Journal of Clinical Technology and Theory Vol.3 Issue 3 EWA Publishing
Available Online: 23 October 2025 DOI: 10.54254/3049-5458/2025.28149

A Review of Treatment Options for Melanoma: From Surgery to Experimental Therapies

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Abstract. Melanoma, originating from melanocytes, is an extremely aggressive and globally relevant public health problem with increasing incidence. Although surgical resection is still the gold standard in early-stage melanoma, numerous advances in the field of oncology have expanded the therapeutic armamentarium, especially for advanced or metastatic disease. Current management of melanoma now encompasses a combination of immunotherapy, targeted therapy, radiotherapy and novelx series of the method of new experimental medical therapy. Immunotherapeutic agents (immune checpoint inhibitors): Anti-PD1 and Anti-CTLA-4 inhibitors have changed the survival curve, providing long-term remissions in a subgroup of patients. The targeted therapies to BRAF and MEK mutations are also known to present quick clinical responses, as well as the development of resistance, which is a significant limitation. Radiotherapy remains essentially palliative, and chemotherapy significantly less effective. In addition, emerging interventions; oncolytic viruses therapy, microRNA therapeutics and epigenetic modulators are being actively studied. Ancillary therapies, such as TCM, are also adjunctive and require cautious combination with Western medicine. In this review, we review current melanoma therapies considering them for clinical advantage (pros) and disadvantage (cons). The aim is to provide clinicians, researchers, and patients with a tool to help them to build knowledge about the new therapies for melanoma, to help make informed, personalized treatment decisions based on the most up-to-date scientific data and clinical practice.

Keywords: Melanoma, Target Therapy, Immunotherapy

1. Introduction

Melanoma is one of the most aggressive types of skin cancer and is characterized by high morbidity and mortality, particularly in its metastatic phase. While melanoma makes up just 1% of skin cancers worldwide, it is responsible for most deaths from the disease. Risk factors for melanoma include sunlight (UV radiation) exposure, having a family history of melanoma, and having many moles or certain types of moles, such as dysplastic nevi. Prognosis is good with early diagnosis, and 5-year survival rates are greater than 90% for localised melanoma. However, survival rates drop steeply after the disease has spread to the lymph nodes or distal sites, calling for a more diversified and aggressive treatment approach.

Surgical resection has been the historical mainstay of treatment for melanoma, especially for early lesions. But the treatment landscape has changed drastically with the recent advent of immune checkpoint blockade and targeted molecular agents. These advances have revolutionized the therapeutics of melanoma, changing a formerly invariable lethal disease into a potentially treatable chronic state for a significant portion of the patient population. However, both the therapies have their limitations such as immune-related adverse effects, drug resistance and variability of patient response depending on tumor genetic and immune context.

This article covers all options in the treatment of melanoma – from traditional treatments such as surgery and radiotherapy as well as the latest treatments like immunotherapy, targeted therapy and experimental treatments. It systematically reviews both the benefits and limits of these strategies and combines the literature to provide a holistic and empirically grounded view. Focus is on the combination and personalized therapeutic strategies for resistance circumvention and favorable treatment responses in patients. The conversation also covers the benefits of adjunctive therapies like TCM (Traditional Chinese Medicine) and how integrative care can enrich the quality of life for our patients. This thread of enquiry, we hope, will help to advance a more sophisticated and nuanced narrative of melanoma treatment, one that raises questions for clinical decision-making and the shape of future research [1–3].

2. Conventional treatment options

2.1. Surgical treatment

Surgical excision remains the cornerstone for early-stage melanoma management. The primary objective is the complete removal of the tumor with clear margins to prevent recurrence. For melanoma in situ (stage 0), a margin of 0.5 cm is typically sufficient. As the tumor thickness increases, wider excision margins are recommended, often up to 2 cm for tumors exceeding 2 mm in thickness [1]. Sentinel Lymph Node Biopsy (SLNB) is a pivotal procedure for staging and prognostication in patients with intermediate-thickness melanomas. If metastasis is detected in the sentinel node, a complete lymph node dissection may be considered. However, recent studies suggest that immediate completion lymph node dissection may not improve overall survival [1].

For advanced melanoma with isolated metastases, surgical resection can offer palliation and, in select scenarios, prolonged survival. However, the role of surgery diminishes as the disease becomes more widespread. Advantages of surgical treatment include: (1) Curative potential: Surgical excision can be curative for early-stage melanomas. (2) Diagnostic value: Provides tissue for accurate histopathological diagnosis and staging. (3) Minimal systemic effects: Compared to systemic therapies, surgery has fewer systemic side effects. Disadvantages include: (1) Limited efficacy in advanced stages: Surgery is less effective for metastatic melanoma. (2) Potential morbidity: Surgical procedures can lead to complications such as infection, scarring, and lymphedema. (3) Incomplete removal risk: Microscopic residual disease may lead to recurrence.

2.2. Radiotherapy with and without chemotherapy

2.2.1. Radiotherapy

Historically, melanoma has been considered radioresistant. Nonetheless, radiotherapy plays a role in specific clinical situations, such as palliation of symptomatic metastases, particularly in the brain or bones, and as adjuvant therapy in high-risk patients following lymph node dissection [2]. In patients with high-risk features, such as extracapsular extension or multiple involved lymph nodes, adjuvant radiotherapy can reduce regional recurrence rates. However, its impact on overall survival remains uncertain. For brain metastases, Stereotactic Radiosurgery (SRS) offers precise, high-dose radiation to tumor sites, sparing surrounding healthy tissue. This modality has shown efficacy in controlling intracranial disease and improving neurological symptoms.

Advantages include: non-surgical option for patients unfit for surgery, Effective in alleviating symptoms from metastatic lesions, and able to improve local control in certain high-risk scenarios.

Disadvantages include: limited Efficacy, side effects, and not curative.

2.2.2. Chemotherapy

Chemotherapy was once the backbone of treatment for metastatic melanoma before the era of immunotherapy and targeted agents. However, due to melanoma's intrinsic resistance to many cytotoxic agents, its role has diminished significantly in recent years. The most commonly used chemotherapeutic agents in melanoma include dacarbazine (DTIC) and temozolomide, which work by alkylating DNA and leading to cancer cell death [3]. Dacarbazine, the only FDA-approved chemotherapy for melanoma for many years, has shown modest response rates of approximately 10–20%, with rare complete responses. Median survival remains low, generally around 6 to 9 months in metastatic cases [3]. Temozolomide is an oral alkylating agent similar to dacarbazine but with better blood-brain barrier penetration. It has been studied particularly in patients with brain metastases. However, like dacarbazine, overall response rates remain low, and benefits are often transient [4].

2.2.3. Combination chemotherapy

Efforts have been made to improve outcomes through combination regimens (e.g., cisplatin, vinblastine, and dacarbazine—CVD), but these have not resulted in significantly improved survival compared to monotherapy and are associated with increased toxicity [4].

Advantages: (1) Option for non-responders: Still considered in patients who are not candidates for immunotherapy or targeted therapy. (2) Brain metastases use: Temozolomide shows some utility in controlling brain metastases due to CNS penetration.

Disadvantages: (1) Low efficacy: Response rates are significantly lower than with modern therapies.

High Toxicity: Includes nausea, vomiting, myelosuppression, and fatigue. (2) Short-lived responses: Rarely produces durable remissions or long-term survival benefits.

2.3. Immunotherapy

Immunotherapy has revolutionized the management of melanoma, particularly in the advanced or metastatic setting. It harnesses the body's immune system to identify and destroy cancer cells. The most impactful agents are immune checkpoint inhibitors, which block proteins that restrain immune responses, allowing T cells to attack tumors more effectively [5].

Checkpoint Inhibitors includes CTLA-4 Inhibitors, PD-1 Inhibitors, Dual Immune Checkpoint Blockade, and LAG-3 Inhibitors: Ipilimumab was the first checkpoint inhibitor approved for melanoma. It blocks the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) receptor, enhancing T cell activation. Ipilimumab improved 10-year survival from ~10% to ~22% in metastatic melanoma [6]. Nivolumab and pembrolizumab block the programmed death-1 (PD-1) receptor on T cells, preventing tumor-induced immune suppression. These agents are better tolerated and more effective than CTLA-4 monotherapy, achieving response rates around 30–40% and 5-year survival in some cohorts exceeding 50% [6, 7]. The combination of nivolumab plus ipilimumab has demonstrated superior efficacy in clinical trials, though with a higher incidence of immune-related adverse events. In CheckMate 067, the combination improved overall survival but caused Grade 3–4 toxicity in more than half of patients [7]. Relatlimab, an anti–LAG-3 antibody, has been paired with nivolumab for patients with previously untreated advanced melanoma. This combination has shown better progression-free survival than nivolumab alone in the RELATIVITY-047 trial [8].

Advantages are as follows: Some patients experience long-term survival and even potential cure. Active across many subtypes and genetic profiles of melanoma. Potential for long-term immune surveillance and recurrence prevention. Disadvantages include: It can include colitis, hepatitis, pneumonitis, and endocrinopathies, which may be life-threatening. Besides, a subset of patients does not respond at all. Immunotherapy can be extremely expensive and requires close monitoring.

2.4. Targeted therapy

Targeted therapy has transformed melanoma treatment by focusing on specific molecular alterations that drive cancer growth. Approximately 40-50% of cutaneous melanomas harbor activating mutations in the BRAF gene, most commonly the V600E mutation, which constitutively activates the MAPK (mitogen-activated protein kinase) signaling pathway leading to uncontrolled cell proliferation [9].

2.4.1. BRAF inhibitors

Drugs such as vemurafenib, dabrafenib, and encorafenib directly inhibit the mutated BRAF protein. These agents produce rapid and often dramatic tumor shrinkage in patients with BRAF-mutant melanoma. Response rates can reach 50-70%, with median progression-free survival (PFS) of 6-8 months [10].

2.4.2. MEK inhibitors

MEK proteins act downstream of BRAF in the MAPK pathway. Combining BRAF inhibitors with MEK inhibitors (e.g., trametinib, cobimetinib, binimetinib) improves efficacy by reducing the development of resistance and delaying disease progression. Dual BRAF/MEK inhibition has become the standard of care for BRAF-mutant advanced melanoma [10, 11].

Advantages: (1) Rapid Clinical Response: Effective for symptomatic patients needing quick tumor control. (2) Improved Survival: Combination therapy extends median overall survival beyond 2 years in some cohorts. (3) Oral Administration: Convenient dosing compared to intravenous immunotherapies. Disadvantages: (1) Resistance Development: Most patients eventually develop resistance, typically within 12-18 months. (2) Adverse Effects: Rash, fever, fatigue, arthralgia, photosensitivity, and secondary skin cancers (e.g., cutaneous squamous cell carcinoma). (3) Limited to Mutation-Positive Patients: Not effective for melanomas without BRAF mutations.

3. Novel therapies

Research continues to push the boundaries of melanoma treatment beyond traditional and targeted therapies. Novel approaches show promise, particularly in refractory or advanced disease.

Neoadjuvant Immunotherapy: Administering immunotherapy before surgical resection (neoadjuvant setting) is emerging as a promising approach. For example, the SWOG S1801 trial demonstrated that patients receiving pembrolizumab both before and after surgery had a 72% recurrence-free survival at 2 years versus 49% in the adjuvant-only group [12].

MicroRNA-Based Therapies: MicroRNAs (miRNAs) regulate gene expression and can influence tumor growth and metastasis. Studies have identified deregulated miRNAs like miR-412 that could be targeted to restore tumor suppressor functions and inhibit melanoma progression [13].

Oncolytic Virus Therapy: Talimogene laherparepvec (T-VEC) is an engineered herpes simplex virus that selectively infects and lyses tumor cells while stimulating a systemic immune response. It is approved for injectable lesions in stage III-IV melanoma and can induce both local tumor regression and distant responses [14].

Advantages: Innovative Mechanisms: Target melanoma through multiple novel biological pathways. Combination Potential: Can be combined with existing immunotherapies for synergistic effects. Localized and Systemic Effects: Oncolytic viruses cause direct tumor cell lysis and systemic anti-tumor immunity. Disadvantages: Limited Availability: Some are experimental or in early clinical trials. Variable Response: Not all patients respond, and biomarkers for prediction are limited. Complex Administration: Some require injections directly into tumors.

4. Traditional Chinese Medicine (TCM) as complementary therapy

Many melanoma patients explore complementary approaches such as TCM alongside conventional therapies to support immunity and alleviate side effects. While not replacements for standard care, TCM modalities may offer adjunct benefits.

Moxibustion involves burning mugwort (Artemisia vulgaris) near acupuncture points to stimulate circulation and immune function. Preliminary studies suggest it might help reduce chemotherapy-induced fatigue and improve blood counts, though high-quality clinical trials are lacking [15].

Herbal Remedies: Astragalus membranaceus: Contains polysaccharides thought to boost immune response and inhibit melanoma growth in preclinical studies [16]. Reishi Mushroom (Ganoderma lucidum): Known for immune-modulating and anti-inflammatory effects. Animal models suggest it can enhance immune function and may slow tumor progression [5].

Advantages: Immune Support: May enhance patient well-being and immune resilience. Reduced Side Effects: Some evidence suggests alleviation of chemotherapy-related fatigue and nausea. Holistic Approach: Supports overall health and quality of life. Disadvantages: Lack of Robust Evidence: Most data come from small or animal studies; rigorous clinical validation is needed. Potential Interactions: Herbs might interfere with pharmacokinetics of conventional drugs. Not Curative Alone: Should not replace established medical treatments.

5. Combinational therapies and resistance control

Given the complexity of melanoma and its ability to develop resistance to single-agent treatments, combining therapies has become a cornerstone strategy to improve outcomes and delay resistance.

5.1. Targeted therapy + immunotherapy

Combining BRAF/MEK inhibitors with immune checkpoint inhibitors (e.g., PD-1 blockers) aims to exploit rapid tumor shrinkage from targeted drugs while stimulating a durable immune response. Clinical trials show promising higher response rates and progression-free survival compared to monotherapies [17].

Advantages: Improved efficacy, synergistic mechanisms that may overcome resistance.

Disadvantages: Increased risk of adverse events such as fever, rash, hepatotoxicity, and immune-related side effects. Managing toxicity is challenging, and optimal dosing schedules remain under study.

5.2. Dual immunotherapy

Using dual checkpoint blockade, such as nivolumab (PD-1 inhibitor) combined with ipilimumab (CTLA-4 inhibitor) or newer combinations with relatlimab (anti–LAG-3), improves response rates and survival compared to single agents [18]. This approach unleashes a more robust immune attack on melanoma cells.

Advantages: Enhanced anti-tumor activity, higher complete remission rates.

Disadvantages: Significantly increased immune-related toxicities, including colitis, pneumonitis, endocrinopathies, requiring close monitoring and sometimes immunosuppressive treatment.

5.3. Genetic retargeting and epigenetic therapy

When resistance emerges, genomic profiling of tumor biopsies can identify secondary mutations or pathway activations, guiding the selection of alternative inhibitors, such as ERK inhibitors to bypass upstream resistance. Furthermore, epigenetic modifiers, like histone deacetylase (HDAC) inhibitors, can restore sensitivity by reactivating silenced genes crucial for tumor suppression.

Advantages: Personalized treatment adapting to tumor evolution; potential to overcome multiple resistance mechanisms.Disadvantages: Still experimental in melanoma; clinical efficacy and safety require further validation.

5.4. Sequential and switch strategies

Switching treatment modalities—for example, initiating therapy with immunotherapy and transitioning to targeted therapy upon progression—may achieve longer disease control by attacking melanoma through different mechanisms sequentially [17].

6. Conclusion

Melanoma treatment has evolved from predominantly surgical intervention to a sophisticated, multi-modal approach combining surgery, radiotherapy, targeted therapy, immunotherapy, novel biological agents, and complementary therapies like TCM. The choice of treatment depends heavily on tumor stage, genetic profile, and patient factors, requiring personalized strategies.

Surgery remains the cornerstone for early-stage melanoma, offering high cure rates. Radiotherapy and chemotherapy play limited but important roles in palliative care and in certain advanced cases. Targeted therapy offers rapid tumor control for mutation-positive melanomas but is limited by resistance. Immunotherapy, particularly checkpoint inhibitors, has revolutionized outcomes, offering durable responses in a subset of patients. Novel therapies like oncolytic viruses, microRNA treatments, and neoadjuvant immunotherapy show promise but require further research. TCM can provide supportive care but should complement, not replace, conventional treatments. Combination and sequential therapies offer improved efficacy by counteracting tumor resistance, although they increase complexity and toxicity management. Continued clinical trials and translational research are vital for further breakthroughs. Physicians and patients must collaborate closely to navigate personalized treatment plans, balancing efficacy, safety, and quality of life. The future holds hope for long-term remission and potentially cures through innovative combinations and targeted interventions.

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