in patients with RPA I and II and long interval after initial resection or SRS.

2. Conclusion

Surgery is still cornerstone in treatment of brain metastasis. Technical advances and other advantages of SRS make SRS as first choice for management of the brain metastasis. However, the studies involving surgical approaches have proven that surgery is beneficial for improving neurological status and survival of patients in most patients harboring brain metastases. For patients underwent surgical resection, local control is essential and can be achieved with one of the adjunct therapies following the surgery. All modalities show similar control rates but their evidence level has not been established yet. The randomized, controlled studies involving surgical resection are summarized in Table 3. There is no phase III study to compare SRS vs. surgery, both of which have overlapping indications; surgery seems superior to SRS in terms of the survival and the rates of local recurrence and neurologic death. In selected subset of patients with a limited number of multiple brain metastases may benefit from resection of all lesions or the dominant lesion. Moreover, reoperation for recurrent brain metastases prolong survival and improved quality of in patients with RPA I and II and long interval after initial resection or SRS. Meticulous and delicate surgical technique aiming at the *en bloc* resection and the resection of infiltrative zone, where possible will lead to better surgical outcome and help to regain the vanished role of surgery in the management of brain metastasis.

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