ONCOLOGÍA
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Multidisciplinary management of brain metastases: an updated review and a paradigm shift

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Abstract

Introduction: Brain metastases (BMs) represent a significant public health problem. An average of 30% of cancer patients develop BM, which is a significant cause of morbidi ty, anxiety, and mortality. Radio- therapy, surgery, and systemic treatment are the mainstays of treatment and have evolved significantly in the last decade.

Pu rpose of the review: Updated information on the epidemiology, diagnosis, prognosis, and treatment of brain metastases from a multidisciplinary approach is provided to enable an individualized approach aimed at cancer control and quality of life. Access to new systemic therapies, surgical techniques, and availability of technology for advanced radiotherapy techniques are also discussed.

Main message: Knowledge of specific mutations and targets of tumor receptors allows the selection of chemoimmunotherapy or current targeted therapies that offer better control potential at the systemic and intracranial levels. The sequence of systemic and local treatments (surgery, radiosurgery, whole brain radiation therapy) should be discussed as part of a multidisciplinary approach.

Conclusion: It is essential to estimate the prognosis of patients with BM, given that th is will determine the therapeutic behavior that can range from symptomatic care to more aggressive treatments such as neurosurgical resection or radiosurgery.

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Keywords:
DeCS: brain metastases, prognosis, treatment, surgery, radiosurgery, immunotherapy, targeted therapy.

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Introduction

The frequent misconception of physicians and patients regarding the prognosis of brain metastases (BMs) (Figure 1) has caused this population to receive less attention, leading to a nihilistic approach to clinical management. However, BMs represent a significant public health problem, considering that their occurrence is ten times more common than primary malignant brain tumors and is a significant cause of morbidity, anxiety, and mortality [1].

Optimizing systemic, neurosurgical, and radiotherapy treatments results in a better cancer survival rate. Furthermore, better access to diagnostic imaging has increased the incidence of BMs. It has been described that 20 to 40% of cancer patients will develop BMs [2, 3].

In the past, BM was considered terminal cancer with a life expectancy of only one month. In 1950, whole-brain radiation therapy (WBRT) was introduced as a standard treatment and increased life expectancy from 4 to 6 months. Later, studies established surgical resection followed by WBRT as the standard treatment for patients with single metastases and good performance status (Karnofski ≥ 70 or ECOG ≥ 2) [4, 5].

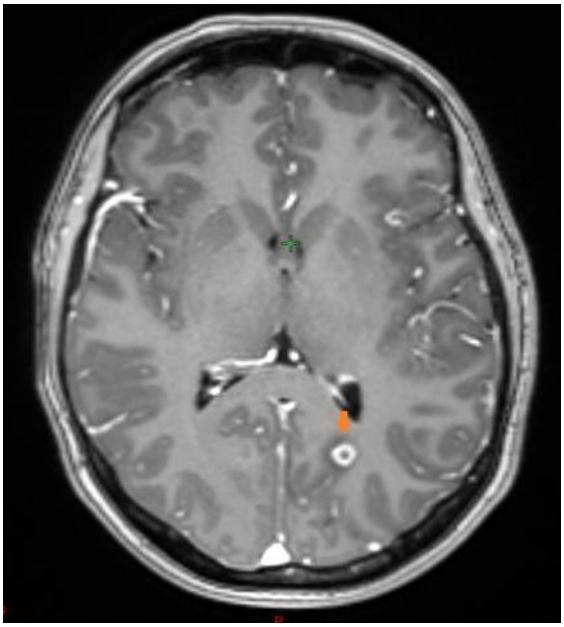

Figure 1. Magnetic resonance image, T1+ gadolinium axial view. The orange arrow shows a 6-mm lesion in the left occipital region, with peripheral postcontrast enhancement accompanied by perilesional edema.

Paradigm shift

The possibility of a cure for oligometastatic disease (number of metastases ≤ 3 or 5) has gained increasing attention in recent years as the field of oncology evolves. The treatment of these patients has changed enormously in recent decades. A few years ago, prognosis and survival were poor, and the disease was poorly controlled. The main goal of treatment of brain metastases is to achieve local control of the metastatic lesion, improve quality of life, prevent death from neurological disease, and improve survival in a subset of patients [5, 6].

Several treatment options are available: surgery, IFRT, radiosurgery (SRS), targeted therapy, and immunotherapy. The choice between these modalities depends on several factors, such as the prognosis of each patient, access to medications, availability of equipment, and treatment techniques [7-9.].

Regarding systemic treatment, a better understanding of the molecular mechanisms related to the development of brain metastases will improve more effective targeted treatment interventions. The molecular component of BM may differ from that of that of the primary tumor. Brastianos et al. performed whole-exome sequencing of 86 brain metastatic tissues and revealed that 53% of cases had alterations that were not detected in biopsies of the primary tumor. In this sense, it is essential to define which patients with BMs benefit from surgical treatment (see section -surgery-) [10, 11].

Epidemiology and clinical presentation

Lung, breast, melanoma, renal cell, and colorectal carcinomas remain the leading causes of adult BMs [10–13]. In the trastuzumab era, the incidence of BMs in patients with HER2-positive advanced breast cancer is 40% to 50%. In patients with ALK-rearranged non-small cell lung cancer, the central nervous system (CNS) is the first site of progression in 46% of patients treated with crizotinib [14, 15].

The clinical presentation can vary widely, from asymptomatic patients to a constellation of neurological symptoms, including headache, motor weakness, sensory disturbances, nausea and vomiting, cranial nerve abnormalities, mental status changes, seizures, ataxia, and speech and language disorders. The appearance depends on the location, size, perilesional edema, cerebrospinal fluid obstruction, or intracranial hypertension caused by the disease [15, 16].

Forecast

Through a multidisciplinary approach, treatment recommendations must balance the durability of intracranial tumor control, quality of life, and treatment side effects. In this context, a better understanding of which patients may survive months or years is clinically relevant [1, 17, 18].

Several models have been published to estimate survival. The first model was described by Gaspar et al. in 1997, discussing recursive partition analysis (RPA). Five more models were described in the following ten years (Table 1). However, these systems continue to assess, at

least in part, the control of the primary tumor, which is a subjective variable and often difficult to assess consistently [19, 20].

The Graded Prognostic Assessment (GPA) was developed from a database of almost 2000 patients accumulated in 4 RTOG protocols; this series was later refined to include patients treated at multiple institutions and to incorporate prognostic factors unique to different cancer types, resulting in the publication of the disease-specific (tumor site) GPA-DS- [21–24].

Viani G. et al. compared the GPA scale with other predictive models and concluded that GPA was the most sensitive method for estimating survival [25.].

Disease-specific GPA (DS-GPA) highlights the heterogeneity in survival among patients with different tumor types and underlines the importance of considering disease-specific variables. For example, for patients with breast cancer and brain metastases, the biological subtype of breast cancer (basal, luminal A, HER2 overexpression, or luminal B) is a crucial determinant of prognosis. Similar to non-small cell lung cancer, EFGR mutation or ALK translocation influences survival [20-24].

The leading cause of death (90%) in BM patients is extracranial disease. Therefore, adequate systemic treatment should be provided in addition to intracranial control of the disease[21].

Table 1. Models to estimate survival in patients with BM

	RPA§	Rotterdam ¥	SIR ‡	BS BM ¤	Overall average *
Age	✓	X	✓	X	✓
performance status	IK.	ECOG	IK.	IK.	IK.
Extracranial metastases	✓	✓	✓	✓	✓
Primary tumor control	✓	X	✓	✓	X
Number of BMs	X	X	✓	X	✓
BM volume	X	X	✓	X	X
response to steroids	X	✓	X	X	X

(§) Recursive partition analysis; (¥) Score Rotterdam; (‡) Score index for Radiosurgery; (¤) Basic Brain Metastasis
Score; (*) Graduated Prognostic Assessment; (KI) Karnofsky index; (ECOG) Eastern Cooperative Oncology Group.

Diagnosis

BM results from hematogenous spread, and the most common site of spread is the gray-white matter junction, where the caliber of blood vessels narrows, thus trapping tumor emboli[13].

Magnetic resonance imaging (MRI) is the "gold standard" imaging study for the diagnosis of these types of lesions because its sensitivity and specificity are superior to computed tomography (CT) and positron emission tomography (PET) [20]. BMs are typically ring-enhancing solid lesions with a pseudospherical shape that typically occur in 80% of the cerebral hemispheres, 15% of the cerebellum, and 5% of the brainstem (see Figure 1) [13, 20].

On MRI, metastatic lesions and primary CNS tumors can be enhanced with contrast material on a 3D T1 volumetric sequence for visualization in different planes; there may be changes in signal intensity on T2-weighted images, especially on FLAIR (fluid-attenuated in-

version recovery) sequences. Contrast enhancement is indicative of blood-brain barrier breakdown, and its different types (annular, nodular, heterogeneous) depend on the characteristics of the primary tumor [21].

The location, size, and number of metastatic lesions are essential factors and must be determined before recommending or initiating the most appropriate treatment. In patients treated with surgical resection, requesting MRI intraoperatively or within the first 72 hours after surgery is recommended to help differentiate between residual tumor and surgical material/bleeding. This recommendation is based on data from studies involving patients with malignant glioma [26-29].

Treatment

Symptom management

Systemic corticosteroids are the mainstay of symptomatic therapy for lesions with peritumoural edema and reduction of high levels of intracranial pressure. They play a role in stabilizing patients awaiting definitive tumor treatment and in the palliative management of edema associated with refractory tumors. Dexamethasone is the standard agent due to its high potency and relative lack of mineralocorticoid activity [30].

Controversy exists regarding the specific indications and doses because most trials in patients with brain metastases did not include the use of corticosteroids as a specific endpoint. In this sense, the initial dose must be individualized depending on the degree of edema and the severity of the symptoms. Since most side effects are also dose dependent, the goal is always to use the lowest dose necessary to control symptoms [31].

In patients with moderate to severe symptoms (e.g., severe headache, nausea, vomiting, and significant focal neurologic deficits), the initial dexamethasone regimen consisted of a 10-mg IV loading dose, followed by initial maintenance. 16 mg daily in two to four divided doses orally or intravenously. A loading dose is usually omitted for patients with milder symptoms, and smaller daily doses (4 to 8 mg divided once or twice daily) are usually adequate and less toxic. Most asymptomatic patients do not require steroids [30-33].

For patients in good clinical condition whose tumor has stabilized with current therapy, a taper may involve up to a 50% dose reduction every four days. An important fact to consider is that high-dose dexamethasone could impair outcomes in patients receiving anti-PD-1 or anti-PD-L1 antibodies [34, 35].

Seizures can occur in up to 25% of patients with BMs. Pharmacologic treatment is indicated in patients experiencing a seizure and those with a history of previously unreported or recognized seizure activity due to tumor activity. Conclusions from two meta-analyses and one systemic review indicate that the prophylactic use of antiepileptic drugs in patients without a history of seizures provides neither immediate nor long-term benefit in patients with BM [36–38]. The preferred treatment for patients with epilepsy and tumor-related seizures, antiseizure medications with minimal liver enzyme-inducing or inhibiting properties, typically include levetiracetam, topiramate, lamotrigine, lacosamide, pregabalin, and zonisamide [3–9].

Surgery

Advances in neurosurgery have drastically changed the treatment of patients with BM, improving survival and quality of life. The success of surgical treatment is based on three main pillars:

comprehensive preoperative evaluation with specific neuroimaging, adequate preparation of the approach and surgical plan, and rational use of intraoperative technology [40-43].

From standard MR imaging sequences to functional neuroimaging, preoperative studies in metastatic disease allow high-resolution detection of lesions and structures at risk, facilitating safe and effective surgical planning [44–47].

For example, keyhole craniotomies and tubular retractors represent a step toward minimally invasive neurosurgical approaches that ensure that patients receive optimal care while minimizing morbidity. On the other hand, techniques such as supramarginal surgery have pushed the limits to achieve more significant tumor resection [48-51].

Similarly, technological innovations in neuronavigation, intraoperative ultrasound, brain mapping, endoscopes, and fluorescence staining have enabled increasingly practical real-time, high-resolution imaging of the brain [50].

The main goals of surgical treatment are to obtain tissue to establish the diagnosis, reduce the symptomatic mass effect and vasogenic edema, definitively treat local lesions, improve quality of life, and prolong overall survival in combination with adjuvant radiotherapy [52
]. In addition, surgery may help confirm or establish the diagnosis in patients with an unclear history of primary cancer or a single brain injury. It has been reported that up to 11% of patients with single lesions have diagnoses other than metastatic disease [51].

Traditionally, the role of surgery in patients with BM has been limited to metastatic lesions with a diameter greater than at least 2 cm, symptomatic lesions, or lesions that can cause life-threatening cerebral edema. The European Association of Neuro-Oncology (EANO) recommends surgery in patients with a limited number (1 to 3) of brain metastases, lesions ≥ 3 cm in diameter (symptomatic or not), lesions with a necrotic or cystic appearance that results in edema and mass effect, posterior fossa lesions with concomitant hydrocephalus and symptomatic lesions in eloquent areas [53].

Surgery alone is not sufficient for local control of brain metastases and must be complemented by whole brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS), with SRS being preferred when safe and especially for small tumor volumes [54–56]. Other authors have indicated that surgery is preferable when, in general, gross total resection is achieved rather than subtotal resection, provided that a more aggressive resection does not result in permanent neurological injury [54, 55].

Whole-brain radiotherapy (WBRT)

Total cranial radiation therapy is the most widely used treatment for multiple brain metastases. -WBRT involves irradiation of the entire brain, including the leptomeninges. It is a widely available technique that can be started quickly and provides symptom relief [45]. A 2018 Cochrane systematic review advocates using a dose of 30 Gy in 10 fractions, and another fractionation used in the palliative setting is 20 Gy in 5 fractions. If the patient is receiving systemic treatment, it is generally recommended to stop it one week before and after WBRT [19, 46].

WBRT should be considered for patients with contraindicated radiosurgery or surgery who have a low GPA-DS score, leptomeningeal disease, and innumerable metastases. On the other hand, the benefit of IFRT compared to supportive care in patients with a survival of fewer than four months is controversial. [45 , 47 , 56-60].

The potential benefits of WBRT must be weighed against the potential risks of toxicity (rash, alopecia, fatigue, memory loss, confusion, and leukoencephalopathy). Prospective evidence demonstrates that the use of hippocampal-avoidance whole brain radiation therapy (HA-WBRT) plus memantine (Figure 2) decreases the involvement of neurocognitive domains in patients with a better four-month prognosis [19, 45, 48].

Another approach in which HA-WBRT has been used is integrated dose escalation in metastatic lesions to improve local intracranial control, reduce the likelihood of intracranial recurrence, and decrease cognitive decline. HA-WBRT plus integrated dose boosting was compared to SRS for multiple brain metastases in the phase 3 "HIPSTER _2020" trial (NCT04277403). These results will be available in 2023.

In the past, WBRT was performed with two opposing parallel fields; prospective data show an increase in xerostomia and dry eye symptoms. In this sense, it is proposed to limit the dose in the parotid and lacrimal (V20Gy < 47% and V20Gy < 15%, respectively). This dose limit is possible with techniques that modulate radiation intensity as used in HA-WBRT [51, 61–64]. In patients with complete resection of a single BM, additional WBRT reduced the incidence of intracranial progression from 70% to 18% (P < 0.001) and local recurrence from 46% to 10% (P < 0.001) in the WBRT groups and observational, respectively [45 , 4 , 9].

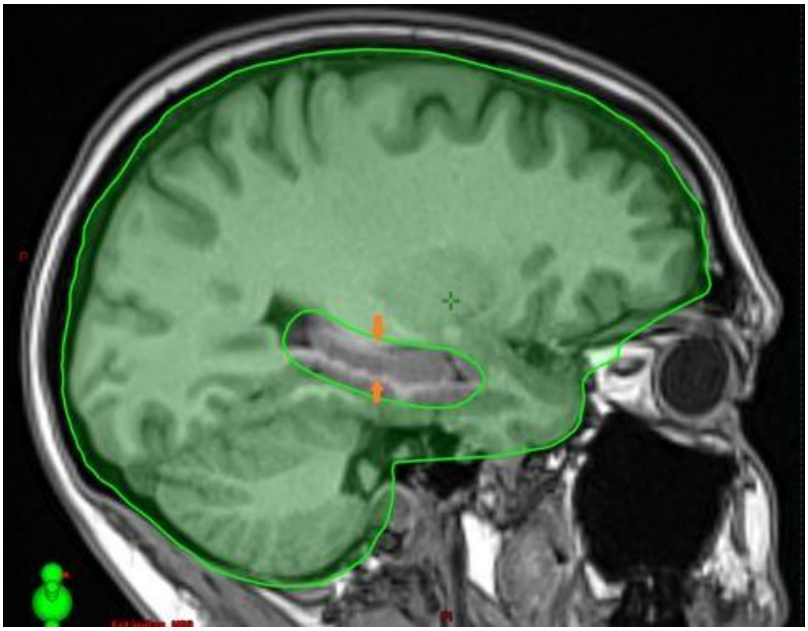

Figure 2. Sagittal view, hippocampal-avoidance whole-brain radiotherapy (orange arrows).

Radiosurgery (SRS)

SRS refers to a single dose of radiation delivered with high precision and focused on brain metastasis to maximize local control while sparing normal brain tissue [56]. Cognitive impairment after WBRT was evaluated in randomized trials comparing SRS versus WBRT plus SRS (Table 2) [19, 51].

SRS without WBRT is associated with a lower risk of cognitive decline and a higher risk of intracranial progression, although a corresponding reduction in overall survival has not been demonstrated [56–61].

These data have turned the WBRT treatment trend due to concerns about cognitive deficits. The consensus of the American Society for Radiation Oncology (ASTRO), the American Society of Clinical Oncology (ASCO), and the International Society for Stereotactic Radiosurgery (ISRS) recommend SRS as the standard of care in patients with 1-4 brain metastases and good prognosis (GPA > 2 points) [62-69].

Patients with these characteristics who present extensive metastases (greater than 2 cm) are more likely to develop radionecrosis if they are treated with SRS; in such a situation, hypofractionated SRS (27 Gy in 3 fractions) may offer better local control and less radionecrosis [70–74].

Patients treated with SRS alone are more likely to have intracranial progression (although controversial, it could also lead to loss of neurocognitive function) [5, 61]. It should be noted

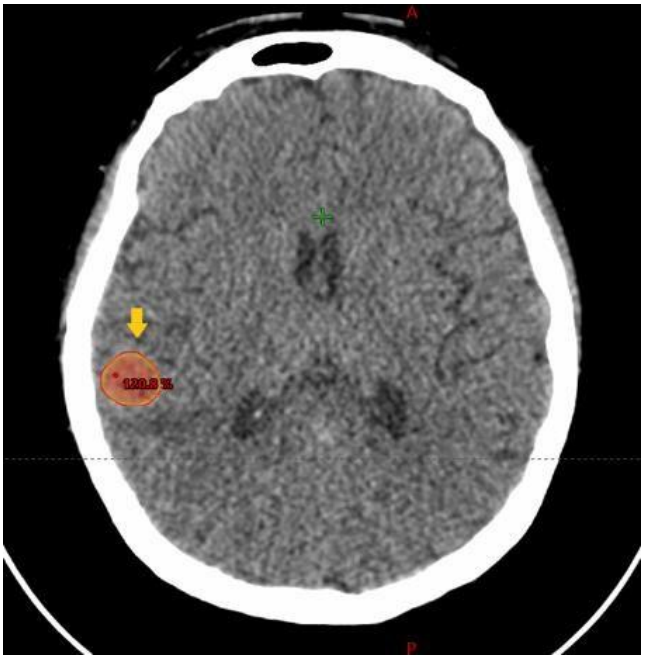

Figure 3. Axial view of the SRS dose 18 Gy. The isodose curve is at 100% (orange arrow).

that approximately 60% of these patients can be salvage treated with another radiation technique [65].

Table 2. Randomized studies comparing cognitive failure between WBRT vs. MR

Study	Treatment	N	Evaluation time	cognitive failure	*P*
MDACC [56] (2001-2007)	SRS [§]	30	4 months	24%	*P* = 0.012
	WBRT [¥] + SRS	28		52%	
RTOG 0614 [57] (2008-2010)	WBRT	252	3 months	72%	*P* = 0.01
	WBRT+M [‡]	256		63%	
RTOG 0933 [58] (2011-2012)	WBRT + HA [¤]	100	4 months	33%	*P* = 0.01
NRG CC001 [59] (2015-2018)	WBRT + M	257	4 months	63%	*P* = 0.01
	WBRT+HA+M	261		54%	
N0574 [60] (ALLIANCE) (2002-2013)	MR	111	3 months	twenty%	*P* <0.05
	WBRT+SRS	102		53%	

([§]) Radiosurgery; ([¥]) Whole brain radiation therapy; ([‡]) Memantine;([¤]) Hippocampal avoidance

SRS has been evaluated as a treatment in patients with more than 4 BMs. Nonrandomized prospective data in patients with newly diagnosed BM suggest that up to 10 metastases with the following characteristics can be treated: total intracranial cumulative volume less than 15 mL, each metastasis < 10 mL in volume, and < 3 cm in greatest diameter, with similar efficacy and no increase in toxicity compared to WBRT [67, 68]. NCCN guidelines and other authors suggest that the utility of tumor volume plays a more critical role in the decision between SRS and WBRT than the number of metastases [69-73].

For patients with "low" total intracranial cumulative tumor volume (<15-30 cc), radiosurgery may be an alternative to HA-WBRT, pending further phase III data. However, the definition of low total intracranial cumulative tumor volume requires prospective validation and is not well defined. For patients with a higher disease burden, HA-WBRT is more suitable due to poor prognosis for overall survival and higher rates of intracranial progression and neurologic death[51].

In addition to all the above features that support the choice between WBRT and SRS as initial treatment, Gorovets D. et al. proposed using a nomogram (based on retrospective data) in the initial evaluation to select the most suitable patients for SRS and to identify the need for salvage therapy after SRS and, consequently, patients in whom SRS has little or no benefit [74, 7, 5].

The use of metastatic brain velocity (BMV) to select the best salvage technique after CRS has been described. Patients with BMVs greater than 13 points may preferentially benefit from WBRT over radiosurgery as salvage therapy to prevent distant intracranial recurrence. Prospective validation of this principle is needed [51, 74].

The superior cost-effectiveness of SRS over SRS plus WBRT in patients with up to 10 brain metastases has been demonstrated in healthcare. How these results translate to other countries is unknown due to differences in reimbursement systems and costs for SRS and individual patient preferences [66].

Finally, SRS has been evaluated in preoperative and postoperative settings to reduce leptomeningeal spread or avoid IFRT in patients undergoing metastasectomy; however, prospective randomized data are lacking to make recommendations. In this regard, two trials III (NCT03750227 and NCT03741673) are currently underway to compare the efficacy of preoperative SRS with postoperative SRS [19].

Systemic treatment

Historically, surgery and radiotherapy have been considered the local therapies of choice for most patients with brain metastases from solid tumors; however, optimal management of this scenario must consider the clinical characteristics of the patient, the tumor subtype, and access to the different treatment options available.

The role of systemic therapy in the management of brain metastases has evolved dramatically in recent years; currently, targeted chemoimmunotherapies offer better control potential both at the systemic and intracranial levels, especially for some types of cancer where specific mutations and target receptors are present, such as melanoma, non-small cell lung cancer, and breast cancer [44, 76].

In patients with symptomatic brain metastases, local therapy should be offered regardless of the systemic therapy used for systemic disease, but in patients with asymptomatic brain metastases, local therapy may be delayed until there is evidence of intracranial progression.

For example, in melanoma based on BRAF mutation status, immunotherapy with nivolumab and ipilimumab or targeted therapy with BRAF/MEK inhibitors, such as dabrafenib plus trametinib, is increasingly being considered as first-line systemic therapy in patients with melanoma. Asymptomatic brain metastases leave locoregional treatment deferred until progression [40, 77–80].

In asymptomatic patients with non-small cell lung cancer mutations in EGFR or ALK, newer tyrosine kinase inhibitors, such as osimertinib, alectinib, brigatinib, and ceritinib, have shown high rates of intracranial responses and prolonged progression-free survival compared with earlier generation tyrosine kinase inhibitors and conventional chemotherapy [41, 42, 81
].

Systemic therapy can also be considered a suitable alternative to initial radiotherapy for selected patients with HER2-positive breast cancer, with the triplet of tucatinib, capecitabine, and trastuzumab due to its better progression-free and overall survival outcomes compared with capecitabine and trastuzumab [4–3].

Notably, all patients with brain metastases receiving isolated systemic therapy should be closely monitored for early progression of central nervous system disease and should undergo locoregional salvage therapy with radiation and surgery [44, 82]. For other malignancies, the evidence for systemic therapy alone or in combination with locoregional treatments is more limited and is not currently recommended as first-line therapy.

Recommendations

1. The prognosis of patients with brain metastases is the most critical factor determining therapeutic behavior. Therefore, it is recommended to use scales (GPA-SD) that allow for estimating survival.

2. Patients with symptomatic brain metastases should be offered local therapy, regardless of the systemic therapy used for systemic disease.

3. In patients with asymptomatic brain metastases, the decision to defer local therapy should be based on a multidisciplinary discussion of the potential benefits and harms to the patient and assess the possibility of targeted systemic treatment (see recommendation no. 8).

4. Surgery is recommended as the first treatment option in patients with large tumors with mass effects to confirm or establish a diagnosis in patients with an unclear history of primary cancer and single brain lesions.

5. For patients with 1-4 brain metastases with a prognosis >4 months (GPA >2 points), radiosurgery is recommended, and if the lesion is >2 cm, fractionated SRS is recommended.

6. Treatment with HA- RCTC is recommended in patients with >4 brain metastases and a prognosis greater than four months.

7. In patients undergoing metastasectomy, HA-WBRT versus radiosurgery should be offered at the surgical site.

8. Systemic treatment with targeted therapies should be considered depending on driver mutations and target receptors (melanoma, non-small cell lung cancer, and breast cancer).

9. Patients with a poor prognosis (< 4 months) should be treated exclusively with corticosteroids and supportive care.

10. Treatment recommendations should be contextualized and applied according to access to targeted therapy, availability of surgical and radiotherapy treatment techniques, costs, and the possibility of salvage treatment.

Conclusions

Estimating the prognosis of patients with BM will determine the therapeutic behavior that can vary from symptomatic care to more aggressive treatments such as neurosurgical resection or radiosurgery.

Abbreviations

HA-WBRT : Total cranial radiotherapy with protection of the hippocampus.
BM : Brain metastasis.
WBRT : Whole-brain
radiotherapySRS : Radiosurgery.

Administrative information

Additional Files

The authors declare none.

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It does not apply to observational studies with a review of databases or medical records.

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The authors declare that they have no conflict of interest or competence.

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