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The incidence of melanoma continues to increase worldwide. In the United States, melanoma is the fifth most common cancer in men and the sixth most common cancer in women. The risk factors contributing to melanoma have largely remained unchanged, but there is a new focus on modifiable risk factors including sun exposure and ultraviolet light. A large public initiative supported by the Centers for Disease Control focuses on educating the public on the risks of sun exposure and indoor tanning. Early detection and resection of melanoma lesions is necessary to prevent metastasis and reduce medical costs.

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Melanoma is a deadly skin cancer linked to ultraviolet radiation exposure. Heritable traits and sporadic mutations modify an individual's risk for melanoma that may be associated with phenotype. Familial/heritable melanomas are broadly used to describe families with an increased incidence of melanomas, although the underlying mutation may be unknown. Mutations associated with melanoma occur in cell cycle regulation, tumor suppression, chromosomal stability, DNA repair, pigmentation, and melanocyte differentiation genes. Genetic testing of individuals with a family history of melanoma may provide additional etiologic information and ensure patients with known markers for cancer development are closely monitored by physicians.

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The melanoma expert panel devised the evidence-based eighth edition American Joint Committee on Cancer staging system by conducting vigorous analyses of stage I, II, and III patients from the International Melanoma Database and Discovery Platform. Key changes in the eighth edition are regarding subcategorization of T1, M1, pathologic stage grouping of stage I and III, and refining the definitions and terminologies used in the staging system. As the knowledge of tumor biology improves,

the staging of melanoma will continue to evolve to enable betterment of care.

### **Pathology of Melanoma**

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**Asmita Chopra, Rohit Sharma, and Uma N.M. Rao**

Melanoma is an aggressive malignancy arising from melanocytes in the skin and rarely in extracutaneous sites. The understanding of pathology of melanoma has evolved over the years, with the initial classifications based on the clinical and microscopic features to the current use of immunohistochemistry and genetic sequencing. The depth of invasion and lymph node metastasis are still the most important prognostic features of melanoma. Other important prognostic features include ulceration, lymphovascular invasion, mitosis, and tumor-infiltrating lymphocytes. This article reviews the pathology of melanoma and its precursor lesions, along with the recent advances in pathologic diagnosis of melanoma.

### **Surgical Management of Primary Cutaneous Melanoma**

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**Daniel Joyce and Joseph J. Skitzki**

Primary cutaneous melanomas are potentially curative with surgical excision alone. Surgical management is based on several factors determined from the initial biopsy, including primary tumor thickness, histologic features including ulceration, and anatomic location. Cosmesis, although important, should be a secondary consideration as oncologic principles take precedence. Pathology has evolved to synoptic reporting with key variables to assist in staging and risk stratification.

### **Surgical Management of Lymph Nodes in Melanoma**

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**Alexandra Allard-Coutu, Barbara Heller, and Valerie Francescutti**

This article provides a comprehensive evaluation of surgical management of the lymph node basin in melanoma, with historical, anatomic, and evidence-based recommendations for practice.

### **Nonsurgical Management of Lymph Node Basins in Melanoma**

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**Rogeh Habashi and Valerie Francescutti**

In this article we provide a critical review of the evidence available for surgical management of the nodal basin in melanoma, with an aim to ensure an understanding of risks and benefits for all lymph node surgery offered to patients, and alternatives to surgical management where appropriate.

### **Management of Locoregionally Advanced Melanoma**

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**David T. Pointer Jr and Jonathan S. Zager**

Melanoma has a unique propensity for locoregional metastasis secondary to intralymphatic transit not seen in other cutaneous or soft tissue malignancies. Novel intralesional therapies using oncolytic immunotherapy exhibit increasing response rates with observed bystander effect. Intralesional modalities in combination with systemic immunotherapy are the subject of ongoing clinical trials. Regional therapy is used in isolated

limb locoregional metastasis whereby chemotherapy is delivered to an isolated limb avoiding systemic side effects. Multimodal treatment strategy is imperative in the treatment of locoregionally advanced melanoma. One must be versed on these quickly evolving therapeutic options.

## **Role of Surgery for Metastatic Melanoma**

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*Laura M. Enomoto, Edward A. Levine, Perry Shen, and Konstantinos I. Votanopoulos*

Complete surgical resection of metastatic melanoma has a known survival benefit. Treatment of metastatic melanoma, however, has become increasingly complex with the introduction of targeted treatments and immune checkpoint inhibitors. Integration of systemic medical therapy and surgical resection has shown promising results, with significantly improved long-term survivals. Results from current clinical trials are awaited to help further delineate the sequence and combination of systemic therapy and surgery.

## **Surgical Considerations and Systemic Therapy of Melanoma**

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*Adriana C. Gamboa, Michael Lowe, Melinda L. Yushak, and Keith A. Delman*

Recent advances in effective medical therapies have markedly improved the prognosis for patients with advanced melanoma. This article aims to highlight the current era of integrated multidisciplinary care of patients with advanced melanoma by outlining current approved therapies, including immunotherapy, targeted therapy, radiation therapy, and other strategies used in both the adjuvant and the neoadjuvant setting as well as the evolving role of surgical intervention in the changing landscape of advanced melanoma.

## **Principles of Immunotherapy in Melanoma**

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*Adedayo A. Onitilo and Jaimie A. Wittig*

Advanced/metastatic melanoma is an aggressive cancer with a low survival rate. Traditional cytotoxic chemotherapies do not appreciably extend life and systemic cytokine/chemokine administration produces toxic side effects. By harnessing the surveillance and cytotoxic features of the immune system, immunotherapies can provide a durable response and are proved to improve disease outcomes in patients with advanced/metastatic melanoma and other cancers. Close monitoring is necessary, however, to identify and treat immune system-related adverse events before they become life-threatening. Because metastatic lesions can respond differently to immunotherapies, modified response criteria have been developed to assist physicians in tracking patient response to treatment.

## **Principles of Targeted Therapy for Melanoma**

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*James Sun, Michael J. Carr, and Nikhil I. Khushalani*

Targeted BRAF and MEK inhibition has become an appropriate first-line treatment of BRAF-mutant advanced cutaneous melanoma. The authors present an overview of the MAPK pathway as well as the other major pathways implicated in melanoma development. Melanoma brain metastases

are a devastating complication of melanoma that can be traced to derangements in cell signaling pathways, and the current evidence for targeted therapy is reviewed. Finally, activating KIT mutations are rarely found to cause melanomas and may provide an actionable target for therapy. The authors review the current evidence for targeted KIT therapy and summarize the ongoing clinical trials.

**Role of Radiation in the Era of Effective Systemic Therapy for Melanoma****189****A. Gabriella Wernicke, Simran Polce, and Bhupesh Parashar**

The role of radiation therapy in melanoma has evolved over the last few decades. There has been a dramatic improvement in radiation delivery with the introduction of intensity-modulated radiation therapy, image-guided radiation therapy, stereotactic radiosurgery, and stereotactic body radiation therapy/stereotactic radiation therapy. More recently, with the introduction of immunotherapy in various malignancies, including melanoma, the role of radiation therapy is being reevaluated. This article describes the evolution of the role of radiation therapy from nonimmunotherapy to the era of immunotherapy.

**Current Clinical Trials in the Treatment of Advanced Melanomas****201****Saro Sarkisian, Suresh Nair, and Rohit Sharma**

The treatment of metastatic melanomas revolutionized during the past decade because of a better understanding of various pathways and mutations that play different roles in the pathogenesis of this disease. The incorporation of immunotherapy was the first in these efforts, followed by targeted therapies as monotherapeutic options, and then in combinations. In this article, we review the historical and landmark clinical trials that changed our treatment paradigm for advanced melanomas, also we review ongoing clinical trials that would be applicable in the near future and would expectedly improve outcomes for these patients.