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Diagnosis and Management of Brain Metastases

[*1]Dr Rajiv Ranjan, [*2] Dr Anita Kumari,
[1]*Assistant Professor, Dept of Neurosurgery, Darbhanga Medical college and Hospital, Darbhanga, Bihar*
[2]*Associate Professor, Dept of Radiotherapy, Nalanda Medical college and Hospital, Patna, Bihar*

Abstract
Brain metastasis are the most common intracranial malignancy in the adult population. Their incidence has increased dramatically over the last 20 years, as a result of the increasing number of cases stemming from lung and breast cancer together with the higher cancer survival rates due to diagnostic and therapeutic advances. More than 40% of cancer patients develop brain metastases during the course of their disease, they appear in 50% of patients with lung cancer, more than 25% of patients with breast cancer and 20% of patients with melanoma. Diagnosis is made using different imaging approaches, such as computed tomography and magnetic resonance imaging, accompanied by clinical manifestations and a history of malignancy supporting the diagnosis of a brain metastasis. Fortunately, our understanding of the biology and molecular underpinnings of brain metastases has greatly improved, resulting in more sophisticated prognostic models and multiple patient-related and disease-specific treatment paradigms. In addition, the therapeutic has expanded from whole-brain radiotherapy and surgery to include stereotactic radiosurgery, targeted therapies and immunotherapies, which are often used sequentially or in combination. Advances in neuroimaging have provided additional opportunities to accurately screen for intracranial disease at initial cancer diagnosis, target intracranial lesions with precision during treatment and help differentiate the effects of treatment from disease progression by incorporating functional imaging. In this Review, we describe the key features of diagnosis, risk stratification and modern paradigms in the treatment and management of patients with brain metastases and provide speculation on future research directions. Current treatment options should be oriented to the patient's current performance, the number of intracranial and extracranial lesions and related factors.

Keywords; *Brain metastases, whole-brain radiation therapy, stereotactic radio surgery, graded prognostic assessment*

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I. Introduction

Brain metastases are the most common intracranial malignant neoplasms in adult patients, with 170,000 new cases per year reported in the USA alone[1]. The incidence of brain metastasis has been on the rise in the last 20 years, due to increase in the number of cases of lung and breast cancer[2] and the fact that cancer survival rates have been increasing with the advancement of new therapeutic and the availability of radiological imaging for diagnosis. More than 40% of patients with cancer develop brain metastases: specifically, they appear in 50% of patients with lung cancer, more than 25% of patients with breast cancer, and 20% of patients with melanoma[3,4].

Multiple epidemiological studies have been conducted regarding brain metastases. Such studies include the initial work done by Goumundsson in Iceland, which reported an incidence of 2.8 cases per 100,000 people[5], and was found as high as 11.1 cases per 100,000. The Barnholtz-Sloan *et al*.[6]'s study derived greater validity from its use of the register of the Metropolitan Detroit Cancer Surveillance System from 1973 to 2001, carrying information on an approximate population of 4.5 million patients, in which the observed incidence of brain metastasis in patients with any kind of neoplasm was 9.6%.

Considerable variability in the incidence of brain metastasis has been found, which may be attributable to limited available data, such as autopsy reports or general hospital records; nevertheless, beginning with the first records of cancer, a similar incidence of brain metastasis has been observed, which may be attributable to the fact that it is an exclusively oncological population limited to a particular state or region and follow-up of the same patients[7].

Generally, lung cancer is the foremost cause of brain metastasis, with studies reporting incidences of 12% to 65%[8] of all patients with primary lung cancer. Among the most commonly associated histologies for brain metastasis are small-cell lung cancer and adenocarcinoma, usually diagnosed after the onset of neurological symptoms. Breast cancer is the main cause of brain metastases in women, with reported incidences between 5% to 30% of all breast cancer cases. Unlike the case of lung cancer, in breast cancer the diagnosis of brain metastasis usually follows well after the initial diagnosis of cancer. Diagnoses of melanoma have

increased over the last several years, and this malignant neoplasm has the greatest capacity to develop into brain metastasis, with incidences from 12% to 90%. Incidences of 7% to 10% with renal cancer and 1% to 4% of gastrointestinal tumors of all patients have been reported[9]. The therapeutic management of patients with brain metastases depends on the localization and number of brain lesions, primary tumor biology, and disease extension. The overall survival from the moment of diagnosis for untreated patients is 1-2 months, which can be extended to 6- 18 months in patients who receive conventional radiotherapy and chemotherapy[4].

Pathophysiology

The genesis of metastasis requires several complex and sophisticated steps to occur first. These include genetic, epigenetic, and biological changes known as the "metastatic cascade"[10]. This process begins with the detachment of a tumor cell from its primary lesion and the invasion of the surrounding tissue, including the basement membrane, which is followed by intravasation in the blood vessels, hematogenous and lymphatic dissemination, the production of circulating tumor cells in brain capillaries, and then extravasation. Finally, the cancer cells must colonize the surrounding tissue and induce angiogenesis and cell proliferation, forming secondary lesions[11].

The blood-brain barrier is a functional and anatomical barrier that plays an important role in the interaction between the cerebral microenvironment and metastatic colonization[12]. In this process, tumor cells survive an inflamed cerebral microenvironment that is appropriate for their development and growth, which is known as their niche[13]. Tumor cells adhere to the endothelium of recipient tissue and act as macrophages, creating pseudopods and penetrating cell-to-cell junctions, subsequently gaining access to normal tissue parenchyma to activate angiogenesis and develop new vessels for its nutrition, in this way promoting the growth of secondary injuries[14]. Circulating cells attract platelets due to the proteins they express on their surface, which protects them from the immune system. Likewise, metastatic cells activate mechanisms to escape immunity by reducing the expression of TAP1, which decreases the effects of T-cell-mediated death[15].

Epidemiology

Brain metastases are a common complication of systemic cancers. Metastases are the most common intracerebral malignancy; resulting in 20–40% of all intracranial tumours. The most common primary tumours causing brain metastases in adults are lung cancer, breast cancer, melanoma, renal cancer and colorectal cancer, with a peak age group of 55–65 years. More than 40% of cancer patients develop brain metastases during the course of their disease: specifically, they appear in 50% of patients with lung cancer, more than 25% of patients with breast cancer, and 20% of patients with melanoma. Most often they are metachronous, but may occur synchronously or even prior to diagnosis of the primary tumour. In general, all solid tumours are able to spread into the central nervous system and rare cerebral metastases (sarcomas, seminomas) may occur. Typically, brain metastases develop 6 months to 2 years after diagnosis and are usually associated with progressive systemic disease.

By definition , solitary brain metastasis is distinguished from singular metastasis. A solitary brain metastasis is defined as the only known metastasis of a tumour in the whole body which happens to be localized in the central nervous system. A singular brain metastasis is defined as single cerebral metastasis with additional metastasis in other organ systems.

Symptoms

Most brain metastasis are detected because of unspecified symptoms depending on size, number, and localization of metastatic lesions. Symptoms usually evolve over a few weeks. Most common are headache, mental and behavioural changes(often first detected by family members), defects of higher cortical function like impaired comprehension, reading, calculation – field cuts and difficulty in performing motor function task, such as eating or dressing. An important, and potentially fatal, initial symptom is the subacute or acute rise of intracranial pressure due to blockage of cerebrospinal fluid (CSF) flow by otherwise asymptomatic metastases in the posterior fossa leading to obstructive hydrocephalus making emergency treatment necessary. Acute and more rare symptoms, including seizures (10-15%) or intratumoral bleeding (10%), common in metastatic melanoma.

A thorough physical examination and history is useful to determine the extent of disease, the possible primary tumour in patients with primary brain metastasis and to asses the patient's prognosis with the Karnofsky performance score as a robust predictor of survival and functional quality of life.

Diagnosis

Magnetic resonance imaging (MRI) is the tool of choice when brain metastasis is suspected, due to its high sensitivity and specificity, which support its high capacity to detect smaller lesions than those that appear in computed tomography (CT) with or without contrast; it is also associated with fewer bone artifacts in posterior fossa. However, if MRI is not available, then CT is a valid option[16]. When lesions appear hyperdense,

one may suspect secondary bleeding, especially in histologies associated with high spontaneous bleeding risk (including choriocarcinoma, melanoma, and renal carcinoma); there are also other findings that are secondary to lesions and that can be easily visualized, such as hydrocephaly, ring-enhancing cerebral lesions, and brain herniation[16,17].

The sensitivity and specificity of CT scans are 92% and 99%, respectively, and they are considerably higher in tumors that have a high incidence of central nervous system metastasis, such as non-small-cell lung cancer[18]. MRI exhibits an ability to detect lesions smaller than 1 cm, up to 70% more sensitive than CT, and this increases in cases of multiple metastases[16]. MRI has other beneficial characteristics, for example, in the use of distinct sequences such as T1, T2, FLAIR, diffusion, and perfusion, which can be used along with spectroscopy to increase sensitivity and specificity[19]. The use of contrast significantly increases its sensitivity and specificity for the detection of brain metastases relative to simple MRI[20].

[Figure 1].

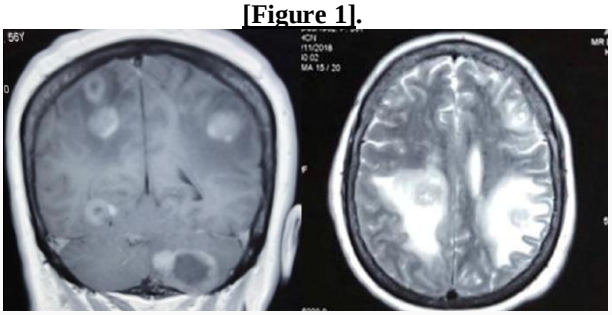


Figure1. Magnetic resonance imaging of a patient with multiple brain metastases. Axial T2 slice sequence shows perilesional edema in the junction of white and gray matter

Spectroscopy can be performed for single or multiple tumor regions (unique voxel or multivoxel) to detect certain ranges of specific metabolites in brain tissue, such as choline, creatinine, lipids, lactate, and N-acetyl-aspartate (NAA)[19,20].

The analysis of these metabolites is helpful for distinguishing metastasis from necrosis, gliosis, and vasogenic edema [Table 1]. Creatinine is the most stable metabolite in brain tissue, although it can be diminished in malignant primary tumors such as high-grade gliomas[21]. Choline is a marker of cell change: It is elevated where there are high-grade cell changes, and it has a relationship with creatinine, such that both appear elevated, which helps orient a diagnosis of brain metastasis[22]. Lipids are a structural component of cell membranes, they appear elevated in the case of severe cell damage, even with necrosis[22]. NAA is found at high concentrations in normal brain tissue, making it a marker for cell integrity and normal tissue structure; this marker appears at low concentrations in brain metastases[21,22].

Table 1 Spectroscopy

Metabolite/marker	Function	As found in brain metastases	Range (parts per million)
Creatinine	Metabolism	Internal standard	3.0
Choline	Cellular membrane turnover	Increased	3.2
Lipids	Necrosis	Increased	0.9-1.4
Lactate	Anaerobic metabolism/necrosis	Increased	1.3
N-acetylaspartate	Neuronal viability	Decreased	2.0

Laboratory tests are of limited value. Tumour markers should be ordered as appropriate according to the known or suspected primary cancer, e.g. α-fetoprotein (AFP) or human chorionic gonadotropin (HCG) in non-seminomatous germ-cell tumours. Cytological analysis of CSF is useful to exclude or establish leptomeningeal involvement.

Median survival of untreated patients is 1∼ 2 months if corticosteroids are added, 4–6 months after whole-brain irradiation [23] and 8–10 months if surgery or radiosurgery is utilised [24, 25]. In addition, survival is superior with a higher Karnofsky score (>70), age<65 years, controlled primary tumour and in the absence of of extracranial metastasis.

Prognostic scales in brain metastases

At present, several useful prognostic scales are available for the clinical decision-making process, the first of which is recursive partition analysis (RPA by Gaspar *et al*.[26]), was formed by the Radiation Therapy Oncology Group (RTOG). [Table 2].

Table 2 : Recursive Partition Analysis (RPA classes)

Prognostic factors	Class I	Class II*	Class III
Age (years)	< 65	Any	Any
Controlled primary tumor	Yes	Any	Any
KPS	> 70	> 70	<7 0
Extracranial metastasis	No	Any	Any
Estimated survival (months)	7.1	4.2	2.3

Abbreviations: RPA: recursive partition analysis; KPS: Karnofsky performance score. *All patients not in class I or III.

Patients with a class III RPA are usually candidates for only supportive care, with local management performed either through surgery or radiotherapy for patients with classes I and II[26,27]. Another scale known as DS-GPA[28,29] which include histology, namely, age, KPS score, presence or absence of extracranial metastasis in the case of lung carcinoma, number of cerebral metastases in the case of lung carcinoma, melanoma, and renal cell carcinoma. Likewise, breast cancer, with its several molecular patterns that determine prognosis, is integrated into this scale [Table 3].

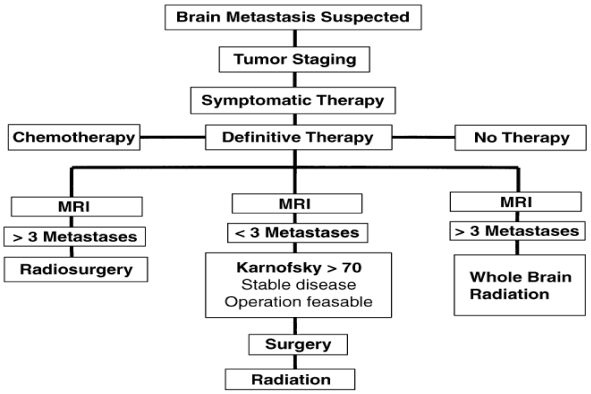
Table 3 : Disease-specific GPA

Disease-specific GPA						
Histology	**Prognostic factors**	**Score**				
		0	**0.5**		**1**	
NSCLC/SCLC	AGE	> 60	50-60		< 50	
	KPS	< 70	70-80		90-100	
	ECM	YES			NO	
	#BM	> 3	2-3		1	
		Score				
		0	**1**		**2**	
MELANOMA/RCC	KPS	< 70	70-80		90-100	
	#BM	> 3	2-3		1	
		Score				
		0	**0.5**	**1**	**1.5**	**2**
BREAST	KPS	< 60	60	70-80	90-100	
	ER/PR/HER2	Triple negative		ER/PR (+), HER2 (-)	ER/PR (-), HER2 (+)	Triple positive
	AGE	> 70	< 70			
		Score				
		0	**1**	**2**	**3**	**4**
GASTROINTESTINAL	KPS	< 70	70	80	90	100

Abbreviations: GPA: graded prognostic index; NSCLC: non-small-cell lung carcinoma; SCLC: small-cell lung carcinoma; RCC: renal cell carcinoma; KPS: Karnofsky performance score; ECM: extracranial metastasis; #BM: number of brain metastases; ER: estrogen receptor; PR:progesterone receptor; HER2: human epidermal growth factor receptor 2

Treatment

Therapy of brain metastasis is a complex and need interdisciplinary approach which include medical oncologist, neurosurgeons and radiation oncologists . Management consists of both symptomatic and definitive therapies. Symptomatic therapy includes corticosteroids for the treatment of peritumoural oedema and anticonvulsants for the control of seizures. Definitive treatment includes surgery, radiotherapy and chemotherapy directed at eradicating the tumour cells.



Symptomatic therapy

Initial approach with brain metastasis is to relieve symptoms, such as headache, vomiting, and neurological focalization; the success of this largely depends on the presence of cerebral hypertension syndrome secondary to perilesional cerebral edema Only patients with brain metastases presenting with seizures should be treated with anticonvulsants; if possible, in the form of monotherapy utilising phenytoin or carbamazepine [25]. Possible exceptions are patients with brain metastases in areas with high epileptogenicity, patients with multiple melanoma metastases [30] and patients with both brain and leptomeningeal metastases [31]. These patients have a higher possibility of seizures and may benefit from prophylactic anticonvulsant therapy. There are no clear rules as to when anticonvulsants should be stopped in patients with documented seizures. Dexamethasone, which acts by reducing the permeability of tumour capillaries [32], is the corticosteroid most commonly used to reduce oedema. The conventional starting dose is high (10–32 mg) followed by 4 mg four times daily, although there is some evidence that lower doses (4–8 mg/day) may be as effective [33]. The twice daily schedule is more rational because of the long half-life of dexamethasone (24–36 h). Once the patient is clinically stable, a slow taper should be initiated with the aim of establishing the lowest effective dose (e.g. taper 2 mg every 5–7 days). In patients with a history of gastric problems, we use a prophylactic proton pump inhibitor (omeprazole) or H2 blocker. Sometimes in immunocompromised patients receiving dexamethasone >4 mg daily Candida prophylaxis and Pneumocystis carinii prophylaxis with TMP-SMX (trimethoprim–sulfamethoxazol) on weekends is used. It should be kept in mind that phenytoin induces hepatic metabolism of dexamethasone and significantly reduces half-life and bioavailability [34]. Conversely dexamethasone may also reduce phenytoin levels (measurement of plasma level necessary).

Definitive therapy

The optimal combination of definitive treatment options for each patient depends on careful evaluation of numerous factors, including localisation, size and number of brain metastases; patient age, general condition and Karnofsky performance status; extent of systemic cancer as well as the tumour's response to past therapy and possible future treatment options.

Systemic chemotherapy

The definitive role of chemotherapy in the treatment of patients with brain metastases has not been defined. Traditionally it had been assumed that the blood–brain barrier prevented chemotherapeutic agents from entering the CNS. However, there is evidence that the blood–brain barrier is in fact partially disrupted in brain metastasis [35,59, 60].

Local therapy

In general, the local treatment of asymptomatic cerebral metastases should be started if systemic tumour disease is controlled, life expectancy is greater than 3 months and the Karnofsky score is at least 60. The indication of surgery or radiosurgery should not depend on technical feasibility, but with the aim of improving quality of life.

Surgical management

Surgery plays an important role in the management of brain metastases, enabling a definitive histologic diagnosis in patients with no previously known history of cancer, allowing clinicians to alleviate the symptoms of intracranial hypertension (thus providing immediate relief to patients), and serving as a primary therapeutic approach. A resection in toto is preferable. One major benefit of surgical resection of a metastasis is the fast resolution of the surrounding oedema.

Due to multidisciplinary treatment protocols of brain metastases, a combination of surgical resection and radiosurgery for multiple lesions is sometimes used. A recently published paper in which radiosurgery was evaluated for its tumour control potency revealed not only a prolonged time to oedema resolution, but, in addition, a local recurrence rate of ~50% [36].

The only randomised study in patients with a single brain metastasis revealed a mean survival of 40 weeks for those receiving surgery and whole-brain radiation in contrast to a mean survival of 15 weeks for those receiving whole-brain radiation alone. Therefore, the benefit of surgical resection in these circumstances is well documented [4]. In addition, the local recurrence rate was 20% in a combined protocol of radiation and surgery and 52% in the radiation alone group. Even more striking in the study was the influence of the Karnofsky score on the outcome. Patients with a Karnofsky score >70 showed a survival of 38 weeks with the combined protocol versus 8 weeks with radiation alone, revealing a highly statistically significant benefit of surgery in combination with radiation ($P<0.005$). Therefore, a surgical resection should be performed if the cerebral metastasis is easily accessible, if a strong surrounding oedema causes neurological deficits, when a metastases has major cystic components or if fast relief of secondary complications is the goal, as for example in the resolution of acute hydrocephalus due to metastases in the posterior fossa. In a patient group in which tumour resection or radiosurgery in combination with whole-brain radiation is performed and a recurrence occurs, a re-operation is indicated if the Karnofsky score is good and no other therapeutic options are available. Mean survival after re-operation is 8.6 months, compared with 2.8 months without re-operation [4]. This difference in survival seems logical since only patients with well controlled systemic disease will survive until a local cerebral recurrence will occur and will therefore profit from a second operation. The American Society for Radiation Oncology recommends surgical resection in patients with an expected survival of at least 3 months, lesions larger than 3-4 cm, and who are amenable to safe, complete resection followed by WBRT or SRS to the cavity[37].

Radiation management

Whole-brain radiotherapy

WBRT has been considered a mainstay treatment for brain metastases since the publication of Chao *et al*.[38], who proposed the first WBRT technique using 250 kv X-rays in 38 patients with brain metastasis. The authors reported that 63% of the enrolled patients demonstrated reduced symptoms associated with brain metastasis, with a relief duration of 3-4 months[38].

Dose and fractionation for WBRT

Dose and fractionation schemes are based, not on the radiation sensitivity of the primary tumor, but rather on the tolerance of healthy brain tissue as described in the QUANTEC report from 2010 (maximum dose [Dmax] of 60 Gy with an estimated rate of symptomatic brain necrosis of 3%)[39]. Taking this into account and with a biologically equivalent dose (BED) with an α/β ratio of 3 for a normal brain, we cite the most used radiation schemes with their BED in Table 4.

Table 4;Most used radiation therapy schemes for WBRT

Dose and fractionation	BED (Gy)
30 Gy/2 weeks	60
20 Gy/1 week	46.67
37.5 Gy/3 weeks	68.75
40 Gy/4 weeks	66.67

Abbreviations: BED: Biologically equivalent dose. Gy: Gray

Since the primary objective of this type of treatment is the palliation of symptoms, the most common prescription dose is 30 Gy in 10 fractions. This is based on the results of the first two randomized trials conducted by the RTOG, in which they compared four different radiation schemes including 3000 rad delivered in 2 weeks and 2000 rad in 1 week, and reported no differences in survival, time to progression, and symptom relief [40].

Considerations that can be taken into account as the physician decides on one fractionation scheme over another are the patient's performance status, estimated survival, and histology of the primary tumor because choriocarcinoma, melanoma, and renal cell carcinoma, among other types, present a higher risk of bleeding[41,42].

The shorter-course fractionation of 20 Gy in 1 week is preferable for most patients with poor performance status, to avoid unnecessary treatment time, as it has demonstrated similar survival benefits as longer treatment schemes[43]. However, other fractionation schemes such as 37.5 Gy in 3 weeks is recommended in patients who have received a stereotactic radiosurgery boost with one metastatic lesion and should be considered in patients with one to three lesions[44].

WBRT, unlike SRS, is associated with lower intracranial relapse, but when the whole brain is irradiated with this technique, it may also lead to greater cognitive deterioration (reflected as short-term memory loss), especially in patients with a longer life expectancy (> 6 months). In Aoyama *et al.*[45], global survival did not significantly differ between treatment techniques (8.0 *vs*. 7.5 months) but there was a difference in the presentation of new metastases (63.7% *vs*. 41.5%) WBRT as shown Figure 5.

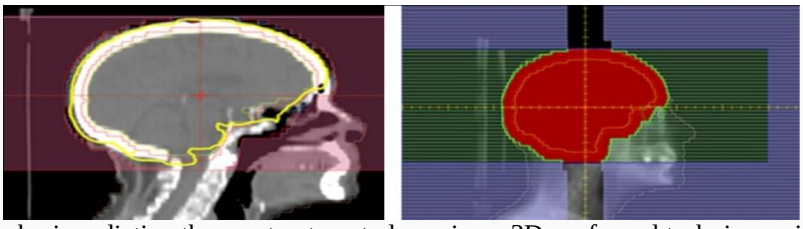


Figure 5. Whole-brain radiation therapy treatment plan using a 3D conformal technique with two opposite lateral fields

Role of radiosurgery in the treatment of brain metastases

SRS-based treatment began in 1951, with its implementation by Lars Leksell. It uses multiple rays of radiation, which converge three-dimensionally on a localized objective, either static or mobile, giving a high dose to a unique fraction with a high fall-off. This minimizes the damage to the adjacent tissue[46]. Mostly more than half of brain metastasis patients present with three or fewer lesions at diagnosis. It has been demonstrated that both surgical treatment and SRS lead to longer overall survival in these patients, especially for one lesions smaller than 30 mm, where SRS has an overall survival comparable to microsurgery. However, it is important to take into account that although brain metastases tend not to invade more than a few millimeters of adjacent tissue, local recurrences are common after resection, meaning that adjuvant treatment with radiotherapy after surgery is imperative[47]. To reduce cognitive impairment in such patients, the use of SRS has grown in use as an alternative to WBRT in the first 6 weeks following surgery, with the goal being to maintain local control in surgery and preserve neurocognitive functions without lowering quality of life[45].

Clinical presentation with a single metastasis appears in only 10% to 20% of patients, where treatment with SRS following surgery improves both local recurrence rates and death due to neurological causes[48,49].

The retrospective series published by Wang *et al.*[50] in 2015 analyzed patients with brain metastases, comparing GammaKnife SRS alone, GammaKnife SRS with WBRT, surgery and SRS (as an adjuvant treatment to the surgical cavity), and a triple modality (surgery, SRS, and WBRT). For patients with a single metastasis and those with multiple lesions, the triple modality treatment was found to have greater positive effects on median survival than GammaKnife SRS alone. That study was not a prospective trial, and it also found better results for bimodal treatment than for GammaKnife surgery alone (as opposed to previous clinical trials). The authors concluded that WBRT is a good alternative as a rescue treatment for patients who had previously received SRS[50,51].

SRS has broadened the terrain of the primary treatment of brain metastasis, especially in patients with good functional status and in those who have one to three metastases at diagnosis with limited extracranial disease[50] [As shown in Figures 6 and 7]. Therefore, it is important to note that better global control of metastasis can be obtained with WBRT and SRS, which have an impact on local control and overall survival[51].

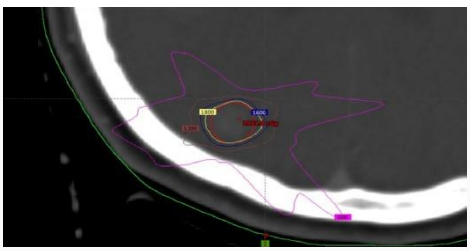


Figure 6. Treatment-planning dose for SRS of a single lesion, with the dose distribution for one target prescribing 20 Gy 95% with the following specification: isodose lines: red 20 Gy, yellow 18 Gy, blue 16 Gy, brown 12 Gy, pink 6 Gy.

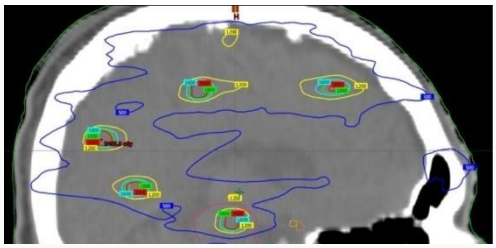


Figure 7. Multiple-target planning showing the dose distribution for multiple targets, prescribing 20 Gy 95% to each of them with the following specification: isodose lines: red 20 Gy, green 18 Gy, light blue 16 Gy, yellow 12 Gy, dark blue 6 Gy.

The utility of SRS for patients with five or more brain metastases is unclear. The only prospective study that has evaluated patients with these characteristics was conducted by Yamamoto *et al*.[53], who assessed 208 patients with 5 to 10 metastases, 531 patients with 2 to 4 metastases, and 455 patients with a single metastasis, with a maximum lesion diameter of 3 cm. The most important result was that the number of brain metastases did not affect overall survival, while the volume of intracranial tumors ranged from 0.02 to 13.9 cc, and the average survival for patients with 5 to 10 metastases was 10.8 months. Deaths from neurological causes did not exceed 10% and there were no significant differences among groups. Finally, it was concluded that the progression of systemic disease was the main cause of death, the initial number of metastases did not impact local control, and the rate of distant metastasis failure was lower in patients with a single metastasis, although this advantage seemed to be lost for those with two or more metastases[53].

Brown's and Chang's trial[52,53] indicated that treatment with WBRT affects cognitive function in a significant way in all analyzed aspects, and opinions on the management of brain metastases converge on the use of SRS, even for multiple brain metastases, to avoid cognitive deficit[48].

SRS treatment dose

As described in the protocol RTOG 9005, treatment dose is inversely proportional to metastatic lesion size. The suggested dose is 24 Gy for tumors smaller than 20 mm, 18 Gy for tumors from 21 to 30 mm, and 15 Gy for tumors from 31 to 40 mm[55]. It is not known whether the dose used for lesions smaller than 20 mm can be safely incremented above 27 Gy; hence, the general consensus still recommends a 24 Gy dose. However, because the organs at risk are so near, a single-dose treatment modality is associated with higher rates of toxicity, meaning that hypofractionated treatment plans are more appropriate for local control with acceptable toxicity[56].

In 2014, Minniti published results of a study of hypofractionated SRS in which lesions under 20 mm received 36 Gy in three fractions, and lesions larger than 20 mm received 27 Gy in three fractions, resulting in 2 years of local control and an overall survival rate of 72% and 25%, respectively[57]. In 2016, Navarria published the results of a similar study, administering a dose of 27 Gy in three fractions to lesions of 21 to 30 mm and a dose of 32 Gy in four fractions to lesions of 31 to 50 mm. The technique resulted in local control and an overall survival at 2 years of 96% and 33%, respectively[58].

II. Conclusion

Although brain metastasis is the most common malignant intracranial tumor, it is closely linked to unfavorable outcomes. Its incidence has increased dramatically, due to a greater number of newly diagnosed cancer patients and the broader therapeutic options available today, which have led to better disease control and longer overall survival. The majority of patients are not candidates for surgical resection, so radiotherapy remains the standard of care. The possibility of a cure for an oligometastatic disease has been gaining increasing attention in recent years. The management of these patients has changed immeasurably over the past few decades: not many years ago, the prognosis and survival of such patients was for a short life expectancy, with poor disease control. At present, there are several treatment options available. The choice among these modalities depends on several factors, such as the functional state of the patient and the availability of equipment and treatment techniques at the given medical center. Before the 1990s there was no GPA prognostic scale, much less an RPA, which are quite useful for decision making.

To date, no prospective studies have evaluated the use of SRS relative to WBRT for patients with more than four brain metastases. However, the current tendency in several hospitals around the world is to avoid WBRT, due to the toxicity and neurological deterioration attendant on that treatment, especially in developed countries. Consequently, there has been a shift to highly sophisticated techniques, such as SRS. A randomized phase III study is currently running at The Odette Cancer Center and the Princess Margaret Cancer Center (University of Toronto) in patients with 5 to 20 cerebral metastases who are receiving treatment with SRS

without WBRT versus SRS plus WBRT, with the primary outcome being to compare neurocognitive decline between the approaches, as this is a common late side effect in patients receiving radiotherapy.

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