

Review

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Diagnosis and management of brain metastases: an updated review from a radiation oncology perspective

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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: specifically, 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. Current treatment options should be oriented to the patient's current performance, the number of intracranial and extracranial lesions, and related factors. Although surgical resection and whole-brain radiotherapy have been standard treatments for many years, numerous treatment modalities have become more easily available and accepted worldwide, producing more favorable and reliable results. Among these is stereotactic radiosurgery, and the latest clinical trials support this treatment.



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Keywords: Brain metastases, whole-brain radiation therapy, stereotactic radiosurgery, graded prognostic assessment

INTRODUCTION

Brain metastases are the most common intracranial malign 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 the last 20 years, resulting from an increase in the number of cases of lung and breast cancer^[2] and the fact that cancer survival rates have been increasing thanks to new therapeutic advances and the availability of central nervous system imaging technologies 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. These have had different methods and limitations; however, a comparison between them can bring an understanding of the incidence of brain metastasis. 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 Percy *et al.*^[6], where the incidence found was as high as 11.1 cases per 100,000. The Barnholtz-Sloan *et al.*^[7]'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^[8,9].

Generally, lung cancer is the foremost cause of brain metastasis, with studies reporting incidences of 12% to 65%^[10] of all patients with primary lung cancer. Among the most commonly associated histologies for brain metastasis are small-cell lung cancer and adenocarcinoma. In a high percentage of patients with lung cancer, diagnosis is performed after the onset of neurological symptoms.

Breast cancer is the main cause of brain metastases in women, with reported incidences between 5% and 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% [Figures 1-3]. Incidences of 7% to 10% of all patients with renal cancer and 1% to 4% of all gastrointestinal tumors have been reported^[11].

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 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”^[12,13]. This process begins with the detachment of a tumor cell from its primary lesion and the invasion of the surrounding tissue,



Figure 1. Left parietal lesion

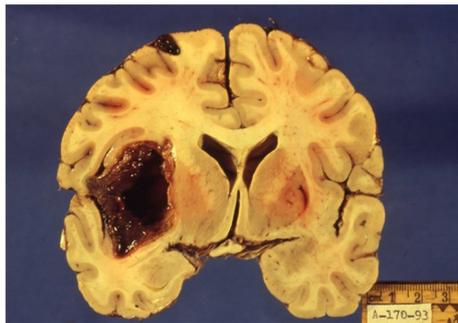


Figure 2. Macroscopic view of a lesion located in the left temporal lobe, with dimensions of 5 cm x 4 cm x 3 cm, from the cystic-necrotic center. A subepidural lesion appears in the parietal region on the same side

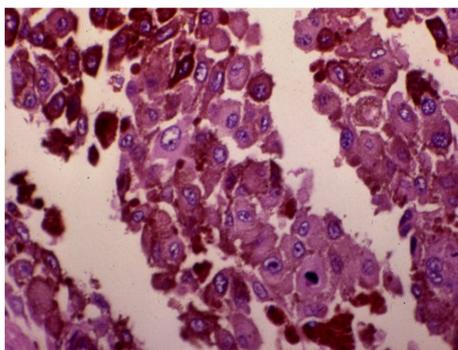


Figure 3. Histologically, this lesion is composed of epithelioid-like cells with moderate eosinophilic cytoplasm and well-defined cytoplasmic junctions between some cells. The nuclei are vesicles with an apparent nucleolus. A brown pigment characteristic of melanocytic cells is seen

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^[14].

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^[15]. In this process, tumor cells survive

an inflamed cerebral microenvironment that is appropriate for their development and growth, which is known as their niche^[16].

Tumor cells can evade growth-suppressing factors and inhibitors of cell proliferation through mechanisms that include resistance to apoptosis, overexpression of Bcl-2 and Bcl-xL, and the inhibition of proapoptotic pathways Bax and Bim^[12]. Tumor cells can be dedifferentiated, migrate to a distant site, survive apoptosis, disseminate, and redifferentiate. The activation of cells in the adjacent stroma by paracrine signaling with pro-tumor factors maintains the growth of the tumor, intensifying genomic instability and epigenetic dysregulation^[11,13].

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^[17]. 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^[18].

DIAGNOSIS

Although clinical manifestations of a history of malignant disease with central nervous system metastasis potential may obviously occur, it will not always be possible to obtain histological confirmation of these lesions [Figure 3]. In such cases, complementary image studies may play an important role in determining the best management for these patients.

Image studies

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 cannot be used, CT is still a valid option^[19].

CT will show isodense lesions in contrast with brain parenchyma, which will intensify with the application of intravenous contrast medium. 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^[19,20].

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^[21]. 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^[19]. 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 sensibility and specificity^[22].

The majority of metastatic lesions are hypointense in T1 sequence images, which can be an indication of hemorrhage and necrosis. In T2 weighted images, the majority of lesions appear hyperintense [Figure 4]. Bleeding appears as acutely hypointense and becomes hyperintense as chronicity develops, while vasogenic edema appears hyperintense. The use of contrast significantly increases its sensitivity and specificity for the detection of brain metastases relative to simple MRI^[23].

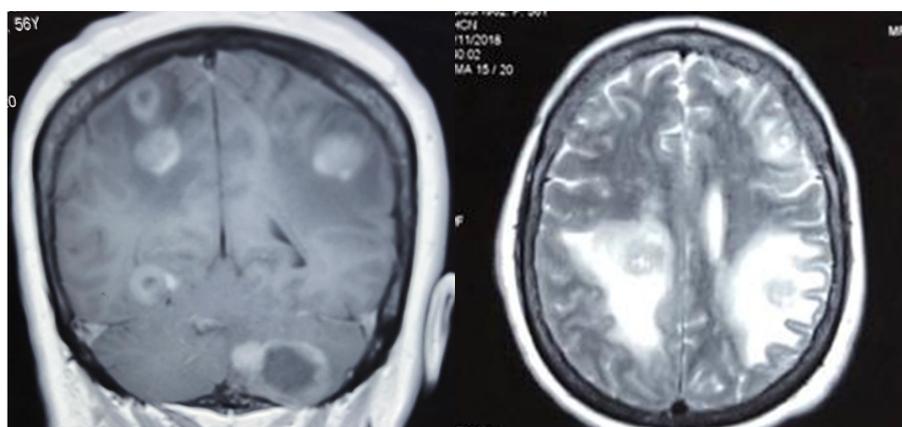


Figure 4. Magnetic resonance imaging of a patient with multiple brain metastases. Axial T2 slice sequence shows perilesional edema in the junction of white and gray matter

Table 1. Spectroscopy

Metabolite/marker	Function	As found in brain metastases	Range (parts per million)
Creatine	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

SPECTROSCOPY

Spectroscopy is an MRI technique that allows the metabolic characteristics of lesions to be evaluated, which may help distinguish between benign lesions and malignant lesions which would be difficult to differentiate using MRI alone. 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)^[22,23].

The analysis of these metabolites is helpful for distinguishing metastasis from necrosis, gliosis, and vasogenic edema [Table 1].

Creatine is the most stable metabolite in brain tissue, although it can be diminished in malignant primary tumors such as high-grade gliomas. It is present in both white and gray matter, which enables it to be used as an internal reference for the remainder of metabolites, which can change in the context of metastatic brain disease^[24,25].

Choline is a marker of cell change: it is a structural part of cell membrane phospholipids, with a greater presence in white matter than in gray matter. It is elevated where there are high-grade cell changes, and it has a relationship with creatine, such that both appear elevated, which helps orient a diagnosis of brain metastasis^[26].

Because lipids are a structural component of cell membranes, they appear elevated in the case of severe cell damage, even with necrosis. Lactate is a main metabolite associated with anaerobic metabolism, and necrosis is common in brain metastases^[26]. 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^[25,26].

Spectroscopy may increase the accuracy of MRI in differentiating tumors from necrosis in patients with metastases who have been irradiated, using choline/NAA and choline/creatine ratios^[26]. According to a meta-analysis of 261 patients, it can also guide a clinician's therapeutic approach by adding information that could contribute to a differential diagnosis of primary malignant tumors such as high-grade gliomas; the study concluded that the most useful spectroscopy parameter is the choline-NAA ratio, preferably using a multi-voxel technique in the peritumoral region^[27]. However, in contrast, a meta-analysis of advanced MRI metrics that included 24 spectroscopy studies found no reliability of this technology in distinguishing high-grade gliomas from metastases using the choline-creatine ratio; the authors had excluded cases in which the choline-NAA ratio was used due to insufficient data^[28].

Hence, there is a lack of robust data supporting the routine use of MRI spectroscopy for differentiating metastases from high-grade gliomas, but it remains an important tool supporting the differential diagnosis of brain metastases from benign and low-grade gliomas and necrosis in irradiated patients^[29].

TREATMENT

The therapeutic approach to patients with brain metastasis is intended 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. Surgical management continues to be the standard of treatment, accompanied by radiotherapy using two different techniques: stereotactic radiosurgery (SRS) or whole-brain radiation therapy (WBRT) (or a combination of these)^[30].

Management of brain edema

The treatment of cerebral edema with systemic steroids such as dexamethasone has been practiced for more than five decades^[31]. Its efficacy is well known in terms of the clinical improvement of symptoms associated with vasogenic edema through its reduction of capillary permeability and regulation of the elevation of tight endothelial junctions involved in the physiology of the blood-brain barrier by binding to glucocorticoid receptors^[32-34].

In actuality, the pharmacological measures previously adopted for the management of edema, including osmotic diuretics such as mannitol and glycerol and loop diuretics such as furosemide, are no longer considered standard for the treatment of cerebral edema secondary to metastasis. Because osmotic diuretics cause a redistribution of fluid from the intracellular space to the extracellular space, they reach a plateau within a few hours, reducing their effectiveness^[35].

Even though there is not a defined dexamethasone scheme, the most utilized dose in patients with clinical cerebral edema is 4 to 8 mg/day^[33].

According to a recent joint update of the American Society of Clinical Oncology and the Society for Neuro-Oncology, they endorse a practice guideline regarding the role of steroids in brain tumors. The recommended dose depends on symptom severity with an initial dose of 8 mg in mildly symptomatic patients and 16 mg in severely symptomatic patients^[36].

Management of seizures

In patients who have not presented with seizures, the use of an antiepileptic agent in a prophylactic manner is currently not recommended, following a systematic review by Perry *et al*^[37]. In that study, no significant differences were found in reduction of risk of convulsive episodes in patients who were recently diagnosed with brain metastases and had never presented with seizures, between administration of the drug and only observation.

Table 2. 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.

By contrast, the use of anticonvulsants in patients with seizures, although it does not have an impact on overall survival, is useful for the relief and decrease of the number of convulsive episodes. The drugs used most often that have been proven to be effective and safe include levetiracetam, oxcarbazepine, and topiramate^[38,39].

INITIAL ASSESSMENT

A therapeutic approach must be preceded by an adequate assessment of the patient's condition, evaluating parameters such as functional status and extracranial disease so that the best available treatment may be offered, without compromising the oncological outcome or overtreating patients in whom poor survival may be anticipated and for whom support measures are more adequate.

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.*^[40]), developed in 1997. This scale was formed by the Radiation Therapy Oncology Group (RTOG) clinical trials that defined three prognostic classes according to four prognostic factors: performance according to the Karnofsky performance scale (KPS), control of the primary disease, presence or absence of extracerebral disease, and age greater or less than 65 years, dividing patients with brain metastases and their respective median survivals into three prognostic classes [Table 2].

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^[40,41].

The histological type of the primary tumor should also be considered an important prognostic factor; however, the previous scale does not take this into account. There is a more specific scale for primary disease that takes melanoma, gastrointestinal tumors, breast cell carcinoma, renal cell carcinoma and non-small-cell lung carcinoma into account. This scale is known as DS-GPA^[42,43].

The prognosis derived from these scales depends on various prognostic factors in relation to each 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].

For more information on the estimation of global survival according to tumor type and characteristics, we recommend visiting a website made for this purpose: <http://brainmetgpa.com/>.

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

Table 3. Disease-specific GPA

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

primary therapeutic approach. However, in recent years it has been displaced by advanced radiotherapy techniques such as SRS.

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^[44].

Whole-brain radiotherapy

WBRT has been considered a mainstay treatment for brain metastases since the publication of Chao *et al.*^[45], who proposed irradiating the whole brain through two opposed lateral fields with the inferior margin of each field lying along the line running from the supraorbital ridge through the external auditory meatus to the foramen magnum; the other margins of the rectangular field project 2 cm beyond the forehead, vertex, and occiput onto bolus bags that surround the head. This was the first WBRT technique described 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^[45].

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%)^[46]. 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](#).

Because the primary objective of this type of treatment is the palliation of symptoms, the most common prescription 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 [[Table 5](#)]^[47].

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

Table 5. Former RTOG dose and fractionation protocols for brain metastases

RTOG brain metastasis protocols			
First study		Second Study	
Scheme	# patients	Scheme	# patients
3000 rad/2 weeks	233	2000 rad/2 weeks	447
3000 rad/3 weeks	217		
4000 rad/3 weeks	233	3000 rad/2 weeks	228
4000 rad/4 weeks	227	4000 rad/3 weeks	227

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^[43,48,49].

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^[50]. 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^[51].

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.*^[52], 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](#).

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^[53].

Luckily, 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 lone 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^[54]. 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^[52].

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^[55,56].

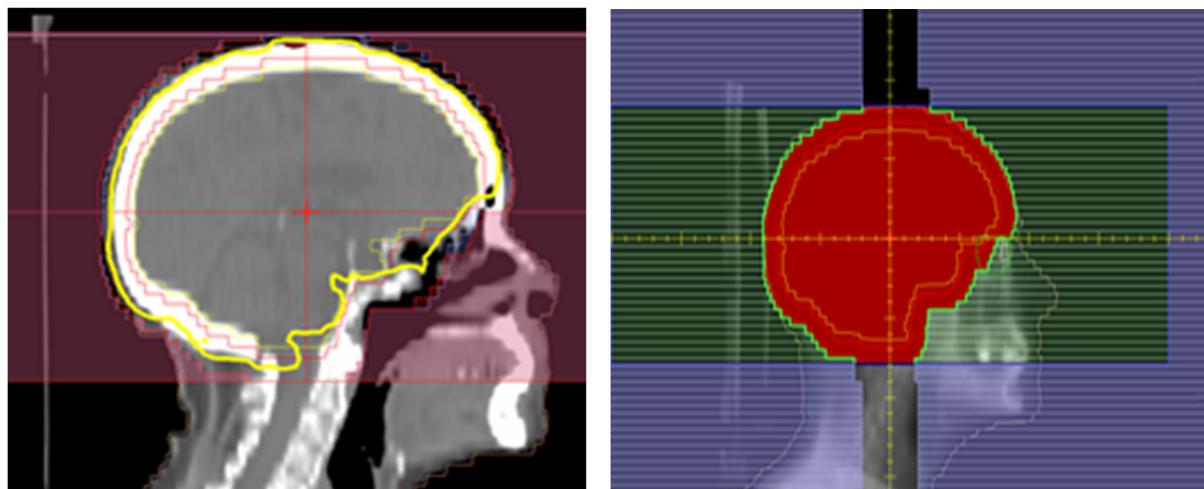


Figure 5. Whole-brain radiation therapy treatment plan using a 3D conformal technique with two opposite lateral fields

One of the first aleatorized studies employed SRS as a boost in patients with one to three brain metastases that had previously received treatment with WBRT, showing an improvement in functional status in all patients and an improvement in overall survival in patients with a single metastasis^[52,57].

The retrospective series published by Wang *et al.*^[58] 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^[58,59].

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^[58] [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]. Patients whose disease is more limited in extent (up to four metastases for SRS protocols) may be treated with WBRT and SRS or SRS alone without improvement in their overall quality of life. A worsening of cognitive performance is found in patients treated with WBRT plus SRS, which affects their quality of life and ultimately their overall survival. These results were found by the trials conducted by Brown *et al.*^[60] and Chang *et al.*^[61]. ASTRO and NCCN guidelines agree in recommending management with SRS in patients with a limited number of brain metastases.

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.*^[62], 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

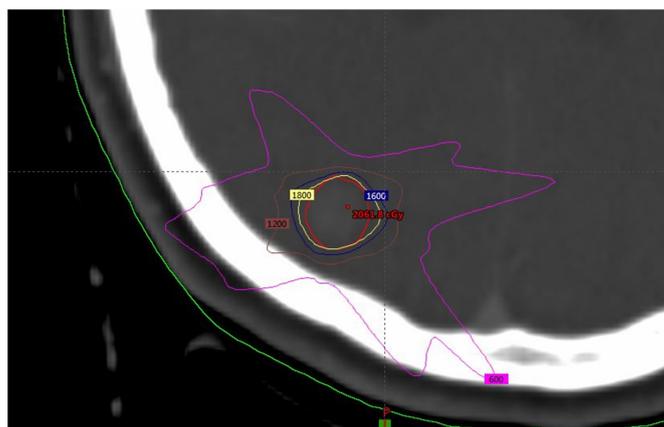


Figure 6. Treatment-planning dose for SRS of a single lesion, with the dose distribution for one target prescribing 20 Gy 95% with the following specification: isodose lines: red 20 Gy, yellow 18 Gy, blue 16 Gy, brown 12 Gy, pink 6 Gy. Software: Eclipse External Beam Planning system version 15.5 HD MLC

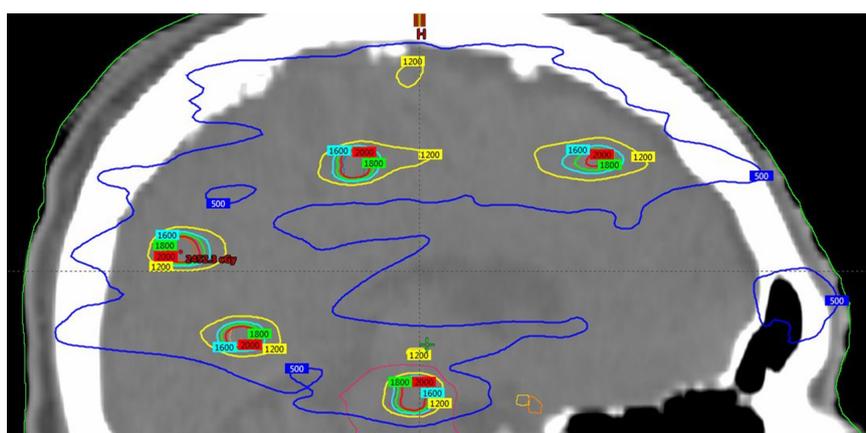


Figure 7. Multiple-target planning showing the dose distribution for multiple targets, prescribing 20 Gy 95% to each of them with the following specification: isodose lines: red 20 Gy, green 18 Gy, light blue 16 Gy, yellow 12 Gy, dark blue 6 Gy. Software: Eclipse External Beam Planning system version 15.5 HD MLC

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^[62].

Because 50% of patients with brain metastases will present with new lesions, it is necessary to continue surveillance using serial MRI when only SRS is used, with the intention of identifying the progression of the disease and enabling early management to limit neurological deficits. Success in the control of new distant metastases varies from 22% to 90%, with different results reported by different studies. Many such studies have reported a correlation between the initial number of metastases and the progression of disease (according to Chang *et al.*^[61], the presence of 15 or more metastases is a risk factor). In addition to age, KPS, histology, and RPA, the total irradiated volume is also likely to impact overall survival, however, neither the number of metastases nor the total volume of treatment is yet considered a criterion for the selection of patients for treatment with SRS^[51].

Brown's and Chang's trial^[60,61] 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^[55].

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^[63]. 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^[64].

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^[65]. In 2016, Navarra 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^[66].

CONTOURING OF BRAIN METASTASES

Before a treatment plan is complete, an MRI with gadolinium contrast should be performed for fusion with axial CT. GTV is defined as gadolinium enhancement, identified in MRI with a 1 mm margin. A 1-3 mm margin is used for GTV in a geometrical form to obtain the total treatment volume (planning target volume)^[63].

SRS boost after WBRT

Several randomized trials that employed SRS as a boost after WBRT in newly detected patients with one to three surgically unresectable brain metastases have reported no added toxicity and improved performance in all patients and also an important benefit in the overall survival of patients with a single metastasis^[51,52,57]. In addition, a recent review of five studies involving 2,728 patients reported a survival benefit in all patients who received a combined modality based on prognostic criteria (RPA or DS-GPA) regardless of the number of brain metastases^[67].

Cavity radiation therapy

A panel of international experts has recommended the following to contour CTV in SRS for patients with completely resected brain metastases. CTV must include the entire surgical cavity showing enhancement of contrast, using axial images in the T1 sequence of brain MRI with gadolinium contrast, excluding edema as determined by MRI. CTV must include the surgical path shown in the MRI or CT. If the presurgical tumor is in contact with the dura mater, CTV must include a 5-10 mm margin, until overlap with bone structures is achieved. If the presurgical tumor is not in contact with the dura mater, the CTV must include a 1-5 mm margin, until contact with bone structures is achieved. If a presurgical tumor is in contact with the venous sinus, CTV must include a 1-5 mm margin along the sinus^[68].

Late toxicity implications: radiation cognitive syndrome

Radiation cognitive syndrome is a poorly understood entity, and currently there is no validated long-term treatment or prevention; 50%-90% of patients who receive WBRT exhibit disabling cognitive function including declines in learning capability, processing speed, memory, and attention. This undermines the patient's overall quality of life. Radiation is associated with inflammation, gliosis, demyelination, vascular abnormalities, and necrosis, which in turn may lead to such cognitive issues^[69].

Cognitive deterioration is usually reported 6 months to 1 year after WBRT, but may be seen as early as 1 month after treatment. In addition, cognitive decline tends to be progressive and irreversible. Many

radiation and pharmacologic approaches to address this syndrome are being studied, and while further data are needed for any one medical solution to become the standard of care, the results generated to date suggest a positive outlook for future treatment options^[70].

As new radiotherapy techniques have appeared, treatment plans have been developed that, in addition to tumor control, aim to reduce cognitive deterioration through the preservation of the hippocampus. Indeed, the RTOG 0933 trial^[71] demonstrated the preservation of cognitive function by reducing the dose to the hippocampus to not more than 9 Gy at 100% of the volume and a maximal hippocampal dose of 16 Gy. This was achieved by manually contouring the hippocampus on a fused MRI-CT image set and expanding by 5 mm to generate “hippocampal avoidance regions.” The mean relative cognitive decline from baseline to 4 months was 7.0%, significantly lower than in controls. The study demonstrated that conformal avoidance of the hippocampus during WBRT was associated with preservation of memory and quality of life. Nonetheless, this procedure poses a risk of generating new brain metastases within the avoidance regions. However, this risk is not fully quantified and further data are needed to validate this technique within a phase III setting.

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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Authors' contributions

All the authors contributed in an equitable way in the conception, bibliographic search and writing of this review article.

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