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Comprehensive Management of Brain Metastases in Patients with Non-Small Cell Lung Cancer: Emerging Therapies

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Abstract

Purpose: The optimal management of BMs remains uncertain due to a lack of high level evidence (as reflected in the lack of consensus in the main clinical guidelines) and the scant data from Randomized Controlled Trials (RCT) in lung cancer patients with BMs, who have been specifically excluded from most trials. The aim of the present article is to review the multidisciplinary management surgery, radiotherapy, and systemic therapy of brain metastases in NSCLC.

Methods: A literature review was made in this study. Neurosurgeons, Medical Oncologists and Radiation Oncologists were involved to carry out a multidisciplinary review in order to offer the most appropriate evidence. At least two specialists per area performed a review using PubMed, Scopus and Cochrane databases.

Results: Three main treatment modalities were identified: Local treatment including surgery, radiotherapy and radiosurgery. The second one, Systemic treatments: chemotherapy, target therapies and immunotherapy and the last modality was the combination of local treatments and the systemic ones.

Conclusion: Surgery and stereotactic radiosurgery are established treatment strategies for patients with NSCLC who develop brain metastases; however the management of 4 brain metastases or more is under investigation. The use of systemic therapy to manage brain metastases in asymptomatic patients is gaining ground, especially in patients with driver mutations. Regarding combination of local treatment and systemic ones, the sequence and the use of concomitant treatment remains unclear. Several trials are trying to answer this question.

Keywords: Brain metastases; SRS; Radiosurgery; Metastases

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Introduction

Non-Small Cell Lung Cancer (NSCLC) is the leading cause of cancer-related mortality. Brain Metastases (BM) the most common type of malignant intracranial tumors are present in 10% to 30% of patients at diagnosis, and more than 50% of patients with NSCLC will develop at least one lesion during the course of the disease [1]. The incidence of BMs in NSCLC has increased in recent years, in part due to the emergence of better diagnostic tests [2].

BMs are associated with a significant deterioration in Quality of Life (QoL) and Worse Overall Survival (OS). Management of these lesions is a significant therapeutic challenge, in part due to

the wide range of local (surgery and radiotherapy) and systemic treatment options (targeted therapies, immunotherapy), which have been shown to improve OS without negatively impacting QoL [2]. At present, the optimal management of BMs remains uncertain due to a lack of high level evidence (as reflected in the lack of consensus in the main clinical guidelines) and the scant data from Randomized Controlled Trials (RCT) in lung cancer patients with BMs, who have been specifically excluded from most trials.

Several different prognostic scales are available to individualize clinical decision-making, most notably the recently developed and validated Lung-molGPA index for NSCLC patients with BMs [3]. This index evaluates the molecular characteristics of the tumor to produce a prognostic score; in patients with the highest index scores, the estimated survival is approximately four years. Currently, the Lung-molGPA is considered the most useful prognostic tool for clinical practice in the era of personalized medicine and targeted therapies.

In this context, the aim of the present article was to review the multidisciplinary management surgery, radiotherapy, and systemic therapy of brain metastases in NSCLC.

Local Treatment

Surgery

Surgical treatment of BMs may be beneficial in appropriately selected patients. Surgery may have several possible aims, including tissue analysis, Local Control (LC), and the prevention of neurological symptoms to maintain QoL. However, surgery must always be planned in a multidisciplinary context. Clinicians must consider not only the primary tumor but also metastases. For the primary tumor, treatment selection must consider several key factors, including the prognosis, physiological condition, and the relative urgency of the different treatments.

Surgery is a highly effective tool to achieve local control of metastatic lesions. While good LC is considered essential in patients with a good prognosis, surgical resection of these metastases may not be indicated in patients with a short life expectancy. The patient's general physical condition must be sufficient to undergo surgery; in patient with lung cancer, respiratory function is a particularly important consideration. The optimal treatment sequence should also be considered, especially in cases with synchronous diagnosis, since Chemotherapy (ChT) and surgery must be separated by at least 2 to 3 weeks. For patients with advanced disease, complications related to previous ChT or radiotherapy increase the risk of surgical morbidity and must also be taken into consideration.

The most appropriate treatment for BMs will depend on several variables, including metastasis-related symptoms and the size, number and location of the lesions. Surgery is generally indicated for single metastatic lesions and data from RCTs confirm the value of this technique in these cases [4]. In patients with multiple BMs, the role of surgery is not as clear-cut due to the limited published data, although some studies have reported good results in patients with up to three lesions [5]. The size of the lesion is an especially important factor when choosing between Surgery and Stereotactic Radiosurgery (SRS). For larger lesions (>3 cm), the data suggest that SRS is less effective than surgery, which means that surgery should be the first option if feasible [6]. By contrast, smaller lesions (<1.5 cm) are usually better candidates for SRS. The optimal approach to lesions between 1.5 cm and 3 cm has not been established [7].

Surgery is more effective than SRS in resolving symptoms related to the mass effect of BMs, and surgery can provide rapid relief in symptomatic cases. The risk of treatment-related morbidity will depend, in large part, on the location of the metastases, which is why an individualized approach is essential. The advantages of surgery include rapid discontinuation of corticosteroids, easier radiographic interpretation of Magnetic Resonance Imaging (MRI) for follow-up purposes, histologic confirmation, and the potential to perform biomolecular studies for more precise selection of targeted therapy.

Technical aspects

Surgical resection of BMs is complex, requiring all of the resources of modern neurosurgery. Image guidance (neuronavigation or ultrasound) is considered essential to perform minimally-invasive surgery to limit the impact on healthy tissue. Surgical safety can be increase through neurophysiological monitoring when working in eloquent areas. When the appropriate technique is used, BMs can be resected through very small incisions with minimal alterations to the brain tissue, thus improving the balance between risks and benefits [8]. Most BMs can be resected safely, with minimal morbidity and discomfort [9]. Moreover, the hospitalization period is brief (1 to 2 days), thus reducing treatment-related discomfort. In patients with multiple or recurrent lesions, a small incision is essential to ensure a rapid recovery and allow patients to receive other adjuvant treatments in the future.

Ideally, en bloc resection should be attempted, as there is a higher risk of leptomeningeal dissemination when a piecemeal resection is performed in lesions located in the posterior fossa [10] or the supratentorial region [11]. Moreover, studies show that en bloc resection is not associated with increased morbidity [12]. The border between the metastatic lesion and brain tissue is well-defined in most cases; as a result, the resection can be performed without harming adjacent healthy brain tissue. Microscopic invasion is common and associated with a higher risk of local recurrence, which is why adjuvant radiotherapy is often required (Figure 1).

Radiotherapy

Whole-Brain Radiation Therapy (WBRT)

Historically, the median survival without WBRT is only 1 to 2 months *vs.* 4 to 6 months in those treated with WBRT. The phase III QUARTZ trial compared best supportive care with [13] and without WBRT in NSCLC patients with BMs who were not candidates for surgery or SRS, finding no significant between-group difference in OS or QoL. However, the study design was criticized due to the high proportion of patients (38%) with poor Performance Status (PS) and the short median survival (eight weeks), which was substantially less than previous studies. Consequently, while the results of that trial provide valuable data about patients with poor PS, the findings cannot be generalized to other patient populations.

The indications for WBRT after surgery or SRS have changed over time. Patchell et al. [14] conducted a RCT in patients with a single resected brain metastasis. After surgery, the patients were randomized to observation or WBRT. Patients in the WBRT arm had significantly lower local failure rates (10% *vs.* 46%, $p<0.001$) and distant failure rates (14% *vs.* 37%, $p<0.01$); no differences in OS were observed. Two studies compared SRS alone to SRS+WBRT [15,16]. In both studies, the local and distant failure rates in the brain were lower in the WBRT arm, without significant between-group differences in OS.

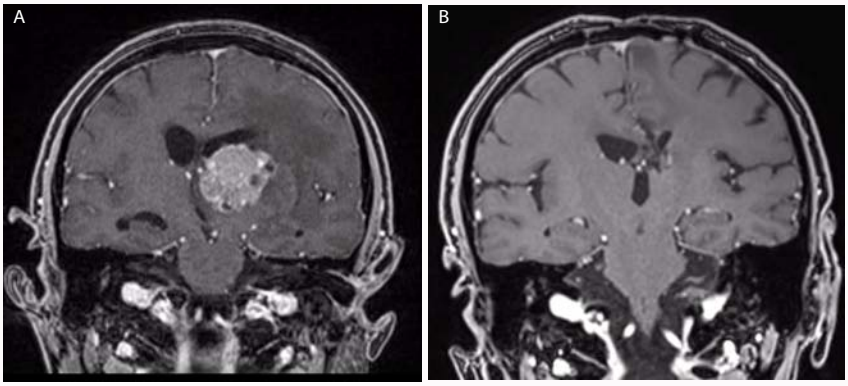

Figure 1: A) Magnetic resonance imaging shows the BM of a lung adenocarcinoma in the left thalamus. The lesion was resected by the interhemispheric route, followed by radiosurgery. B) The postoperative image one year later shows no recurrence, the patient made a functional recovery.

The neurocognitive impact of WBRT has been evaluated in four studies that compared outcomes in patients who underwent surgery or SRS with or without WBRT [16-19]. In all four studies, the WBRT arm experienced greater deterioration in neurocognitive function. These findings underscore the importance of protecting the hippocampus to minimize neurotoxicity in patients undergoing WBRT. These patients should also be given neuroprotective agents to further minimize the adverse effects of radiotherapy on neurocognition [20].

In summary, the available data indicate that WBRT reduces intracranial recurrence rates by approximately 50% and increases LC by 15% to 30%; however, it does not improve OS. Given the potential neurotoxicity associated with WBRT, SRS is increasingly accepted as the treatment of choice. In fact, if close monitoring with MRI is feasible, in most cases WBRT is not performed. Nevertheless, WBRT still has a role in the management of BMs in selected patients, such as those with symptomatic NSCLC and multiple large metastases (size >3 cm, volume >20 cc) and a poor Lung mol-GPA index score (<1.5). It also has a role in treating patients without driver mutations who are symptomatic and/or in those who develop disease progression to ChT. The use of adjuvant WBRT in surgically-treated patients is becoming increasingly rare, since SRS is the preferred approach in most cases.

The association between the Biologically Effective Dose (BED) of WBRT and OS remains unclear. Clinical guidelines, such as those published by the National Comprehensive Cancer Network (NCCN), recommend doses of 20 Gy to 40 Gy delivered in 5 to 20 fractions. Li et al. retrospectively evaluated 595 patients treated with WBRT between the years 2013-2015, stratifying the patients into four groups based on the radiation dose (no radiotherapy; <30 Gy, 30 Gy to 39 Gy; and >40 Gy). Median OS and intracranial Progression-Free Survival (PFS) rates were significantly higher ($p<0.001$) in the two high dose groups (30 Gy to 39 Gy and >40 Gy) than in the no radiotherapy or low dose (<30 Gy) groups. There were no significant differences ($p>0.50$) between the two high dose schemes [21].

WBRT +/- boost

Several studies have shown that WBRT combined with a boost is associated with better OS and LC rates in patients with a limited number of BMs [15,17,22]. Two types of boost are available, Sequential Boost (SEB) or Simultaneous Integrated Boost (SIB). A retrospective study in China (n=52) compared WBRT (30 Gy at 3 Gy/fx) + SEB (12 Gy at 4 Gy/fx) to WBRT (30 Gy at 10 Gy/fx) + SIB (40 Gy at 4 Gy/fx) in patients with a limited number of BMs (≤ 10) [23]. The SEB arm had better one-year survival rates (60% *vs.* 47%), longer median survival (15 *vs.* 10 months, $p<0.05$), and less cognitive impairment (significantly higher Mini-Mental State Examination [MMSE] scores at 3 months in the SEB arm, $p<0.05$).

Dobi et al. [24] retrospectively compared 468 patients with BMs treated with SEB or SIB, finding a higher OS rate in the SEB group. Several factors could explain this finding. First, tumor cells treated with WBRT experience develop hypoxia and SEB allows for a sufficient re-oxygenation time, which increases the radiosensitivity of tumor cells. Second, overlap of the treated area is lower when SEB is utilized. Finally, SEB is associated with less damage to normal brain tissue.

Radiosurgery

In recent decades, interest in SRS for the treatment of BMs in patients with NSCLC has increased substantially. SRS has several important advantages over surgery, including non-invasiveness, the capacity to treat lesions located in the eloquent cortex or multiple brain areas, and better compatibility with systemic therapies. In fact, SRS has become the treatment of choice for BMs in this patient population due to the lower impact on neurocognition and QoL compared to WBRT, and to the fact that this technique can now be performed in many radiation oncology departments (Table 1).

SRS was initially established as the standard treatment in patients with ≤ 3 to 4 metastases, with WBRT as a boost. In 2004, the RTOG 9508 boost study showed that this combined approach improved the neurological status of patients with good PS and 1-3 BMs, [22] and significantly improved OS in patients with unresected single brain metastases. In 2006, Aoyama and colleagues reported the result of the first RCT comparing SRS to SRS+WBRT in patients with up to four metastases (67% diagnosed with NSCLC) [15]. Although the one-year LC rate was higher in the WBRT group, there were no differences in OS or neurocognitive function. This finding confirmed that SRS could be used as salvage therapy for locally-recurrent lesions.

In recent years, several studies have assessed the role of SRS in the management of patients with multiple brain metastases [4-15,25-27], finding no significant differences between SRS and WBRT in terms of survival. Recently, the results of a phase III trial (NCT 01592968) comparing SRS to WBRT in patients with 4-15 BMs were presented at the 2020 meeting of the American Society for Radiation Oncology (ASTRO). In that trial, the two treatment modalities had comparable

Table 1: SRS *vs.* SRS +WBRT.

STUDY	Patient number	NSCLC %	Number of BMs	% LC SRS/ SRS +WBRT	% distant relaps SRS/ SRS +WBRT	Median OS (months) SRS/SRS +WBRT	% neurological deaths SRS/SRS +WBRT	Neurological deterioration/QoL SRS/ SRS +WBRT
JRSOG-99, Aoyama et al. [15]	132	66	1-4	27/11	64/41	8/7,5	19/23	Earlier deterioration in SRS
MD Anderson, Chang et al. [16]	58	67	1-3	33/0	55/27	15,2/5,7	RC+RTHC riesgo de muerte HP: 2,1, 96% CI:0,8-6,0	24/52
EORTC22952, Kocher et al. [18]	359	53	1-3	31/19	48/33	10,7-10,9	44/28	Global health 9 months: 63/52 Physical function 8 weeks: 52/42 Neurocognitive function 8 weeks: 81/74 Neurocognitive function 12months: 80/69
Alliance N0574, Brown et al. [19]	213	68	1-3	27/10	30/8	10,4/7,4	NA	Neurocognitive function 3 months 64%/92% P<0.001 QoL change -0.1/-20 P=0.001

Table 2: SRS in multiple brain metastases: Randomized trials underway

STUDY	Group	Randomization	Number of BMs	Primary objective
NCT 03550391	Canada Cancer Trial Group	SRS *vs.* WBRT+memantine	5-15	OS, neurocognitive function
NCT 02353000	MAASTRO Clinic	SRS *vs.* WBRT	04-10	QoL, neurocognitive function
NCT 03075072	Brighman and woman's Hospital/Dana Farber	SRS *vs.* WBRT	05-20	QoL
NCT 03775330	Sunnybrook Odette Cancer Center	SRS *vs.* WBRT+SRS	05-20	Neurocognitive function

OS outcomes, but SRS was associated with less cognitive impairment [28]. Several randomized trials are currently underway to compare these two treatments (Table 2), and the findings are expected to better define the optimal approach.

Based on the results of the RTOG 9005 trial [22], the optimal lesion size for a single dose of radiotherapy (18 Gy to 24 Gy) is 2 cm to 3 cm. Larger lesions require higher doses, but this increases the risk of adverse effects, thus effectively limiting the dose that can delivered, which in turn would negatively impact local control. To overcome these limitations, hypofractionated treatment generally 2 to 5 fractions and total dose of 24 Gy to 30 Gy is recommended in patients with large lesions. A meta-analysis published in 2019 found that hypofractionated radiotherapy reduces the risk of radiation necrosis [29], with comparable or better local control rates at one-year in patients with BMs or a large surgical bed (>3 cm or >14 cm^3).

Postoperative radiosurgery

Local recurrence rates after surgical resection of BMs can be as high as 70% [30], although adjuvant WBRT or SRS significantly reduce the local recurrence rate to as low as 3% (range, 3% to 28%) [14]. SRS is the most widely used treatment because survival outcomes are comparable to WBRT but with less neurotoxicity. The results of ongoing trials, such as the ESTRON trial in Germany [31] or NCT01372774, will confirm whether postoperative SRS should be the standard of care in patients with resected BMs.

A recent meta-analysis of 15 studies (3,458 patients) evaluated the role of postoperative SRS after excision of brain metastases [32]. At 12-months of follow-up, local and intracranial disease control rates were 83.7% and 52.8%, respectively. Local control rates were better with hypofractionated SRS compared to single fraction SRS. Radiation necrosis was described in 6.9% of the patients and Leptomeningeal Disease (LMD) in 13%.

The role of preoperative SRS has also been assessed [33]. The rationale for this approach is that it can reduce LMD rates, allows for better contouring of the lesion, which reduces the volume of irradiated healthy brain tissue. Two phase III studies (NCT03750227, NCT03741673) are currently comparing preoperative to postoperative SRS. The results of those trials will help to establish the therapeutic algorithm for patients with BM who are candidates for surgery.

Systemic Therapy

The role of systemic therapy in BM has been limited by the Blood-Brain Barrier (BBB), as the brain and meninges are "sanctuaries" for tumor cells, even in patients who present a systemic response to ChT. The emergence of targeted agents and immunotherapy in recent years has altered the treatment of metastatic NSCLC, in part because the BBB has less of an impact on the effectiveness of these new agents compared to older drugs. In this regard, the latest generations of targeted agents are notably more active due to their capacity to cross the BBB to reach the brain parenchyma; moreover, immunotherapy can activate the immune system outside of the Central Nervous System (CNS). Nevertheless, systemic therapy for BMs should form part of a multidisciplinary strategy. The main aim of ChT and first-generation targeted agents was systemic disease control, while local treatments (radiotherapy and surgery) were mainly aimed at controlling brain lesions. However, due to the greater activity of these new agents in the brain, these therapies can now be used to achieve disease control in this location. The most relevant clinical trials involving systemic therapies for the treatment of BMs, including ChT, targeted agents, and immunotherapy in patients with NSCLC, are shown in Table 3.

Chemotherapy and combined therapies

The combination of platinum-based ChT and pemetrexed is the most commonly used ChT regimen in stage IV NSCLC, even though the pivotal phase III trials did not include patients with BMs [34]. A phase II trial of first-line cisplatin-pemetrexed for patients with stage IV NSCLC and BMs not eligible for surgery or

Table 3: Systemic therapies: evidence and efficacy in NSCLC with brain metastases.

Biomarker	Line	Treatment	Year	Study	Brain metastases only?	Prior RT permitted	RR	PFS, months	OS, months
EGFR	1st	Afatinib	2015	LUX-Lung 3 [56]	No	Yes	82.10%	11.1	19.8
	1st	Afatinib	2015	LUX-Lung 6 [56]	No	Yes	60%	8.2	22.4
	2nd	Osmertinib	2017	AURA, AURA2 [57]	No	Yes	54%	NR	NA
	2nd	Osmertinib	2017	AURA 3 [58]	No	Yes	71%	8.5	NA
	1st	Osmertinib	2018	FLAURA [41,59]	No	Yes	91%	15.2	NR
ALK	1st	Brigatinib	2018	ALTA-1L [60]	No	Yes	78%	NR	NA
	1st	Alectinib	2017	ALEX [61]	No	Yes	81%	NR	NR
	1st and 2nd	Alectinib	2017	J-ALEX [62]	No	Yes	NA	1st: NR 2nd: 20.3	NR
	1st	Crizotinib	2016	PROFILE 1014 [42]	No	Yes	77%	9	NR
ROS1	2nd	Ceritinib	2017	Pan Korean Study [63]	No	Yes	63%	All: 9.3 Crizotinib naïve: 19.3	24
	1st	Entrectinib	2017	STARTRK-2 [64]	No	Yes	71%	19.1	NA
PD-L1	1st and 2nd	Pembrolizumab	2019	KEYNOTE-001 KEYNOTE-010 KEYNOTE-024 KEYNOTE-042 Pooled analysis [43]	No	Yes	26.10%	NA	NA
Chemotherapy	1st	Pemetrexed+cisplatin	2011	[35]	Yes	No	41.90%	4	7.4

OS: Overall Survival; RT: Radiotherapy; NA: Not Applicable/Not Available; NR: Not Reached

SRS reported intracranial and extracranial response rates of 42% and 34.5%, respectively [35]. For patients with squamous cell NSCLC, in which pemetrexed is not indicated, no specific phase II trials of platinum-based combinations have been performed in patients with BMs; however, some studies have reported response to ChT in this patient subpopulation, even without initial radiotherapy [36-38]. Antiangiogenics combined with ChT have been shown to improve both PFS and OS in NSCLC, although no specific trials have been carried out to evaluate this treatment approach in patients with BMs. Nevertheless, phase III trials evaluating docetaxel-nintedanib and docetaxel-ramucirumab have included patient subgroups with BMs [39,40], finding that the efficacy and safety outcomes for these combined treatments are similar in all patients.

Epidermal Growth Factor Receptor (EGFR) inhibitors

Between 10% and 30% of patients with NSCLC harbor EGFR mutations. Tyrosine Kinase Inhibitors (TKIs) are the main treatment for this subgroup of patients with stage IV disease. The most important trials of EGFR TKIs in patients with BM are summarized in the table. Osimertinib, a third-generation TKI, is a highly efficacious treatment, as evidenced by the excellent response rates obtained in the phase III FLAURA trial. In that RCT, patients with measurable BM treated with osimertinib had an intracranial response rate of 91% *vs.* only 68% in patients treated with first-generation TKIs [41].

ALK and ROS1 inhibitors

ALK gene rearrangements account for 3% to 5% of cases of NSCLC and this genetic mutation is associated with a higher risk of presenting BM at diagnosis or of developing these lesions during the course of disease. Genetic alterations in the ROS1 gene are less common (1%), but also associated with CNS dissemination. A study comparing crizotinib to ChT in patients with ALK rearrangements found better intracranial disease control with crizotinib [42]. Although crizotinib was the first drug to block this target, newer ALK inhibitors have proven even more effective at reducing the risk of brain progression. Consequently, the current treatment recommendation in this patient population is ALK TKI monotherapy, even in patients with brain metastases.

Immunotherapy

PD1 and PDL1 Immune Checkpoint Inhibitors (ICI) are the preferred treatment for patients with NSCLC with high PDL1 expression without driver mutations. These agents yield similar results in patients with and without BMs, provided that the brain lesions have been treated with local therapy and the patient is asymptomatic without corticosteroid treatment [43]. However, the effect of immunotherapy in patients who do not receive local treatment is not known due to the lack of clinical data.

Systemic Treatments Combined with Radiotherapy

Radiation therapy and targeted therapies

First-generation TKIs (gefitinib, erlotinib) achieved good response rates in patients with BMs [44,45], raising the possibility that radiotherapy could be delayed in these patients. However, recent studies have shown that upfront radiotherapy combined with TKIs results in better intracranial PFS and OS in patients with EGFR-mutated NSCLC than TKI monotherapy [46]. Other studies have shown that SRS combined with TKIs in patients with ≤ 3 BMs produces clinical outcomes that are comparable to WBRT, but with less neurological toxicity, making this the preferred therapeutic regimen [47,48]. However, it is important to note that those data are based on retrospective studies, which have important methodological limitations. The development of second-generation TKIs (osimertinib and alectinib in patients with EGFR mutations) and third-generation TKIs (ALK translocations) both of which show more activity in the brain than first-generation agents raise additional questions about the need for radiotherapy in asymptomatic patients. Consequently, randomized trials are needed to compare various combinations of

third-generation TKIs and local treatments (SRS and WBRT) to determine the optimal treatment sequence in these patients.

Radiotherapy and immunotherapy

Studies conducted in patients with metastatic melanoma to the brain have shown that combined treatment with SRS and ICIs is superior to monotherapy, with a low radiation necrosis rate (5%) that is comparable to that achieved with SRS alone [49,50]. However, in patients with metastatic lung cancer to the brain, the only available data to support this therapeutic approach come from retrospective studies [51,52] and one meta-analysis [53]. At present, although it is not clear whether combined therapy improves OS; concomitant therapy has been shown to improve local control and the duration of response when compared to sequential treatment, with no increase in the incidence of adverse effects in patients treated with SRS [54]. However, there are still many unresolved questions regarding the role of this combined approach. In addition, the definition of "concomitant" in this context remains unclear, as some authors consider radiotherapy to be concomitant when administered within five times the half-life of the immunotherapy agent. The optimal treatment sequence is also uncertain; it is not clear whether SRS should be performed before or after starting immunotherapy. Similarly, the impact of corticosteroids, which are routinely administered with SRS, on the efficacy of immunotherapy has not been determined yet [55], although trials currently underway are expected to resolve these questions.

Conclusions

The treatment paradigm of patients with metastatic NSCLC has undergone major changes in recent years. The management of brain metastases requires a comprehensive approach to select the most appropriate treatment, which requires an accurate assessment of estimated survival, the precise localization of the metastatic lesions, and assessment of the patient's symptoms.

Surgery and stereotactic radiosurgery are established treatment strategies for patients with NSCLC who develop brain metastases and considered standard treatment in patients with three or fewer BMs. In patients with more than four metastases, SRS has shown good results. Randomized controlled trials currently underway will help to more precisely define the role of SRS in this patient population. Hypofractionated SRS for the treatment of bulky metastases is associated with a lower incidence of radiation necrosis and better local control.

The use of systemic therapy to manage brain metastases in asymptomatic patients is gaining ground, especially in patients with driver mutations. In the future, the combination of systemic therapies (TKIs and immunotherapy) with SRS is likely to further improve local control and quality of life.

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