Review Article

Immune Checkpoint Inhibitors Combined With Radiotherapy in Metastatic Melanoma: Impact on Overall Survival and Tumor Control

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Abstract

Metastatic melanoma is an aggressive malignancy characterized by a high mutational burden that confers strong intrinsic immunogenicity, enabling recognition by the host immune system. This biological feature has positioned immune checkpoint inhibitors as a cornerstone of modern melanoma therapy, leading to significant improvements in survival outcomes. Nevertheless, durable responses remain limited by immune evasion mechanisms, intratumoral heterogeneity, and the development of primary or acquired resistance. In this context, radiotherapy has emerged as a relevant immunomodulatory strategy rather than a purely local or palliative treatment. Beyond its cytotoxic effects, radiotherapy promotes immunogenic cell death, enhances tumor antigen release, and induces remodeling of the tumor microenvironment, thereby potentiating systemic antitumor immune responses.The combination of radiotherapy with immune checkpoint inhibitors is supported by a

strong biological rationale and growing clinical evidence. Preclinical and clinical studies demonstrate that this approach can amplify T-cell activation, facilitate antigen presentation, and promote systemic immune effects such as the abscopal phenomenon. Clinically, combined therapy has been associated with higher objective response rates, improved progression-free survival, and enhanced local and systemic tumor control compared with immunotherapy alone, particularly in challenging scenarios such as brain metastases or resistance to anti–PD-1 monotherapy. While short-term overall survival benefits remain less consistent, longer-term disease control suggests meaningful therapeutic synergy.Treatment efficacy is influenced by several factors, including the timing of radiotherapy relative to immunotherapy, radiation dose and fractionation, irradiated tumor volume, and patient-specific immunological characteristics. Although combined treatment is associated with a high incidence of immune-related adverse events, available evidence indicates that toxicity remains manageable and does not significantly exceed that observed with immunotherapy alone when appropriate monitoring is applied.

Key words

Tumor microenvironment, abscopal effect, immunogenic cell death, treatment sequencing, brain metastases, immune-related toxicity.

Introduction

Metastatic melanoma is characterized by an aggressive clinical course and a persistently poor prognosis, with limited survival rates despite advances in systemic therapies. Conventional treatment modalities, including chemotherapy and targeted therapies, have historically been constrained by the development of therapeutic resistance, underscoring the need for novel and more effective treatment strategies [1]. In this context, a major therapeutic shift has occurred with the introduction of immune checkpoint inhibitors, such as anti–PD-1 and anti–CTLA-4 antibodies, which have fundamentally transformed the management of metastatic melanoma by enhancing the immune system's capacity to recognize and eliminate malignant cells [2]. Although these agents have demonstrated substantial improvements in survival outcomes, a significant proportion of patients fail to achieve durable responses, highlighting the limitations of monotherapy and the growing interest in rational combination approaches [3].

Against this background, radiotherapy has emerged as a relevant immune-modulating strategy rather than solely a local treatment modality. Beyond its cytotoxic effects, radiotherapy can induce immunogenic cell death, enhance tumor antigen presentation, and favorably alter the tumor microenvironment, thereby increasing tumor susceptibility to immune-mediated attack [4, 5]. Through these mechanisms, radiotherapy has the potential to transform immunologically "cold" tumors into "hot" tumors, which are more responsive to immune checkpoint inhibition, further supporting its integration with immunotherapy-based regimens [2].

The rationale for combining radiotherapy with immune checkpoint inhibitors lies in their complementary mechanisms, aimed at amplifying systemic antitumor immunity and achieving improved local and distant tumor control. This synergy may give rise to systemic responses such as the abscopal effect, in which regression occurs in non-irradiated metastatic lesions [1, 6]. Clinical evidence suggests that this combined approach can result in higher objective response and disease control rates compared with immune checkpoint inhibition alone, particularly in clinically challenging scenarios such as melanoma with brain metastases [3]. Moreover, concurrent radiotherapy and immunotherapy have been associated with prolonged survival

and distinctive immune-related phenomena, including pseudoprogression and abscopal responses, which reflect enhanced systemic immune activation and reinforce the biological plausibility of this therapeutic strategy [7].

The objective of this article is to critically analyze the impact of combining immune checkpoint inhibitors with radiotherapy in metastatic melanoma, with a particular focus on overall survival and tumor control, by integrating current clinical evidence and underlying biological mechanisms that support this therapeutic strategy.

Methodology

This manuscript was developed as a narrative review focused on the clinical and biological rationale for combining immune checkpoint inhibitors with radiotherapy in patients with metastatic melanoma, with the objective of integrating current evidence on treatment outcomes, immune mechanisms, and therapeutic interactions relevant to overall survival and tumor control. The content was organized from a clinically oriented perspective, emphasizing the immunobiology of melanoma, the mechanisms of action of immune checkpoint inhibition, the immune-modulating effects of radiotherapy, and their synergistic interaction, while prioritizing clinical applicability and pathophysiological coherence over rigid methodological structuring.

The narrative synthesis was supported by selective consultation of peer-reviewed literature published between 2021 and 2026 in English or Spanish and indexed in PubMed, Scopus, and Web of Science. Studies were incorporated when they addressed key aspects of combined radiotherapy and immunotherapy in metastatic melanoma, including clinical efficacy, survival outcomes, tumor control, treatment sequencing, toxicity profiles, and immunological correlates of response, while non–peer-reviewed publications, studies with incomplete or duplicated data, or those not directly related to therapeutic evaluation were excluded. The literature was examined through a qualitative and integrative approach to extract and organize information on biological rationale, clinical outcomes, and factors influencing treatment response and safety. Artificial intelligence–based resources were used exclusively as complementary tools to support thematic organization and conceptual integration of clinical and immunobiological data, enabling the development of a coherent and concise synthesis that highlights the potential clinical value and current limitations of combining immune checkpoint inhibitors with radiotherapy in metastatic melanoma.

Immunobiology of Metastatic Melanoma

Melanoma is considered a highly immunogenic malignancy largely due to its elevated mutational burden, which leads to the generation of numerous neoantigens capable of being recognized by the immune system [8]. Within this immunogenic context, the presence of tumor-infiltrating lymphocytes plays a central role in mediating effective antitumor immune responses, and their abundance has consistently been correlated with improved clinical outcomes in patients treated with immune checkpoint inhibitors [4]. In parallel, radiotherapy has been shown to further enhance the immunogenicity of melanoma by increasing tumor antigen presentation and promoting the release of tumor-derived antigens, thereby potentially augmenting the efficacy of immune checkpoint inhibitors when both modalities are combined [9, 10].

Despite this intrinsic immunogenicity, melanoma is capable of deploying multiple immune evasion strategies that limit durable treatment responses. One of the most prominent mechanisms involves the expression of immune checkpoint molecules that suppress T-cell activation and attenuate effective antitumor immunity. Additionally, intratumoral heterogeneity contributes to immune escape by enabling distinct melanoma cell populations to adapt to immune pressure, ultimately fostering resistance to therapy [11]. At the molecular level, reactivation of oncogenic signaling pathways such as the MAPK cascade

has been identified as a relevant mechanism of resistance to immune checkpoint inhibition, further emphasizing the need for combination therapeutic strategies capable of overcoming these adaptive barriers [12].

These immune escape mechanisms are closely linked to the characteristics of the tumor microenvironment, which plays a pivotal role in disease progression and therapeutic resistance. In melanoma, the tumor microenvironment comprises a complex network of immune and stromal components, including cancer-associated fibroblasts, M2-polarized macrophages, and myeloid-derived suppressor cells, all of which can promote tumor growth and limit responsiveness to immune checkpoint inhibitors [13]. A so-called "cold" tumor microenvironment, defined by low immune cell infiltration, is typically associated with poor responses to immunotherapy. In this setting, radiotherapy can induce meaningful microenvironmental remodeling, converting immunologically cold tumors into more inflamed, or "hot," environments that are more amenable to immune checkpoint inhibition [9, 10]. Moreover, the presence of specific immune cell subsets within the tumor microenvironment, such as B cells and T follicular helper–like cells, has been associated with improved responses to immune checkpoint inhibitors, whereas dominance of macrophage and monocyte populations has been linked to therapeutic resistance, underscoring the prognostic and predictive relevance of microenvironmental composition in metastatic melanoma [14].

Immune Checkpoint Inhibitors in Metastatic Melanoma

Immune checkpoint inhibition in metastatic melanoma is primarily mediated through blockade of the CTLA-4 and PD-1/PD-L1 pathways, both of which play central roles in downregulating antitumor immune responses. CTLA-4 functions as an inhibitory receptor that limits early T-cell activation and proliferation. Pharmacological inhibition of CTLA-4 with agents such as ipilimumab removes this regulatory constraint, thereby enhancing T-cell priming and expansion and ultimately promoting increased antitumor immune activity [15, 16]. In parallel, the PD-1/PD-L1 axis operates predominantly in peripheral tissues and within the tumor microenvironment. PD-1, expressed on activated T cells, interacts with PD-L1 on tumor cells to suppress T-cell effector function. Monoclonal antibodies such as nivolumab and pembrolizumab disrupt this interaction, leading to reinvigoration of exhausted T cells and restoration of effective immune-mediated tumor cell killing [8, 15].

Clinically, immune checkpoint inhibitors have demonstrated substantial efficacy in metastatic melanoma, particularly when used as monotherapy. Agents such as nivolumab have been associated with meaningful improvements in overall survival, establishing immune checkpoint blockade as a cornerstone of modern melanoma treatment [15]. Beyond monotherapy, the combination of immune checkpoint inhibitors with radiotherapy has gained increasing attention, as this approach has been shown to further improve objective response rates and progression-free survival compared with immune checkpoint inhibition alone. For example, combined treatment strategies have demonstrated higher objective response rates, reaching 35%, compared with 20.39% observed with immune checkpoint inhibitors alone, suggesting a clinically relevant synergistic effect [17]. Additionally, dual immune checkpoint blockade, such as the combination of ipilimumab and nivolumab targeting CTLA-4 and PD-1 simultaneously, has been associated with enhanced therapeutic efficacy, albeit at the cost of increased toxicity [16, 18].

Despite these advances, several limitations remain that constrain the broader effectiveness of immune checkpoint inhibitor–based therapies. Resistance to immune checkpoint inhibition may be present at treatment initiation or develop over time, with contributing mechanisms including

low intrinsic tumor immunogenicity and genetic alterations that impair immune recognition and response [15, 19]. In addition, immune-related adverse events represent a significant clinical concern, particularly in the context of combination therapies, which are frequently associated with higher rates of severe toxicity compared with monotherapy. These adverse events can involve multiple organ systems and require vigilant monitoring and timely management to minimize morbidity [3]. Furthermore, variability in individual patient responses and the high economic burden associated with immune checkpoint inhibitors pose additional clinical challenges, reinforcing the need for personalized treatment strategies and continued research aimed at optimizing therapeutic efficacy and safety [8, 15].

Role of Radiotherapy in Metastatic Melanoma

The role of radiotherapy in the management of melanoma has evolved substantially over time. Historically, radiotherapy was used predominantly with palliative intent in metastatic melanoma, aiming mainly to alleviate symptoms rather than achieve durable disease control. More recently, however, advances in radiotherapy techniques and a deeper understanding of tumor–immune interactions have highlighted its potential contribution to systemic disease control, particularly when combined with immune checkpoint inhibitors. This combination has drawn attention due to its ability to induce systemic immune-mediated responses, including the abscopal effect, in which regression is observed in non-irradiated tumor sites [1, 20].

The integration of radiotherapy with immunotherapy has been associated with improved overall response rates compared with immune checkpoint inhibitor therapy alone, although its definitive impact on overall survival remains less clearly defined. This observed synergy is largely attributed to the capacity of radiotherapy to increase tumor antigen visibility and enhance immune system activation, thereby potentiating the effects of immune checkpoint blockade [17, 21].

Different radiotherapy approaches have been explored in this setting, each with distinct clinical implications. Conventional radiotherapy, which typically involves fractionated doses administered over several weeks, continues to be primarily employed for palliation and local tumor control at symptomatic sites [20]. In contrast, hypofractionated radiotherapy delivers higher doses over fewer treatment sessions and has been associated with increased complete response rates when combined with anti–PD-1 therapies, particularly in patients who have failed prior systemic treatments [22]. Stereotactic radiotherapy, characterized by highly precise tumor targeting and minimal exposure of surrounding tissues, has also gained prominence. When combined with immune checkpoint inhibitors, stereotactic approaches have shown potential benefits in the management of brain metastases, although their effects on local control and disease-free survival remain under active investigation [23].

Clinically, radiotherapy continues to serve multiple roles in metastatic melanoma. For local control, it is effective in limiting tumor progression, especially when used alongside immune checkpoint inhibitors, which may amplify systemic immune responses and contribute to tumor regression beyond the irradiated field. Radiotherapy also remains a cornerstone of palliative care, providing symptom relief in advanced disease, with the addition of immunotherapy offering the potential to further improve quality of life by prolonging progression-free survival [20, 24]. In the setting of oligometastatic disease, radiotherapy can be directed toward selected metastatic lesions, with the goal of achieving long-term disease control when combined with systemic treatments such as immune checkpoint inhibitors [25].

Biological Rationale for Combining Radiotherapy and Immunotherapy

Radiotherapy can induce a form of cell death that is immunogenic in nature, thereby increasing the visibility of tumor cells to the immune system through the release of damage-associated molecular patterns (DAMPs) [5]. This process is characterized by a coordinated series of molecular events, including the translocation of calreticulin to the tumor cell surface, the extracellular release of adenosine triphosphate, and the secretion of high-mobility group box 1 protein. Together, these signals promote the activation and maturation of dendritic cells and facilitate efficient presentation of tumor antigens to T lymphocytes, thereby linking local radiation-induced cytotoxicity to adaptive immune activation [26].

In parallel with these local immunogenic effects, radiotherapy enhances the release of tumor-derived neoantigens, which are subsequently captured by antigen-presenting cells and presented to T cells, leading to amplification of systemic immune responses [27]. This antigen-driven process is essential for the activation and clonal expansion of tumor-specific CD8+ T cells, which acquire the capacity to recognize and eliminate not only irradiated tumor cells but also malignant cells at distant, non-irradiated sites. As a result, radiotherapy contributes to the development of a systemic antitumor immune response that extends beyond the local treatment field [4, 5].

The systemic immune activation induced by radiotherapy underlies the abscopal effect, a phenomenon in which localized irradiation leads to regression of metastatic lesions outside the irradiated area through immune-mediated mechanisms [1, 27]. The combination of radiotherapy with immune checkpoint inhibitors has been shown to enhance both the frequency and magnitude of this effect, as immune checkpoint blockade further augments T-cell activation and effector function, enabling more effective immune recognition and destruction of tumor cells at distant sites [20, 28]. Clinical studies have consequently reported improved overall response rates and survival outcomes in patients treated with combined radiotherapy and immune checkpoint inhibitors compared with radiotherapy alone, underscoring the therapeutic potential of this synergistic approach to achieve systemic tumor control in metastatic melanoma [20, 29].

Clinical Evidence for Combination Therapy

Evidence from prospective trials and retrospective studies supports the potential clinical benefit of combining radiotherapy with immune checkpoint inhibitors in metastatic melanoma. A systematic review and meta-analysis including 624 patients across 12 studies, encompassing both prospective and retrospective designs, demonstrated that the addition of radiotherapy to immune checkpoint inhibition was associated with a higher overall response rate of 35% compared with 20.39% observed with immune checkpoint inhibitor monotherapy. Despite this improvement in tumor response, no significant advantage in overall survival was identified at 6 and 12 months, whereas a statistically significant improvement in progression-free survival was observed at 12 months ($P = 0.005$), suggesting enhanced disease control over time [17]. Complementary findings were reported in studies focusing on melanoma brain metastases, where combined treatment achieved higher local efficacy, with a pooled overall response rate of 42% and a disease control rate of 85%, exceeding the outcomes observed with immune checkpoint inhibitor monotherapy [3].

When survival endpoints are examined in greater detail, the combination of radiotherapy and immune checkpoint inhibitors appears to exert a more pronounced effect on progression-free survival than on short-term overall survival. Although early overall survival benefits were not statistically significant, the observed improvement in progression-free survival at 12 months points toward a potential long-term advantage in disease stabilization [17]. This

effect becomes particularly evident in patients with confirmed failure to anti–PD-1 monotherapy, in whom the addition of radiotherapy resulted in a substantial extension of both progression-free and overall survival. In this subgroup, patients receiving radiotherapy achieved a progression-free survival of 16.8 months compared with 2.2 months in those who were not irradiated, highlighting the potential of radiotherapy to overcome therapeutic resistance [22].

Beyond survival metrics, combined radiotherapy and immune checkpoint inhibition has consistently been associated with improved local and systemic tumor control. Enhanced local control has been especially notable in the management of brain metastases, where disease control rates were significantly higher than those achieved with immune checkpoint inhibitors alone [3]. In addition to local effects, systemic tumor control has been evidenced by the occurrence of the abscopal effect, which was observed in 31.5% of patients receiving late radiotherapy, indicating meaningful immune-mediated responses in non-irradiated tumor sites [22].

Importantly, emerging data suggest that specific patient subgroups may derive greater benefit from this combined therapeutic approach. Treatment sequencing appears to influence outcomes, with patients receiving radiotherapy followed by immune checkpoint inhibitors demonstrating higher overall response and disease control rates, along with a trend toward improved progression-free survival. Furthermore, immunological characteristics, including higher frequencies of memory T cells and activated CD8+ T cells, have been associated with superior clinical outcomes, indicating that patients with favorable immune profiles may be particularly well suited for combined radiotherapy and immunotherapy strategies [25].

Treatment Sequencing and Technical Considerations

The timing of radiotherapy relative to immune checkpoint inhibitor administration has emerged as a critical determinant of therapeutic efficacy in metastatic melanoma. Concurrent delivery of radiotherapy and immune checkpoint inhibition has been consistently associated with improved clinical outcomes compared with sequential treatment approaches. In patients with melanoma brain metastases, concurrent treatment has been shown to confer superior overall survival and progression-free survival, supporting the concept of temporal synergy between local radiation-induced immune priming and systemic immune checkpoint blockade [7, 30]. Further evidence indicates that administration of immune checkpoint inhibitors within three months of stereotactic radiosurgery or stereotactic radiotherapy is associated with improved local tumor control without a concomitant increase in the risk of radiation necrosis, underscoring the safety and efficacy of close temporal integration of these modalities [31]. Moreover, initiating immune checkpoint inhibitor therapy shortly before radiotherapy, including intervals as short as eight days prior to radiation delivery, has been reported to be safe and may further enhance survival outcomes, suggesting that early immune activation may potentiate the effects of subsequent radiotherapy [32].

In addition to timing, radiotherapy dose, fractionation, and irradiated volume significantly influence treatment outcomes when combined with immunotherapy. High-dose stereotactic radiotherapy has been favored for achieving superior local control and survival benefits, with total doses of at least 60 Gy being associated with improved overall survival [7]. Fractionation strategies such as single-fraction stereotactic radiosurgery and hypofractionated stereotactic radiotherapy delivered over three to five fractions have demonstrated effectiveness in combination with immune checkpoint inhibitors, with stereotactic radiosurgery appearing particularly advantageous for smaller metastatic lesions [31]. The volume of irradiated disease also plays a relevant role, as smaller metastatic

volumes, defined as 3 cm^3 or less, have been correlated with more favorable clinical outcomes, likely reflecting both improved local control and enhanced immune-mediated effects [7].

Special considerations apply to the management of brain and extracranial metastases in this combined therapeutic context. In patients with brain metastases, the combination of stereotactic radiosurgery and immune checkpoint inhibitors has been associated with improved local and intracranial control, particularly when dual immune checkpoint blockade is employed [33]. Although the blood–brain barrier represents a physiological obstacle to effective immunotherapy, stereotactic radiation can transiently disrupt this barrier, potentially facilitating immune cell infiltration and enhancing the efficacy of immune checkpoint inhibitors within the central nervous system [34]. In extracranial metastatic disease, concurrent radiotherapy and immune checkpoint inhibition has been shown to promote systemic immune activation, including the induction of abscopal responses, which may contribute to prolonged survival and broader tumor control beyond the irradiated sites [7].

Safety, Toxicity, and Clinical Management

The use of combined radiotherapy and immune checkpoint inhibition in metastatic melanoma is associated with a high incidence of treatment-related adverse events, reflecting the intensified immune activation induced by this therapeutic strategy. In patients receiving concurrent treatment, overall adverse event rates have been reported as high as 76.0%, with grade 3 or higher toxicities occurring in 23.5% of cases, and fatigue emerging as the most frequently observed adverse event across different treatment sequences [35]. Common immune-related adverse events include arthralgia, enterocolitis, and anemia, whereas severe but less frequent complications such as pneumonitis and myocarditis represent clinically significant concerns that require careful surveillance [36]. Interestingly, certain immune-related adverse events, particularly rheumatologic and cutaneous manifestations, have been associated with improved survival outcomes, suggesting that these toxicities may reflect heightened immune activation and potentially serve as surrogate biomarkers of therapeutic response [37].

Despite concerns regarding additive toxicity, available evidence indicates that radiotherapy administered in combination with immune checkpoint inhibitors does not substantially increase the incidence of severe adverse events compared with immune checkpoint inhibitor therapy alone. Real-world data support the notion that the immunomodulatory effects of radiotherapy do not translate into a disproportionate increase in high-grade toxicity when integrated with immunotherapy [36]. Consistent with these observations, the addition of palliative radiotherapy to immune checkpoint inhibitors in advanced melanoma has been shown to be both effective and safe, without a significant rise in severe immune-related adverse events, reinforcing the feasibility of this combined approach in routine clinical practice [24].

Given the complexity of immune-related toxicities, optimal patient care requires a structured and multidisciplinary management strategy. Prompt recognition and timely intervention are essential, with management tailored to the type and severity of the adverse events observed. Within this framework, imaging plays a pivotal role in the evaluation of suspected immune-related adverse events, as it facilitates differentiation between treatment-related toxicity, tumor progression, and infectious processes, thereby guiding appropriate clinical decision-making and ensuring safe continuation or modification of therapy [38].

Conclusions

Metastatic melanoma exhibits a strong intrinsic immunogenicity driven by its high mutational

burden and immune cell infiltration; however, adaptive immune evasion mechanisms and an immunosuppressive tumor microenvironment frequently limit durable responses to immune checkpoint inhibitors, underscoring the need for combination strategies capable of overcoming resistance.

Radiotherapy has evolved from a purely palliative modality to a biologically relevant immunomodulatory treatment that enhances tumor antigen presentation, promotes systemic immune activation, and synergizes with immune checkpoint inhibition, resulting in improved response rates, progression-free survival, and local and systemic tumor control, including the induction of abscopal effects in selected patients.

The clinical benefit of combining radiotherapy with immune checkpoint inhibitors is influenced by treatment sequencing, radiotherapy dose and technique, tumor burden, and individual immunological profiles, while maintaining an acceptable safety profile; these factors highlight the importance of personalized, multidisciplinary approaches to optimize efficacy and manage toxicity in metastatic melanoma.

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