Review

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Review

Current Treatment Paradigms for Advanced Melanoma with Brain Metastases

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Abstract: Melanoma brain metastases (MBM) remain a major therapeutic challenge, requiring a multidisciplinary approach integrating systemic and local therapies. The advent of immune checkpoint inhibitors and targeted therapies has markedly improved patients' survival, with the combination of Ipilimumab and Nivolumab now considered as first-line systemic treatment for patients with asymptomatic MBM. Radiotherapy plays a crucial role, with stereotactic radiosurgery (SRS) now preferred over whole-brain radiotherapy (WBRT) due to its efficacy and lower risk of neurocognitive impairment. Retrospective data suggest a potential synergy between systemic therapy and SRS and emerging clinical evidence suggests that this combined approach may offer enhanced disease control and could become the standard of care. Key unresolved questions include the ideal sequencing of SRS with systemic treatments, the optimal radiation dose to balance efficacy and neuroprotection, and the identification of predictive biomarkers to refine patient selection. Emerging research focuses on tumor microenvironment interactions and novel radiosensitizers to enhance therapeutic outcomes. Furthermore, artificial intelligence-driven models integrating radiomics, radiogenomics, and metabolomics hold promise for advancing precision medicine in MBM management. Ongoing prospective clinical trials are crucial to establishing standardized treatment guidelines, ensuring a personalized, patient-centered approach that optimizes survival while preserving quality of life.

Keywords: melanoma; brain metastases; immunotherapy; targeted therapy; radiotherapy; stereotactic radiosurgery; multidisciplinary treatment

1. Introduction

Melanoma is a highly malignant tumor which develops from melanocytes; its primitive lesions, which are predominantly located in the skin, can also be found in mucous membranes and exhibit a strong inclination to aggressively metastasize to multiple organs, including the brain.

Brain involvement unfortunately represent a common scenario in patients diagnosed with advanced melanoma; nearly 30–40% of patients present brain metastases at some point during their disease course [1].

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Advancements in systemic treatments, such as the use of immune checkpoint inhibitors and targeted therapies, together with the improvements in radiotherapy and surgical techniques, have significantly extended survival rates for many melanoma patients. As a result, longer-term disease control has led to an increased incidence of brain metastases.

Risk factors for the development of Melanoma Brain Metastases (MBM) include male gender, head or neck as primary site of disease, the presence of nodal or visceral metastases, high serum lactate dehydrogenase (LDH) levels and high Breslow thickness of the primary lesion [2].

Initial clinical presentation of MBM includes headache, neurological impairment and seizures. Around 80% of MBM develops in the cerebral hemispheres, with a further 5% and 15% of MBM being located in the brain stem and cerebellum, respectively [3].

The prognosis for patients with MBM remains poor, with median survival rates often reported to be in the range from 6 to 9 months, although newer therapies have begun to improve these outcomes [4].

Early detection and accurate diagnosis are essential for tailoring the most effective treatment options and improving patient outcomes. Identifying MBM might be challenging because the brain represents a common site for metastases from several types of primary cancers and, furthermore, symptoms can be nonspecific. Clinical presentation varies widely depending on the size, number, and location of metastases; most typical symptoms include headaches, seizures, focal neurological deficits, cognitive changes, and visual disturbances. As the disease progresses, these symptoms tend to worsen [5].

Magnetic Resonance Imaging (MRI) is the gold standard modality for tracking brain metastases. Besides its high sensitivity, it provides detailed images of brain structures, being particularly effective in the detection of small or early metastatic lesions. Computed Tomography (CT) may be used in emergency settings when rapid imaging is required, however CT scans tend to be less sensitive for the detection of smaller lesions, and this may lead to false negative findings. Positron Emission Tomography (PET) scans, which are used to assess the activity of cancerous cells, can also be of help in identifying metastases which may not be clearly visible with other imaging techniques [6].

In case of diagnostic uncertainty and inconclusive neuroimaging, a biopsy can be performed. Brain tissues can be obtained via proper surgical procedures or through less invasive approaches, such as stereotactic biopsy.

Tissue specimens examination is essential for differential diagnosis and melanoma confirmation. Despite sharing many histological features with primary cutaneous melanoma, MBM show some typical traits that can help differentiate between the two of them.

MBM lesions often show infiltration of the brain parenchyma by malignant melanoma cells, typically arranged in sheets, nests or single-file patterns. Invasive growth into surrounding tissues, including perivascular spaces, is common. This infiltrative growth pattern, often without a well-defined border, is in sharp contrast with the more localized growth of some primary brain tumors and other metastases. The presence of necrosis, hemorrhage, and inflammation is not unusual. MBM often follow hematogenous dissemination, proving cancer aggressiveness, and biopsy specimens can show the presence of melanoma cells within blood vessels or brain parenchyma [7].

The diagnosis of MBM can be made with the identification of malignant melanocytes that show atypical features such as large cells with pleomorphic nuclei, a high nuclear-to-cytoplasmic ratio, irregular nuclear contours and abundant cytoplasm. The cytoplasm may contain melanin pigment, which is a hallmark of melanoma cells [8].

In cases where melanin is not visible, immunohistochemistry (IHC) is commonly used. IHC markers such as S100 protein, HMB-45, and Melan-A are specific to melanoma cells and help to differentiate it from other malignancies [8]. Additionally, SOX10 has emerged as a useful marker for identifying melanocytic tumors, including metastatic melanoma.

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2. Systemic Therapy

The treatment of metastatic melanoma may represent a challenging scenario in patients with clinically relevant metastatic sites, especially in case of brain involvement. Nowadays, multidisciplinary management is key: choosing the best therapeutic approach can have a profound impact on patients' outcome [9].

From 2011 the advent of novel systemic strategies, such as Immunotherapy (IO) and Targeted Therapy (TT), has changed the natural history of metastatic melanoma. Before the availability of these drugs, first-line chemotherapy containing dacarbazine, alone or in combination with other chemotherapeutics, had shown very limited activity, with Progression-Free Survival (PFS) rates of less than 2 months and only 25% of patients alive at 1 year; furthermore, no drug has shown activity in subsequent lines [10,11].

Currently available medications for the treatment of metastatic melanoma have the ambition of making cancer a chronic disease. The therapeutic approach usually ranges from single-agent schedules (monotherapy) to combination therapies, with the possibility of integrating locoregional treatments without increasing toxicity and rather improving patients' prognosis.

2.1. Immunotherapy

The first IO agent approved for the treatment of metastatic melanoma was Ipilimumab. This anti-CTLA4 monoclonal antibody was approved by the FDA in 2011 and showed survival advantage when compared with standard therapy [12,13]. Subsequently, two other immune check-point inhibitors (anti-PD1) received the approval as first line treatment options. In 2015, the use of Pembrolizumab demonstrated improved Overall Survival (OS) and PFS when compared with Ipilimumab; furthermore, the safety profile was in favor of the anti-PD1 molecule [14]. At the same time, Nivolumab showed comparable efficacy in the same setting of patients and this led to its approval by the FDA [15].

The next effort in immunotherapy was to combine the two strategies, anti-CTLA-4 and anti-PD1, with the aim of further increasing the therapeutic outcome. Hodi et al. demonstrated that the combination achieved the best median OS of approximately six years [16].

More recently, a new immunotherapy combination was approved: the association of Nivolumab with Relatlimab (an inhibitor of Lymphocyte-activation gene 3 - LAG-3) demonstrated an advantage in terms of PFS when compared with Nivolumab alone; furthermore, this combination showed a better safety profile than the Ipilimumab/Nivolumab combination [17].

2.2. Targeted Therapy

The BRAF gene mutation (the most common is V600E) can be found in almost 50% of melanoma cases and represents a relevant therapeutic target. BRAF and MEK inhibitors (BRAFi and MEKi) block the uncontrolled proliferation mechanism permanently activated in BRAF-mutated cells; in addition, the combination of the two molecules prevents resistance and reduces toxicity.

Vemurafenib/Cobimetinib, Dabrafenib/Trametinib and Encorafenib/Binimetinib are examples of BRAFi/MEKi combinations. These treatment schedules showed – when compared to standard treatments or BRAFi monotherapy – an advantage in terms of response rate (RR), PFS and OS [18–20]

Targeted Therapy (TT) is generally associated with a more rapid clinical response, so it can be particularly useful in symptomatic patients, leading to tumor shrinkage in a relatively short time interval [21].

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2.3. Treatment Combination and Sequencing

No head-to-head comparison studies have been conducted between immunotherapy and molecularly targeted therapy in the first-line setting; nonetheless, several trials have explored and compared different therapeutic sequences.

The DREAMSeq trial randomized BRAF MT patients to receive either first-line ipilimumab/nivolumab followed by dabrafenib/trametinib or the reverse sequence. The authors find out that starting with ipilimumab/nivolumab combination improves OS rather than administering dabrafenib/trametinib as, front line therapy [22]

The phase 2 SECOMBIT trial randomized BRAF-mutant patients into three treatment arms corresponding to three different sequencing strategies: in arm A, patients received Encorafenib/Binimetinib as first line followed by Ipi/Nivo as second line, in arm B patients received first line Ipi/Nivo and Encorafenib/Binimetinib as second line therapy, while in arm C patients received induction therapy with Encorafenib/Binimetinib for 8 weeks followed by Ipi/Nivo, and - at disease progression - Encorafenib/Binimetinib. The trial showed that Combo immunotherapy as first line, preceded or not by induction treatment with TT, offers the best outcome in terms of OS. TT confirmed its efficacy in terms of RR and remains a valid second line strategy [23].

Combining BRAFi/MEKi therapy was therefore tested with the aim of obtaining both a rapid response and a long-term disease control. Three combination triplets were tested: Atezolizumab/Vemurafenib/Cobimetinib, Pembrolizumab/Dabrafenib/Trametinib and Spartalizumab/Dabrafenib/Trametinib; only the first one received the FDA approval in 2020 showing a statistically significant advantage in PFS. However, the real clinical benefit of a triple combination strategy is still controversial and limited by the toxicity profile [24–26]

As a general rule, the choice of first line treatment and subsequent schedules to be adopted is still challenging and it has to be tailored for each patients considering several factors, both patient-related (age, comorbidities, symptoms) and disease-related (presence of brain metastasis, presence of visceral disease with impaired function, possibility of loco-regional approaches); furthermore, clinicians need also to consider possible previous treatments eventually received in different settings (adjuvant or neoadjuvant) when a therapy for advanced disease is undertaken [27,28].

3. Local Therapy

Standard brain-directed therapies, such as neurosurgical resection, stereotactic radiosurgery (SRS), and whole-brain radiation therapy (WBRT), are commonly employed to manage brain metastases (BM). However, tumor heterogeneity and the complex scenario of tumor microenvironment (TME) may often hinder their efficacy [29].

Determining the optimal treatment approach for brain metastases remains among the most debated issues. Local therapy selection requires careful consideration of several factors [30], including (a) size, number and location of the lesions, (b) the presence or absence of neurological symptoms, (c) the status of extracranial disease, expected survival, patient age, and performance status, (d) prior treatment history, (e) potential treatment-related toxicities, and (f) finally the expected efficacy of systemic therapies. Ongoing advancements in radiation therapy have introduced novel treatment options, leading to improved clinical outcomes for patients with melanoma brain metastases. However, the therapeutic management of brain metastases remains challenging and demands a multidisciplinary approach [31].

3.1. The Role of Surgery

Significant advancements in surgical techniques have revolutionized the invasive approach to brain metastases, including those from melanoma (MBM). Procedures such as awake craniotomy, functional monitoring, and intraoperative magnetic resonance imaging (MRI) have been pivotal in improving gross total resection rates while minimizing surgical morbidity. Historically, surgery has

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been a cornerstone of MBM treatment, particularly in patients with a limited number of lesions, symptomatic mass effects, or those requiring histological diagnosis due to diagnostic uncertainty [30]

Surgical resection remains crucial for patients presenting with large, symptomatic tumors unresponsive to supportive care or lesions deemed unsuitable for stereotactic radiosurgery (SRS). It provides both therapeutic and diagnostic benefits, especially when other intracranial pathologies need to be excluded. Modern technologies, including neuro-navigation, fluorescence-guided surgery, and intraoperative MRI, have enhanced the precision and safety of resections, even in proximity to eloquent brain regions [32]

Optimal patient selection is essential, as surgery is most effective in individuals with controlled extracranial disease and good performance status (e.g., Karnofsky Performance Score >70).

In patients with poor prognoses, the role of surgery may shift toward palliation, focusing on symptom relief rather than survival extension. For example, surgical intervention can rapidly alleviate severe symptoms caused by mass effects or intracranial pressure when other measures fail. It is recommended in cases of CNS metastasis-associated hemorrhage, a condition more frequently observed in melanoma brain metastases [33].

However, the role of surgery is limited by the localization of lesions, particularly in eloquent brain regions, and the potential risks of intra- and post-operative complications.

Research highlights that surgical resection, followed by adjuvant therapies, may enhance the efficacy of systemic treatments by alleviating intracranial disease-associated immunosuppression [34].

Although surgery historically represents a fundamental approach for the therapeutic management of MBM, it generally requires adjuvant treatments, such as radiotherapy. Clinical evidence underscores the importance of surgery in improving survival outcomes when combined with other treatments. For instance, retrospective data by Fife et al. demonstrated superior survival among patients undergoing surgery or surgery plus radiotherapy compared to non-surgical management (8.9 and 8.7 months for surgery and surgery + RT vs. 3.4 and 2.1 months for RT alone and supportive care, respectively) [35].

Moreover, randomized trials have shown that postoperative radiotherapy, such as whole-brain radiotherapy (WBRT), significantly reduces local recurrence rates, intracranial progression, and neurological mortality. Patchell et al. reported recurrence rates of 18% with surgery plus radiotherapy versus 70% for surgery alone [36]. These data are in line with Redmond et al. [37] and underscore the pivotal role of RT in addressing microscopic disease, improving local control and preventing intracranial progression.

3.2. The Role of Radiotherapy: From WBRT to SRS

Radiotherapy (RT) is a key component of the multidisciplinary management of melanoma brain metastases, bridging local control of disease with systemic strategies.

Whole-brain radiotherapy has been traditionally the standard approach for achieving comprehensive intracranial control, targeting visible metastases and microscopic disease. It has been widely regarded as the primary treatment modality for patients with multiple melanoma brain metastases [31].

WBRT, both in the postoperative setting and after previous SRS, has been a standard approach for decades. The most commonly adopted dose-fractionation regimens were 30 Gy in 10 fractions or 35 Gy in 14 fractions [38].

However, over the years, it has become evident that the use of WBRT is linked with significant neurocognitive decline, especially in memory and executive function, verbal fluency deterioration, fine motor skills, immediate recall, and delayed recall [39].

This issue has led to the development of Hippocampal-Avoidance Radiotherapy (HA-RT) for the treatment of brain metastases; this technique has shown prolonged preservation of cognitive

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function, when delivered together with memantine administration, without a detrimental effect on survival outcomes and toxicity, as described by Gondi et al. [40,41].

Given the radioresistant nature of melanoma, WBRT has demonstrated particularly limited efficacy in MBM treatment, with median survival ranging from 3 to 6 months in the absence of concurrent systemic therapy [42,43].

There is no clear evidence to support its use in combination with modern systemic therapies, particularly immune checkpoint inhibitors, and it is rather reserved for patients whose brain metastases have progressed during systemic therapy and who are not suitable for further surgery or SRS. According to the European consensus-based interdisciplinary guideline, WBRT is considered a palliative treatment that does not extend survival and is no longer recommended for managing melanoma brain [44].

3.3. Stereotactic Radiosurgery

Over the past several decades, the use of Stereotactic Radiosurgery (SRS) has spread worldwide, and it became the most frequently employed localized treatment for metastatic brain tumors [45].

Its safety and efficacy in terms of local control and survival were also tested in the clinical scenario of MBM patients [31,46]. Of note, SRS has emerged as the preferred radiotherapy modality for patients with a limited number of metastases (typically ≤5), delivering greatly conformal high-dose radiation to target lesions while sparing healthy surrounding brain tissue. Since SRS can be completed in as few as one to five sessions, it avoids delays in systemic therapy [38,47].

Advances in imaging, particularly through earlier detection of intracranial metastatic lesions via MRI, have further expanded the application of SRS, as smaller lesions identified earlier in the disease course tend to respond more favorably to this approach [33].

Concerning the postoperative setting, randomized controlled trials (RCTs) have demonstrated that applying SRS to the resection cavity significantly reduces local recurrence rate compared to cases where no adjuvant treatment is administered after surgery [48]. Moreover, postoperative SRS offers distinct advantages over WBRT, preserving cognitive function without compromising overall survival duration [49,50].

Pedersen et al. [51] recently showed data from a nationwide study involving 838 unselected patients with MBM (2015–2022); of these, 230 patients underwent brain metastasis surgical excision and 30 received postoperative SRS; no significant difference in OS, intracranial PFS, or local control rates were demonstrated between patients who received postoperative SRS and those who did not.

Other studies have consistently demonstrated that SRS achieves superior local control rates, often exceeding 80% at 12 months, while significantly reducing cognitive and quality-of-life impairments compared to WBRT [52].

Brown et al. [49] conducted a randomized, controlled phase 3 trial involving adult patients (18 years and older) from 48 institutions across the USA and Canada to evaluate the impact of SRS on survival and cognitive function compared to WBRT in individuals with resected brain metastases. The median overall survival was 12.2 months for SRS and 11.6 months for WBRT. The study found that SRS to the surgical cavity led to better cognitive outcomes than WBRT. Based on these findings, the authors concluded that SRS should be considered a standard of care approach as a less toxic alternative to WBRT.

A single-center, randomized, controlled phase 3 trial compared post-operative stereotactic radiosurgery to observation in patients with completely resected brain metastases. The median follow-up was 11.1 months. At 12 months, freedom from local recurrence was 43% in the observation group and 66% in the melanoma SRS group. This trial, which included patients who underwent surgical resection for one to three brain metastases, demonstrated that post-operative SRS to the resection cavity significantly prolonged time to local recurrence compared to observation. Additionally, the findings confirmed that surgical resection alone is inadequate for achieving durable local control of brain metastases [48].

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Resection followed by postoperative SRS presents several challenges. First, the risk of leptomeningeal disease (LMD), particularly the nodular subtype, is increased, as well as the possibility of developing radionecrosis (RN). Another issue to be considered is the variability among clinicians in defining the target volume, which can impact treatment consistency. To address these limitations, neoadjuvant SRS administered before resection has been proposed as a potential alternative approach in an international collaboration, the INTERNEO analyses, one of the largest cohorts of patients undergoing neoadjuvant and multi-fraction SRS for brain metastases (17% from melanoma) and also one with the with the longest median follow-up. Neoadjuvant SRS showed lower LR, RN, and nLMD rates, allowing for decreased cumulative treatment time of surgery and SRS [53].

A phase III trial from the USA comparing pre-operative to post-operative SRS is currently enrolling (NCT05438212).

In a randomized trial by Yamamoto, SRS without WBRT in patients with five to ten brain metastases was shown to be non-inferior to that delivered in patients having two to four brain metastases [34]. This finding has been reinforced by a meta-analysis evaluating tumor control probabilities for various lesion sizes treated with SRS or fractionated SRS (fSRS)[37].

For tumors ≤20 mm in diameter, single-dose SRS at 24 Gy achieved a 1-year local control rate of 95%. In contrast, larger tumors (21–40 mm) showed better outcomes with fractionated schedules: three to five fractions delivering 27–35 Gy yielded an 80% 1-year local control rate, suggesting that fractionation may be more effective for treating larger lesions [37].

The integration of SRS into clinical practice has also been possible due to the advancements in systemic therapies, particularly immune checkpoint inhibitors (ICIs) and targeted agents, which exhibit synergistic effects with SRS in controlling melanoma brain metastases [47].

SRS-induced immunogenic cell death has been proposed to enhance the efficacy of ICIs by promoting an abscopal effect, potentially improving systemic disease control [54].

Moreover, evidence supports the concurrent or sequential use of SRS with systemic therapies to optimize therapeutic synergy, as shown in preclinical and clinical studies [55].

Despite many advantages, SRS presents some limitations. Patients with extensive metastatic disease (>10 lesions) or diffuse intracranial burden may still require WBRT or systemic therapies as their primary treatments. Nonetheless, ongoing research continues to refine the role of SRS, particularly in combination with novel systemic agents, further solidifying its place in the evolving therapeutic landscape for melanoma brain metastases.

Table 1. SRS guidelines recommendations.

European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization of Research and Treatment of Cancer (EORTC) (44)	Eligible patients with brain metastases should be treated with stereotactic radiotherapy. Surgery can be an option when stereotactic radiotherapy is not possible.	Consensus rate: 100%
European Society for Medical Oncology (ESMO) consensus *[56]*	• Postoperative SRS to the resection cavity should be considered after complete resection of MBMs.	Consensus rate: 97%

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	• SRS with concurrent immunotherapy or targeted therapy appears to be safe, although strong evidence is lacking. • SRS is the preferred local treatment modality for limited asymptomatic BMs, with 'limited' BMs defined as 1–4 BMs with a maximum diameter of 4 cm or 5–10 BMs with the largest tumour <10 mL in volume and <3 cm in the longest diameter and a total cumulative volume of ≤15 mL.	Consensus rate: 90%
Cancer Council Australia *[57]*	SRS for single or small number of asympto- matic brain metastases (≤ 3 in diameter) to maximise local tumour control	
The US National Comprehensive Cancer Network (NCCN) guidelines *[58]*	Primary treatment for limited and multiple asymptomatic melanoma brain metastases	
ASTRO (American Society for Radiation Oncology)) *[59]*	• For patients with resected brain metastases, radiation therapy (SRS or WBRT) is Strong recommended to improve intracranial disease control.	Strong recommendation

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	• For patients with resected brain metastases and limited additional brain metastases, Strong SRS is recommended over WBRT	

Table 2. WBRT guidelines recommendations.

European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization of Research and Treatment of Cancer (EORTC) (44)	Whole brain radiotherapy can no longer be recommended for the treatment of melanoma brain metastases.	Consensus rate: 100%
European Society for Medical Oncology (ESMO) consensus *[56]*	• WBRT is not recommended after complete resection or SRS of MBMs. • The routine use of WBRT in MBMs not amenable to SRS and in LMD is discouraged and should be restricted to carefully selected patients.	Consensus rate: 100%
Cancer Council Australia *[57]*	WBRT used as the last-line palliative therapy for patients with multiple brain metastases that have progressed on systemic therapy and/or local therapy.	
The US National Comprehensive Cancer Network (NCCN) guidelines *[58]*	Disseminated systemic disease with poor systemic treatment options: Hippocampal avoidance with WBRT (HA-WBRT) + memantine	

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ASTRO (American Society for Radiation Oncology) *[59]*	For patients with favorable prognosis (estimated using a validated brain metastasis prognostic index) and brain metastases ineligible for surgery and/or SRS, WBRT is recommended as primary treatment. (HA-WBRT plus memantine)	Strong recommendation

4. RT+IO combinations

Combining systemic therapy with a local treatment, namely SRS, recently came out as a valid therapeutic option for patients with melanoma brain metastases. Several retrospective series demonstrated improved outcomes in terms of intracranial control of disease, and encouraging data concerning PFS and OS have also been described [46]. The initial success of the multimodal strategy seems to indicate a possible synergism between the two approaches; the so called "abscopal effect", which refers to a radiotherapy-induced anti-tumor response in unirradiated sites of disease, has been extensively reported in the literature [60] and it may represent the evidence of the augmented efficacy of Immune Checkpoint Inhibitors (ICIs) in stage IV melanoma. More specifically, the administration of stereotactic radiotherapy as metastases-directed therapy could enhance tumor antigens presentation to CD8 T cells and induce the release of pro-inflammatory cytokines, ultimately leading to hyperactivation of the immune response and immunogenic cell death outside the irradiated areas [61]. Despite this intriguing rationale, the evidence that we have collected so far on the combined approach comes from retrospective series as we currently lack data from specifically designed randomized trials, which could help us addressing the open issues on its safety and the optimal therapeutic sequence.

In 2022, Franklin et al. analyzed the impact of radiation therapy in a large real-world cohort of 450 patients diagnosed with melanoma brain metastases (MBM) and receiving three different schedules of first-line systemic therapy (combined CTLA-4 and PD-1 blockade, PD1 blockade monotherapy or BRAF+MEKTT). The authors found out that the addition of Stereotactic Radiotherapy led to a significantly longer median survival irrespective of the systemic treatment received, and SRS was confirmed as independent prognostic factor for OS in their multivariate analysis; of interest, a positive effect on OS was also demonstrated for those patients receiving conventional radiotherapy, which included post-operative RT to the tumor cavity or whole-brain radiotherapy (WBRT). Concerning toxicity, radionecrosis was described in four patients received SRS and ICIs; timing of SRS – before or during systemic treatment- couldn't be included in the multivariate analysis for the limited number of cases [62].

A multicenter retrospective series conducted by Mandalà et al. demonstrated an improved OS in MBM patients receiving IPI-Nivo combination and SRS when compared to those receiving WBRT (30.5 months vs 18.2 months), irrespective of radiation being performed in a concomitant (within two weeks from IO start/end) or sequential manner; furthermore, the authors demonstrated a statistically significant OS benefit with the addition of SRS to immunotherapy COMBO rather than COMBO alone, both in asymptomatic and symptomatic patients [63].

The association of SRS with combination immunotherapy proved to be superior to exclusive SRS in the group of MBM patients included in the metanalysis by Badrigilan et al.; in this study, the benefit

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of SRS was greater when radiotherapy was administered concomitantly with ICIs (not more than four weeks between the two treatments) rather than sequentially (ICIs prescribed more than four weeks before or after radiation) [64].

Interestingly, in another metanalysis [65] it was shown that the co-administration of SRS with systemic therapy was associated with improved OS than SRS alone only if ICIs were prescribed; on the contrary, no benefit was registered in those patients receving SRS + targeted therapy with BRAF/MEK inhibitors when compared to the ones treated with exclusive SRS.

Important data on the safety of the combined radio-immunotherapy approach can be ruled out from the pooled analysis by Congzhou Sha et al., which included nearly 14000 patients, including MBM, treated with ICIs alone and 1442 patients treated with ICIs + radiotherapy. The authors demonstrated comparable grade 3-4 toxicity in patients treated ICI + RT compared to ICI alone in the setting of melanoma brain metastases, NSCLC, and prostate cancer [66].

5. Discussion and Conclusion

During the recent decades, the advent of immunotherapy has dramatically altered melanoma therapeutic landscape and, in parallel, SRS seems to be on the way to fully replace WBRT for the treatment of brain metastases due to its increased efficacy and major safety. Despite the considerable amount of retrospective data that suggests the benefit and the potential synergies of SRS with systemic therapy, currently there is no consensus on the use of the combined treatment strategy for patients diagnosed with melanoma brain metastases [31].

Several pending issues need to be addressed, including the optimal time-interval between systemic therapy start and SRS, the appropriate radiation dose to be delivered to obtain brain tumor control without impairing neurocognitive function and, on this regard, the need for the development of novel targeted therapies and radiosensitizers who could further maximize the therapeutic index of the combination strategy [67].

Current lines of research are exploring the molecular landscape of metastatic melanoma, in order to identify immuno-related predictive biomarkers which could anticipate response to systemic therapy or unveil the development of therapeutic resistance. Furthermore, in the setting of melanoma brain metastases, there is growing interest in the possible crosstalk between tumor cells and the surrounding microenvironment, with the identification of signaling pathways which may be crucial for tumor progression and therefore appealing as possible therapeutic targets [68].

The difficulty in obtaining samples has historically limited the research horizons for metastatic cancer with brain involvement. In this scenario, AI offers the potential to overcome this issue by creating integrated models and platforms which include radiomics, radiogenomics and metabolomics data to improve our current knowledge and to guide specifically targeted therapeutic approaches [69].

Results from multiple ongoing prospective clinical trials are eagerly awaited in order to better define the standard of care in the setting of MBM patients, starting from the assumption that multidisciplinary shared-decision making remains key and the proposed therapeutic approach should be patient-tailored and aiming to preserve patients' quality of life.

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