Melanoma in Clinical Practice

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Editors

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Preface

Of the three commonest skin cancers, malignant melanoma is the most lethal, with increasing worldwide incidence over the past 50 years. It is notable that melanoma is one of the most common cancers in the 15–30 year age group with preventable risk factors, and its survival is significantly impacted by the stage at clinical presentation. Prevention and early detection, therefore, remain powerful tools in curbing this disease. Differentiating atypical, pigmented lesions from benign versus neoplastic can be challenging, given the large variety of melanocytic tumors with benign, intermediate, and malignant biological behavior, as well as overlapping clinical and histopathological features between the entities.

Over the years, melanoma staging has developed with improved prognostication to better guide the management of patients. Surgery is the mainstay of treatment for early-stage disease. Data from landmark clinical trials have impacted practice guidelines in recent decades, moving away from prior extensive and morbid surgeries of the primary lesion and regional nodes to more optimized surgeries that provide a better balance of the risk–benefit ratio for the patient.

During the past decade, with an improved understanding of the genetic drivers of melanoma development and progression and the immunologic basis of host responses to cancers, oncologists have seen an explosion of novel treatments for metastatic melanoma which has enabled them to offer patients effective therapies that significantly improve patient survival and quality of life. Despite these giant steps in melanoma therapy, there is still much room for optimizing therapies to extend the survival benefit to a greater number of patients, with better predictability of response, and for a longer duration. The breakthroughs afforded by these remarkable new therapies are a testament to decades of basic and translational research and meaningful collaborations between academia and industry to forge advances in patient care through a streamlined process.

This book provides a comprehensive review of clinical, basic, and translational research in melanoma, current standards for the diagnosis and treatment of localized, regional, and advanced disease, and forward-looking

remarks on what may be expected in the field in the near future. Specific chapters are dedicated to melanoma epidemiology, melanoma biology, and disease prevention, diagnosis, and treatment in a detailed yet readable format highlighted by inclusion of key study data. Specific attention is also paid to rarer variants of melanoma and melanoma of specific populations such as children that may have atypical clinical presentations and behaviors.

Boston, MA, USA Rhoda M. Alani, MD
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Rhoda M. Alani, MD and Debjani Sahni, MD

To my husband Philip Cole and children, Hannah and Matthew Cole, for their tremendous support throughout my career. You bring me so much joy and always inspire me to be my best self. To my colleagues, teachers, mentors, trainees, and patients who have taught me greatly about science, medicine, and life. To Debjani Sahni, MD, who was the driving force behind this awesome endeavor and whose brilliance, kindness, tenacity, and dedication never cease to amaze me.

Rhoda M. Alani, MD

I am grateful to my family in getting me to where I am today. In particular, I am thankful to my two very patient children, Sophia and Neve, who had to sacrifice their time with me during the composition of this book, and to my husband Anik, for his ongoing support.

I would like to thank Rhoda Alani, MD, who is an exceptional mentor to me, for giving me the opportunity to coedit this book with her, and for always encouraging and supporting me to take on the next step in my career pathway.

Debjani Sahni, MD

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About the Editors

Rhoda M. Alani, MD, serves as the Herbert Mescon Endowed Professor and Chair of Dermatology at the Boston University School of Medicine and Boston Medical Center. She received her MD degree with Honors and Distinction in Research from the University of Michigan Medical School and completed her internship in internal medicine at Yale-New Haven Hospital and a residency in dermatology at Harvard Medical School followed by post-doctoral training at Harvard Medical School and Memorial Sloan-Kettering Cancer Center. From 1999 to 2009, Dr. Alani was the director of the Laboratory of Cutaneous Oncology at the Johns Hopkins University School of Medicine where she also served as the director of the Melanoma and Pigmented Lesion Clinics in Dermatology. Dr. Alani's research focus is in understanding the molecular basis of melanoma development and progression with the aim of translating her laboratory findings to improve the prevention, detection, diagnosis, and treatment of melanoma. Her current research efforts seek to understand the epigenetic basis for melanoma development and progression and are supported by the National Institutes of Health, Department of Defense, and the Melanoma Research Alliance. Dr. Alani is a member of Phi Beta Kappa and Alpha Omega Alpha Honor Societies, the American Academy of Dermatology, the Society for Investigative Dermatology, the Society for Melanoma Research, and the American Association for Cancer Research and was elected to the American Society for Clinical Investigation in 2005 and to the American Dermatological Association in 2011. She is the author of numerous scientific publications and is the owner of several US patents related to melanoma biomarkers, novel melanoma therapies, and imaging systems for improved melanoma detection.

Debjani Sahni, MD, is the G. Robert Baler Endowed Professor and Director of the multidisciplinary Cutaneous Oncology Program at the Boston University School of Medicine and Boston Medical Center, where she specializes in the medical management of advanced skin cancers. She completed her medical school training at the United Medical and Dental Schools of Guy's and St Thomas' Hospitals in London, UK. After acquiring her Membership of the Royal College of Physicians (MRCP), she completed dermatology residency at the St John's Institute of Dermatology in London. She subsequently undertook a cutaneous oncology fellowship at Dana-Farber Cancer Institute and Brigham and Women's Hospital, Harvard Medical School, Boston. Dr. Sahni serves as the director of the Cutaneous Oncology Fellowship Program and the director of the unique and highly respected International Graduate Program in Dermatology (IGPD). First established in 1988, the IGPD offers international postgraduate doctors the opportunity to train in dermatology, utilizing state-of-the-art facilities and therapies available in the USA. Her academic interests include teaching and mentoring for which she is the recipient of several teaching awards and an external examiner for postgraduate dermatology training exams internationally. Dr. Sahni's clinical research interests focus on the epidemiology and treatment of skin cancers, and she is the author of multiple scientific papers.

Part I

Understanding Melanoma: Background, Etiology and Histologic Diagnosis

Melanoma Prevention

1

Elizabeth J. R. Orrin, Pamela B. Cassidy, Rajan P. Kulkarni, Elizabeth G. Berry, and Sancy A. Leachman

1.1 Introduction

Cutaneous melanoma inflicts a heavy global health burden. It continues to increase in incidence worldwide, and deaths from the disease occur primarily in the United States (18%) and Europe (45%) (http://gco.iarc.fr). In the United States alone, the current melanoma mortality rate stands at 2.1 deaths per 100,000 every year [1] with estimated annual treatment costs of $3.3 billion [2]. Late diagnosis confers a particularly high mortality rate [3]. The five-year survival of patients with localized melanomas is almost 99% but drops to 25–50% for those with distant metastases [4]. Early excision leading to cure has become increasingly frequent, yet overall mortality has continued to increase in many countries. In the United States, mortality has recently fallen significantly and it is unclear whether this is due to increased use of novel targeted- and immunotherapies, better detection, or a combination of the two. Prevention of lethal melanoma, including early detection, is an important component in our arsenal to control and overcome this too frequently fatal disease.

Definitions: Primary, Secondary, and Tertiary Prevention

There are three categories of intervention designed to reduce the burden of melanoma: primary, secondary, and tertiary prevention. As the name implies, *primary prevention* targets the root cause of the disease. In the case of cancer, and specifically melanoma, the primary cause is

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mutations that lead to a stepwise progression to malignancy [5]. Because ultraviolet radiation (UV) exposure is the best characterized, established, and modifiable environmental cause of mutations in melanoma, most primary prevention for melanoma aims to block or ameliorate the effects of UV-induced mutagenic insults in otherwise healthy individuals.

Secondary prevention of melanoma consists of interventions that are effective when the transformation to malignancy has already occurred (or is imminent) and prevention depends on *both* detecting and removing the early cancer before it attains metastatic or lethal potential. Secondary prevention can also involve stopping the progression of transformed cells to lethal cancers. Because most melanoma is visible on the surface of the skin prior to the development of metastatic potential, melanoma early detection (secondary prevention) can include skin screening by patients and providers with the naked eye and with more advanced tools designed to improve detection. These tools include dermoscopy, reflectance in vivo confocal microscopy, and a myriad of burgeoning molecular diagnostic and prognostic tests. Less clear within the field of secondary prevention is the question of whether atypical nevi, which are non-obligate precursors of melanoma [6], have progressed sufficiently towards malignancy to be considered pre-lethal, and should therefore be excised. In various contexts, a pre-lethal melanocytic lesion may be defined as an atypical or dysplastic nevus, melanoma in situ, or invasive melanoma. For the purposes of this chapter, a broad definition is applied. Any form of screening for melanoma is considered secondary prevention based upon the intent to remove an existing lesion that appears to be dangerous.

Tertiary prevention aims to reduce recurrence and further spread of metastases, usually following successful treatment of a melanoma that has already metastasized to the lymph nodes or other distant organs. Tertiary prevention modalities such as the use of adjuvant therapy or radiation therapy will not be discussed in this chapter.

Chemoprevention, also known as *therapeutic prevention*, entails the use of an exogenous agent (therapy, drug, natural product) to intervene in the process of tumorigenesis in the primary, secondary, or tertiary setting, and can sometimes target more than one category of prevention. Categorization as a primary, secondary, or tertiary preventive therapeutic (or multi-category) depends on the mechanism of action. If the agent prevents normal skin from transforming into a pre-lethal state, it is a primary preventive and if it prevents progression of an existing pre-lethal primary lesion, it is a secondary preventive. If the agent has preventive effects on both normal and pre-lethal lesions, it can be classified as both a primary and a secondary preventive therapeutic agent.

Melanoma Risk Factors

Because prevention interventions can lead to unintended harms, the risk of any intervention should be appropriate for the level of risk in the individual and/or population. Stratifying risk in different individuals and populations aids in assessing the suitability of a particular intervention. The Fitzpatrick skin type (or phototype) is one of the best characterized and most utilized scales for assessing an individual's response to ultraviolet radiation and risk for melanoma (Fig. 1.1 and Table 1.1). The scale is as follows: Type I (very white skin, often freckled) always burns, and never tans; Type II (white skin) usually burns and minimally tans; Type III (cream-white to light brown skin) sometimes mildly burns and tans uniformly; Type IV (dark olive to moderate brown skin) burns minimally and always tans well; Type V (dark brown skin) very rarely burns and tans very easily; and Type VI (very dark brown to black skin) never burns [15]. Skin types I and II are associated with approximately double the risk of developing melanoma relative to skin type IV. Despite its widespread use in assessing skin vulnerability to UV damage and skin cancer, reproducibility of the scale, even when performed by dermatologists, can be challenging without standardization [16].

A notable gap in current data-based guidelines is the lack of definition of the level of risk that warrants routine screening by providers. Several risk calculators have been published and some are available online [17–25]. However, to date,

Fig. 1.1 Fitzpatrick phototypes. Figure provided courtesy of the War on Melanoma™

none have been widely applied to national screening programs or studied with respect to risk or cost benefit. Johnson et al. [26] have published a summary of literature concerning the relative risk (RR), of developing melanoma. This study examines genetic, iatrogenic, and environmental risk

Table 1.1 Risk levels for melanoma as determined by risk factors—Reference population for relative risk is a general population without the risk factor except as noted

Risk level	Melanoma risk factors	Melanoma risk (RR except as noted)[a]
Moderate risk	Total common nevi >15 [1]	1.5
	Total common nevi 41–60 versus <15 [1]	2.2
	1 atypical nevus	1.5
	2 atypical nevi	1.5
	High density of freckles vs low	2.1
	Blue eye color vs dark [2]	1.5
	Hazel eye color vs dark [2]	1.5
	Green eye color vs dark [2]	1.6
	Light brown hair vs dark [2]	1.6
	Blond hair vs dark [2]	2.0
	Fitzpatrick I phototype	2.1
	Fitzpatrick II phototype	1.8
	History of sunburn [4]	2.0
	Indoor tanning use in any gender [7]	1.7[c]
High risk	Total common nevi 61–80 vs < 15 [1]	3.3
	3 atypical nevi [1, 4]	3.0
	4 atypical nevi [1, 4]	4.4
	Red hair vs dark [2]	3.6
	Family history of melanoma in one or two first-degree relatives [2, 8]	1.7–3
	History of AK and/or KC [2]	4.3
	CLL [9]	3.9[b]
	Indoor tanning use in women aged 30–39 years [7]	4.3
	Transplant recipient [10, 11]	2.2–4.6[b]
Ultra-high risk	Total common nevi 101–120 vs <15 [1]	6.9
	5 atypical nevi [1]	6.4
	Personal history of melanoma [12]	8.2–13.4
	CDKN2A mutation carrier [13]	14[e]–28[f]
	3 or more relatives on the same side of the family affected [8]	Up to 35–70
	Indoor tanning use in women aged <30 years [7]	6.0[c]
	MC1R R/R genotype[d] and ≥20 nevi >5 mm vs wildtype *MC1R* and 0–4 nevi [14]	25.1[c]

AK actinic keratosis, *KC* keratinocyte carcinoma, *CLL* chronic lymphocytic leukemia
[a]RR = relative risk
[b]Standardized incidence ratio (SIR)
[c]Odds ratio (OR)
[d]Patients with loss-of-function mutations commonly associated with the red hair phenotype in both alleles of the *MC1R* gene
[e]Absolute risk by age 50
[f]Absolute risk by age 80

factors. They recommended assignment of risk factors into moderate, high, and ultra-high-risk categories (Table 1.1). Petrie et al. have extended this concept of risk categories to include different outreach and screening methodologies by risk class and provider specialty [27].

1.2 Primary Prevention (Table 1.2)

Ultraviolet radiation (UV) is currently the most important modifiable risk factor for melanoma development and is classified as a group 1 car-

Table 1.2 What simple primary preventative messages should we regularly be giving to patients?

Clothing
• Cover up with clothing. Tighter knit and darker clothes give better ultraviolet protection.
• Some clothes carry a UPF rating; a UPF of 20+ gives good protection. However, good protection can still be achieved with nonspecialist clothing.
• UV dyes that increase the UPF of clothing can be effective.
Sunscreen
• Sunscreen reduces the rate of skin cancer, including melanoma.
• Apply sunscreens before going in the sun. Most people underuse sunscreens; one ounce (a full shot glass) is required to cover the entire body covered only by a swimsuit.
• Use broad-spectrum sunscreens marked as SPF 50 or greater.
• For those concerned about the environmental impact or safety of chemical sunscreens, we recommend physical sunscreens.
Supplements, antioxidants and vitamin D
• There is currently no drug, supplement, or natural product known to lower melanoma risk.
• Sunscreens are very unlikely to cause vitamin D deficiency. However, if you are concerned, talk to your doctor about your individual risk of vitamin D deficiency.

cinogen by the International Agency for Research on Cancer (IARC). UV is a "complete carcinogen," meaning that it is capable of facilitating both initiation of skin cancers and the progression of premalignant lesions. Until other environmental or nutritional risk factors are identified, primary prevention for melanoma focuses on reducing an individual's exposure and/or sensitivity to UV.

1.2.1 Ultraviolet Radiation Exposure and Effects

There is up to a fourfold variance in an individual's solar UV exposure depending on global location and time of year [28]. The dose and wavelength of UV exposure can vary in different climates, elevations, and environments based on how much UV has been absorbed or reflected by the surrounding environment or atmosphere [29]. Elevation, time of day, and season all influence the distance sunlight travels through the atmosphere, which changes the amount and wavelengths of radiation that reach the earth's surface. Another source of variation is the degree to which a particular wavelength is absorbed by the earth's ozone. UVB (280–315 nm) is absorbed to a greater degree than UVA (315–400 nm) (approximately 95% and 5%, respectively). UVC (100–290 nm) is highly mutagenic, but it is almost completely absorbed by the earth's atmosphere and is not relevant to melanoma pathogenesis [28].

UVA and UVB affect the human body differently due to degree of penetration in the skin, the different energy levels they contain, and the varying absorption spectra of chromophores in the skin [30]. The epidermis of the skin serves as a barrier to UV through absorption by its constituent chromophores and by scattering. For UV wavelengths <300 nm, amino acids, nucleic acids, and melanin are the main chromophores. For UVA the main chromophore is melanin. Longer wavelengths of UV penetrate deeper into the skin [31].

UVA is most effective at causing tanning of the skin, while UVB is 1000 times more effective at producing erythema than an equivalent dose of energy in the UVA portion of the spectrum [32]. Effects of UVA on the skin include immediate pigment darkening, within minutes, and persistent pigment darkening, which may last for a day. Delayed tanning is initiated by a response to DNA damage in keratinocytes, which initiate the synthesis of α-melanocyte-stimulating hormone (α-MSH) by the p53-driven expression of the gene encoding its pro-hormone, *POMC*. Activation of pigment synthesis in melanocytes ensues when α-MSH activates its receptor, the melanocortin-1 receptor (MC1R) [33].

1.2.2 UV-Induced DNA Mutagenesis

Both UVA and UVB are carcinogenic. UV-induced DNA damage that can result in mutations occurs by two main mechanisms:

DNA Damage Via the Generation of Photoproducts Including Cyclobutane Pyrimidine Dimers (CPDs)

Damage to DNA in the skin occurs when adjacent pyrimidine bases, cytosine (C) and thymidine (T), are chemically linked by the formation of a cyclobutane ring giving rise to cyclobutane pyrimidine dimers (CPDs). These reactions are driven by i) absorption of a UV photon by a pyrimidine base and/or ii) energy transfer to a pyrimidine base from the reaction of melanin with UV-induced reactive oxygen species (ROS) and nitric oxide [34]. The majority of the mutations generated when DNA damaged in this manner is replicated are CC > TT or TC > TT substitutions. CPDs can be removed by translation-coupled nucleotide excision repair. However, if this process is deficient, CPDs are transformed into carcinogenic mutations found primarily in skin cancers, including melanoma. Transcription factor binding sites are particularly susceptible to mutations by this mechanism due to perturbations in the DNA structure induced by binding of the transcription factor, that favor CPD formation [35].

Oxidative DNA Damage

This process is primarily caused by UVA. Damage occurs indirectly by the formation of ROS by UV [36]. The predominant product of the reaction of ROS with DNA is 8-oxo-guanine (8-oxoG). If this damage is not repaired by the base-excision repair (BER) machinery, G:C to T:A mutations can occur [37].

1.2.3 UV Exposure Avoidance

UV Index

The UV index (UVI) is a tool for communicating risk from UV as part of efforts to influence sun protective behaviors. UVI can be determined from model calculations or direct measurements, such as the use of data from spectrophotometers or broadband detectors [38].

The higher the UVI, the greater the risk. US UVI values can range from 1.5 to 20 [39]. Unfortunately, low levels of general public awareness and comprehension have limited the utility of the UVI [40].

Shade

The use of shade is an integral part of public health policies and interventions. The AAD (American Academy of Dermatology) shade program is one example. The provision of shade in public places has been incorporated into government policy in a number of countries; for example, the city of Toronto, Canada, became one of the first to introduce a shade policy in 2007 [41]. Such interventions can be effective in encouraging shade-seeking behavior; interventional studies have shown that when shade structures are provided in public schools, students use the shade [42]. However, since structures do not block all reflected UV, the degree of protection may be less than users anticipate. A study at a Texas lake randomized lightly pigmented individuals (Fitzpatrick Phototype I-III) [16] to application of SPF 100 sunscreen or use of a beach umbrella for 3.5 h. The umbrella group sustained significantly more sunburns compared to those using sunscreen (142 versus 17) [43].

1.2.4 Sunscreen

Sunscreen is one of the most important pillars of skin cancer prevention; however, recent environmental and health concerns that are discussed below, threaten to limit use.

Active Ingredients

Sunscreens contain two types of active ingredients: chemical compounds (organic aromatic hydrocarbons) and/or physical agents (inorganic or mineral compounds) (Fig. 1.2). Chemical sunscreens are often a combination of between 2 and 6 benzene ring-containing substances capable of absorbing light in the UV range; the most commonly used of these is oxybenzone. Five percent of sunscreens are combinations of chemical and physical filters [46]; the physical filters scatter and reflect UV energy, and can be used alone or in combination with chemical agents to enhance UV absorption by the chemical filters instead of

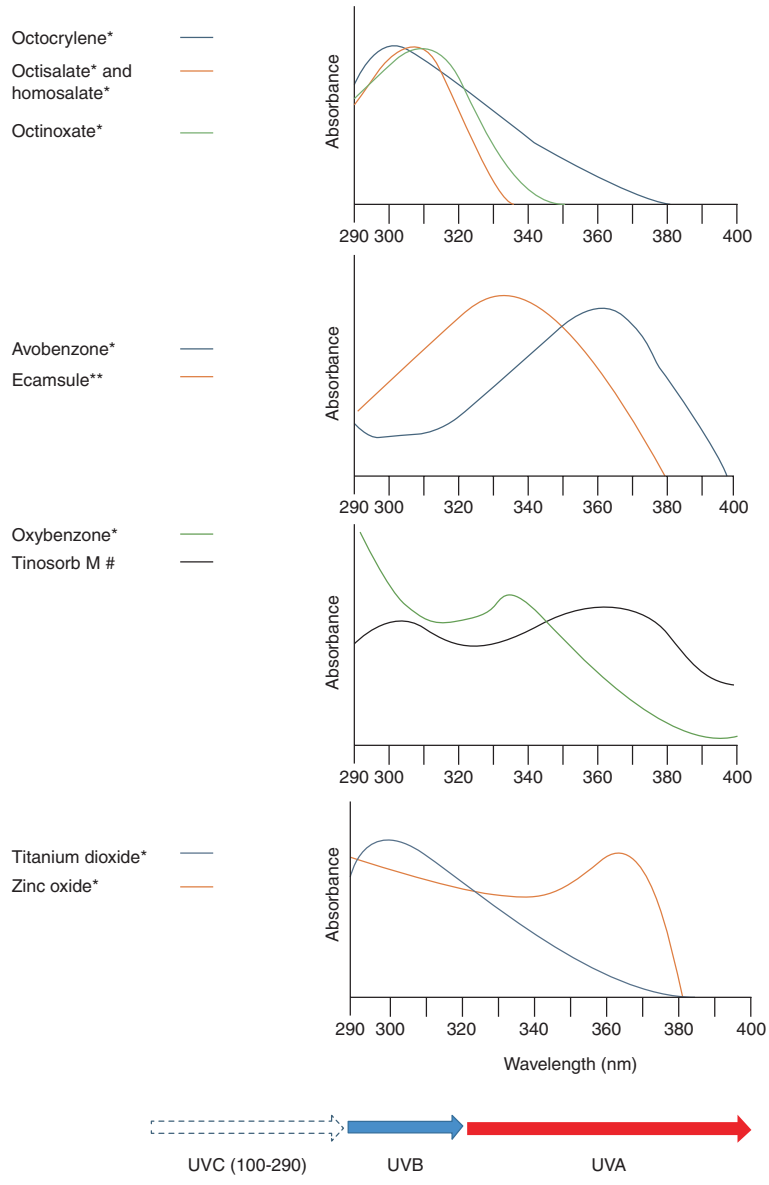

Fig. 1.2 Absorption spectra of sunscreens. Shown at the top are absorbance spectra for chemical sunscreens that absorb light primarily in the UVB range. Next are spectra for agents that absorb most strongly in UVA. Third are two broad-spectrum chemical sunscreens that absorb both UVB and UVA light. At the bottom are the absorption spectra of physical (mineral) sunscreens titanium dioxide (TiO_2) and zinc oxide (ZnO). Spectra illustrate relative maxima and minima in absorption; the magnitudes of the peaks do not reflect the relative molar extinction coefficients (a measure of how strongly the chromophore absorbs light of a given wavelength). *In 1999, the US FDA issued a monograph (see reference [44]) stating that all of these ingredients could be used as sunscreens, in combination, as long as the resulting product had an SPF of at least 2. New rules proposed in 2019, stated that of these, only TiO_2 and ZnO are currently deemed GRASE (generally regarded as safe and effective) [45]. The remaining compounds were deemed to have insufficient data for a determination of GRASE, and the FDA has requested additional information. Until this information is gathered and a new ruling on over-the-counter (OTC) sunscreens is approved, the "FDA generally does not intend to object to the marketing of OTC sunscreen products that do not have an approved new drug application (NDA)" provided that they comply with previously published FDA standards. **Ecamsule has an approved NDA and is marketed in the US by L'Oreal. #Tinosorb M is not approved for use in the United States although it is used in sunscreens in Europe and Japan

the skin [47]. Sunscreens vary significantly in the wavelengths of UV light that they absorb (Fig. 1.2) [44, 45, 48–52].

Sun Protection Factor

Sun protection factor (SPF) is a measure of a sunscreen's ability to prevent UV-induced erythema when applied uniformly at 2 mg/cm^2. Current methods measure the ratio of minimal erythemal dose (MED) with sunscreen to the MED without sunscreen, in vivo, using a solar simulator. An SPF of 50, for example, would give 50 times the protection compared to skin without sunscreen. SPF primarily assesses erythemogenic wavelengths, predominantly UVB [53]. Individual countries have UVA protection scales such as the UK star rating, but in spite of the importance of UVA protection in sunscreen, there is no globally recognized scale. The US Food and Drug Administration (FDA) has recently proposed that any sunscreen of >15 SPF be broad spectrum. They also proposed that broad-spectrum protection should increase in proportion to SPF [54].

Sunscreen Regulation

Sunscreen is considered an over the counter medication by the FDA. Currently, the FDA limits designations of SPF at 50+. However, a number of trials have shown greater protection with sunscreens with a rating of 50+. Kohli et al. [55] compared SPF 50+ to 100+ in a randomized blinded split body trial of beachgoers over five consecutive days. At the end of the 5 days, 56% of individuals had more sunburn on the SPF 50+ side compared to 7% on the 100+ side. In 2019, the FDA proposed a new rule which would increase the maximum SPF to 60+.

Sunscreen Efficacy

Sunscreens reduce erythema and concurrent DNA photodamage in the epidermis [56]. They are also thought to ameliorate important changes in the epidermis before erythema has occurred [57] such as p53 expression, which is elicited by DNA damage.

There has been one randomized controlled trial that measured melanoma risk as an outcome of sunscreen use, the Nambour skin cancer prevention trial. The trial was initially designed to study the effects of sunscreen on keratinocyte carcinoma. Individuals were randomized to daily self-application of SPF 16 sunscreen on sun exposed skin, versus control (their normal discretionary use of sunscreen). The primary end points of BCC and SCC incidence (in areas of sunscreen application) were assessed over a period of 4.5 years. SCC incidence was lower in the daily sunscreen group (1115 vs 1832 per 100,000). No difference in the incidence of BCC was established [58]. Follow-up of a further 8 years showed a persistent reduction in SCC rates in the treatment group [59]. Even after the intervention ceased, those who had previously irregularly used sunscreen prior to the trial were more likely to use sunscreen if they had been randomized to the daily sunscreen group [60]. After trial completion, a 10-year follow-up study specifically assessed the effect on melanoma incidence, and found that the risk for invasive melanoma was reduced in the intervention group (hazard ratio 0.27; CI 0.08 to 0.97 $p = 0.045$) [61].

Currently, no evidence exists to show superiority of chemical or physical agents for skin cancer prevention.

Risks Associated with Physical and Chemical Sunscreens

Although physical sunscreens can leave a chalky residue and are therefore less cosmetically acceptable than chemical sunscreens, they are relatively inert, less irritating, and have a more established safety profile than chemical sunscreens. Our own studies using both colon cancer and keratinocyte cell lines showed that TiO_2 nanoparticles are nontoxic at a dose of 100 μg/cm^2 and ZnO had an LD_{50} of 12 μg/cm^2 in both cell lines [62]. Our analysis of the effects on global gene transcription in keratinocytes in culture showed some responses that we could attribute to the Zn^{+2} liberated from ZnO. We also found upregulations of the unfolded protein response and oxidative stress response that were unique to the ZnO nanoparticles. Unlike chemical sunscreens, ZnO and TiO_2 nanoparticles do not penetrate the dermis and therefore do not

have substantial potential for systemic absorption [63].

Two studies in 2019 from FDA-based groups [64, 65] demonstrated the potential for systemic absorption of chemical sunscreens. Maximal use (2 mg/cm^2 of sunscreen applied to 75% of body surface area 4 times per day for 4 days) of commercially available chemical sunscreens in healthy individuals resulted in detectable plasma concentrations of the active ingredients. These concentrations exceeded the level normally set by the FDA for the recommendation of toxicological assessments including carcinogenicity and reproductive studies in topical therapies. Absorption of excipients or vehicle agents was not assessed.

No harmful effects of systemic absorption in humans have yet been proven, but estrogenic effects have been seen in animal models. Sclhumpf et al. [66] demonstrated increased uterine weight in rats when chemical sunscreens were administered topically or orally. However, critics of these studies have argued that the equivalent dose used in these studies would not feasibly be achieved with "real world" sunscreen use in humans, where sunscreen is typically underapplied [67]. Short-term studies have shown no effect on thyroid or reproductive hormones in humans [68, 69].

In addition to their potential for systemic absorption, the chemical UV filters can act as contact sensitizers. Of contact allergy cases presenting to a dermatologist, those caused by sunscreen have been reported as varying between <1% and 15.4% [70, 71]. The allergen most frequently implicated is oxybenzone.

Several studies have suggested that long-term use of facial sunscreens may be linked to frontal fibrosing alopecia (FFA) [72, 73]. Some have theorized that sunscreen nanoparticles (particularly titanium dioxide) penetrate the follicular infundibulum and trigger a lichenoid reaction. However, overall there seems to be insufficient information to support a link between FFA and sunscreen [74]. Evidence comes primarily from cross-sectional and survey-based studies, which are prone to recall bias and unable to establish specific sunscreen ingredients accurately. There is also little evidence of causality; an alternative explanation might be that increased sunscreen use has occurred as a behavior change following hair loss [74].

There has been increased concern recently regarding the environmental impact of chemical sunscreens, particularly in marine environments. Chemical filters are lipophilic and difficult to remove from wastewater, and have also been shown to bioaccumulate in fish [75]. Chemical sunscreens have been detected in coral tissue [76], and oxybenzone was shown to cause bleaching of coral [77], a harmful process where coral expels its normal symbiotic algae and becomes white. This has led to upcoming sales bans, effective January 2021, of octinoxate- and oxybenzone-containing sunscreens in Hawaii and Key West, Florida. However, there are other possibly more significant causes of bleaching such as global warming [78]. Other contributing factors include acidification with temperature rise, overfishing, and herbicide contamination [79].

Barriers Limiting Effective Use

Data suggests that most people use sunscreen incorrectly [80, 81]. To be consistently effective at the SPF level claimed, sunscreen requires frequent reapplication (at least every 2 h, more frequently with sweating or water exposure) of at least 2 mg per square centimeter of exposed skin. For most adults, this equates approximately to using a full shot glass or approximately one ounce per application [82]. In a real-world situation individuals only apply between 0.39 and 1 mg/cm^2 [83]. Furthermore, individuals often apply sunscreen after UV exposure has started.

Sunscreen use is low among certain groups. Men are much less likely to use sunscreen for photoprotection [84]. Regular sunscreen use is associated with healthy behaviors such as not smoking and complying with aerobic activity recommendations [85]. Low income is an enormous barrier to sunscreen use. It is estimated that a family of four following standard sunscreen application recommendations for a week would need to spend between $178.20 and $238.40 [86]. In fact regular use of sunscreen has been associated with an annual household income of

>$60,000 [85]. Other factors influencing reduced use of sunscreen include previous use of sunbeds [87] and a positive view of suntans [88]. Patient concerns regarding the environmental impact of sunscreens and systemic absorption will also inevitably depress compliance rates.

1.2.5 UV Protective Clothing

Similar to SPF, Ultraviolet Protective Factor (UPF) ranks the protective capacity of clothing as a proxy measure of garment sun safety. Clothing with a high UPF (≥20) transmits <5% of UV to the skin [89]. Although the garment industry now specifically markets UPF clothing, almost 90% of summer apparel has a UPF >10, which provides equivalent protection to SPF 30 sunscreen [90]. Factors influencing UPF include fiber type, construction, color, degree of stretch, dampness, and degree of wear. Weave construction is the most important factor. Tighter knit materials transmit less UV between threads [89]. Darkly colored fabrics also reduce UV transmission compared to those with lighter colors. Synthetic fibers such as polyester have a better ability to absorb UV in comparison to cotton and wool fibers [91]. The UPF of fabric is reduced when items are stretched, wet, or have significant wear. Swimwear can lose up to 90% of its initial UPF rating when stretched by 20% [90].

Additives may further improve the UPF of fabrics. UV dyes, such as SunGuard™, include Tinosorb FD, a stilbene disulfonic acid triazine derivative that absorbs UV light and increases the UPF of garments [92]. The dye is invisible to the human eye, and laundering a white t-shirt in the presence of the dye increases UPF of the cloth by 407%. Some clothes are also available with impregnated UV filters such as titanium dioxide. Cases of contact allergy have been encountered [93].

Public health initiatives, such as the "Pool Cool" program, have emphasized the importance of sun safe clothing [94] (Table 1.2). The "Sun-Safe Clothing" study was a large, interventional, randomized controlled trial that examined the effects of photoprotective clothing. A cohort of children in the high UV environment of North Queensland, Australia was randomized to wear UPF clothing or regular clothing at daycare centers. After 3 years, the UPF group had significantly fewer melanocytic nevi than the regular clothing group (12 vs 16 per child, $p = 0.02$) [95].

1.2.6 Therapeutic Prevention

To date, sunscreens are the only therapeutic agents that have a demonstrated beneficial impact on melanoma incidence. However, other agents have shown promise. Oral nicotinamide and topical DNA repair enzymes (such as T4 endonuclease (T4N5)) are effective for preventing keratinocyte carcinomas and/or decreasing actinic keratoses, precursor lesions that have phenotypic and environmental risk factors in common with melanoma [96, 97]. In addition, synthetic analogs of α-MSH are under development as sunless tanning agents (reviewed in Jeter J et al. [98]). The potential for these compounds to prevent melanoma in humans is not known because they have not yet been evaluated in any clinical trial for which melanoma incidence was the endpoint.

Antioxidants deserve special mention as a specific class of candidate therapeutic prevention agents. Many patients believe that antioxidant topical or oral supplements can reduce cancer risk, despite a lack of evidence [99]. Meanwhile, prevention researchers have coined the term "Antioxidant Paradox" to acknowledge that some antioxidants can contribute to an increased risk for some cancers, including lung cancer (increased by β-carotene) [100], prostate cancer (increased by vitamin E) [101], and squamous cell carcinoma of the skin (increased by selenium) [102]. Carcinogenesis is a multistage dynamic process, and the effects of antioxidants can vary according to the stage of tumor development at which agents are administered [103]. New evidence suggests that reactive oxygen species participate in well-regulated "redox networks" that control many signal transduction pathways and cell fate decisions [104]. Flooding these systems with antioxidants may in some

cases provide a survival benefit for both tumors and initiated cells [98, 105]. Topical antioxidants could have a role in melanoma prevention at the initiation stage as this modality avoids unnecessary systemic exposure. However, the safety as well as the efficacy of such agents must be demonstrated in the appropriate preclinical and clinical models.

1.2.7 Vitamin D

An important consequence of UV protective measures may be a reduction of vitamin D production by the skin. Vitamin D is an essential compound that promotes gut calcium absorption and maintains normal serum calcium and phosphate levels. Approximately 90% of vitamin D is synthesized by UVB-catalyzed reactions in the skin and the remaining 10% is acquired through dietary intake. At serum levels of 25-hydroxyvitamin D below 25 nmol/L, the risk of symptomatic musculoskeletal diseases including osteoporosis and osteomalacia rises significantly [106].

Patients who have been treated for melanoma are more likely to be vitamin D deficient. Among patients at a tertiary melanoma referral service, the frequency of deficiency increased from the time of primary melanoma diagnosis to subsequent follow ups [107].

Additionally, a recent meta-analysis has suggested that while there was no significant difference in vitamin D levels between those with melanoma versus controls, vitamin D deficiency was associated with higher Breslow thickness and mortality in the cohort with melanoma [108].

Photoprotection Still Allows Adequate Endogenous Vitamin D Production

Young et al. [109] compared the optimal use of SPF 15 sunscreen versus a control group who used their usual methods of sun protection in a study of subjects who were vacationing in sunny locations. Participants in the former group were monitored to ensure that the correct amount of sunscreen was being applied. Optimal sunscreen use still allowed substantial vitamin D production while protecting from sunburn. The discretionary sunscreen group experienced a significant level of sunburn. Thus, we can conclude that vitamin D synthesis can occur at relatively low UV levels [110], and that even when used optimally, sunscreens do not completely block UV transmission to the skin.

Bioequivalence of Oral Vitamin D

There is no evidence that endogenously produced vitamin D is more bioavailable than vitamin D supplementation taken orally [111]. Interventional studies comparing oral vitamin D and UV exposure have shown that both can effectively raise 25-hydroxyvitamin D serum levels. A Norwegian crossover study found that high dose oral vitamin D was equally effective at raising 25-hydroxyvitamin D compared to ten whole body sunbed sessions with a total dose of 23.8 standard erythema doses (SED) [112].

1.2.8 Population-Based Interventions

Population-based primary prevention interventions to reduce melanoma incidence are wide-ranging and include measures to make sun exposure safer, such as implementation of community shade structures, and environmental protections including the 1985 Montreal protocol to curb production of ozone layer-depleting chlorofluorocarbons [113]. However, the cornerstone of population-based melanoma prevention is behavioral interventions.

Behavioral interventions can reduce UV exposure by informing individuals of risks, and changing attitudes toward sun protective behaviors. Australia has led the way in population-based behavioral interventions as the country has the highest incidence of melanoma in the world, with 49 cases per 100,000 per year [114]. In the 1980s, amidst growing concern surrounding high skin cancer rates and the thinning ozone layer, the Anti-Cancer Council of Victoria (ACCV) launched the SLIP!SLOP!SLAP! campaign. The campaign used an animated, singing seagull to encourage the public to “slip on a shirt, slop on a

sunscreen and slap on a hat." Subsequently, the Australian nationwide SunSmart campaign was launched to reduce the burden of melanoma through changes in attitudes and behaviors. SunSmart provided targeted education for healthcare workers and teachers, and more widespread media advertisements for the general public. School systems could receive SunSmart accreditation for introducing policies such as requiring broad-brimmed hats as part of the school uniform [115, 116]. Currently, 71% of primary schools in Australia have received SunSmart accreditation [117]. The SunSmart campaign also lobbied for lower tax for sunscreen and removal of restrictions that had previously limited sunscreen sales to pharmacies [116]. Australia became one of the first countries to ban commercial tanning facilities.

In the decade after the initiation of the SLIP!SLOP!SLAP! campaign, evidence for its efficacy began to emerge. In the state of Queensland, a decline in invasive melanomas in young adults was first seen in the 1990s [118], and this change has persisted. Between 1995 and 2014, the age-specific incidence of invasive melanoma for those 40 years and younger declined in the state [119]. Age-specific mortality also decreased for males and females under 40 years of age. The only demographic group that saw a significant increase in mortality rate was for men over 60 years [119].

Many major health organizations have advocated for curtailing the use of tanning beds, particularly by those under 18 years of age. Globally, legislation on this topic varies. Brazil and Australia have banned commercial tanning facilities, while several European countries prohibit tanning bed use for minors under 18 years of age. In North America, there is a patchwork of legislation as tanning beds are regulated at the state/provincial or local level in the United States and Canada. Currently in the United States, more than 40 states have laws banning or partially restricting the use of tanning beds by minors under 18 years of age [120, 121].

Unfortunately, education alone may not necessarily translate to sustained behavior change. In the United Kingdom, where more than 90% of people report being aware of sun protective measures for children, the rates of sunburn remain high (approximately 38% of children per year) [122]. A barrier to any behavioral intervention is the prevalent perception that tanning is healthy and attractive. Wearing long-sleeved photoprotective clothes and broad brimmed hats during summer months are often at odds with Western societal norms, particularly amongst teenagers. Rossi [123] suggested a model of behavior change, where individuals move through several stages of behavioral change (precontemplation, contemplation, preparation, action, and maintenance). However, proponents of many interventions fail to appreciate that individuals may not be in a state of preparedness for new information.

1.3 Secondary Prevention

1.3.1 Risk Stratification

Risk stratification increases the safety and cost-effectiveness of melanoma screening by targeting the delivery of the most invasive, expensive, and time-consuming preventative efforts to those at the highest risk. For the purpose of this chapter, we will divide early detection interventions into those most suitable for individuals based on their estimated risk of developing melanoma, low, moderate, high, or ultra-high (see Table 1.1).

There is currently no consensus in the United States on the use of total body skin examination (TBSE) for population-based skin cancer screening of asymptomatic adults. In 2016, the US Preventive Services Task Force (USPSTF) concluded that "current evidence is insufficient to assess the balance of benefits and harms of visual skin examination by a clinician to screen for skin cancer in adults" [124]. However, the organization did note that individuals with a suspicious skin lesion or with significant skin cancer risk factors are outside the scope of this recommendation. They did not provide additional guidance on the level of risk or provide detail regarding populations that should be screened regularly.

The USPSTF recommendation faced criticism for a number of reasons. The UPSTF cited diagnosis of keratinocyte carcinoma as a harm of screening, yet morbidity associated with delayed diagnosis of keratinocyte carcinoma was not considered. The number of excisions made per melanoma diagnosis, 20–55, was considered too high [125]. However, some have argued that considering the morbidity and mortality of melanoma, that this number needed to treat is entirely justifiable and likely much lower in the hands of experienced clinicians [26].

In response to the USPSTF statement, Johnson et al. proposed rational, risk-based, data-driven screening guidelines for the population that would most benefit from at least annual TBSEs [26]. The group modeled these guidelines after recommendations in countries with similar melanoma risk, and included risk factors with RR or OR similar to those of cancers that have received USPSTF recommendations of Grade A or B. Ultimately, the team concluded that adults aged 35–75 years should receive annual TBSEs if they had one or more of the following risk factors: history of actinic keratoses or keratinocyte carcinomas, mutation in *CDKN2A* or other high-penetrance melanoma predisposition gene, family history of melanoma, fair skin, many freckles, blonde or red hair, more than 40 nevi, more than 2 atypical nevi, severely sun-damaged skin, history of blistering sunburns, or history of indoor tanning. Additional risk assessment tools are described in the Introduction.

1.3.2 Interventions in Low-Risk Individuals

1.3.2.1 Education

Educational outreach efforts aimed at early melanoma diagnosis and self-screening practices can target the wider population or specific groups. There is an association between patients being better informed about melanoma and earlier diagnosis. In a cohort of patients in France with primary melanoma, both delay in diagnosis and tumor thickness was associated with low awareness about melanoma [126].

The AAD "SPOT skin cancer" campaign is a public initiative to increase melanoma awareness and self-diagnosis. Their campaign material has used a distinctive orange spot logo and promoted the use of the ABCDE rule. The ABCD mnemonic has been used in public health messaging for almost 35 years, having been published originally by Friedman et al. in 1985 [127]. It consists of a set of simple criteria for when a skin lesion needs to be assessed by a dermatologist. Among the factors associated with melanoma self-detection is knowledge of the ABCD rule [128]. A study of lay people's ability to discriminate benign and malignant pigmented skin lesions found that giving information about the ABCD rule enhanced their ability to identify malignant lesions. However, they were likely to subsequently overestimate the danger of benign lesions [129].

Educational outreach efforts aimed at early melanoma diagnosis and self-screening practices can target the wider population or specific groups. In a cohort of patients in France with primary melanoma, both delay in diagnosis and tumor thickness was associated with low awareness about melanoma [126]. An educational campaign aimed at early referral of melanoma in the west of Scotland increased the local incidence of melanoma with a greater relative proportion of thin melanomas. The campaign consisted of written information distributed widely to places of work such as factories, health centers, and government buildings [130]. A similar campaign in Italy spanned 6 years; researchers mailed written pamphlets on melanoma and skin self-examination (SSE) to a population of 243,000. A significant trend toward a lower stage of melanoma was seen when health data was compared to the pre-campaign period, with mean thicknesses of 2 mm versus 1.5 mm $p < 0.02$ [131].

Hairdressers may have an important role in alerting patients to head and neck melanomas which carry a poorer prognosis [132]. An interventional study among hairdressers found that a brief educational video was effective in increasing awareness about melanoma risk and understanding of the ABCDE criteria [133]. Other professionals such as tattoo artists and massage

therapists provide additional resources for melanoma detection (https://www.ohsu.edu/war-on-melanoma/skincare-professionals).

1.3.2.2 Skin Self-Examinations

The AAD recommends that all members of the public perform skin self-exams. They demonstrate a model Skin Self-Examinations (SSE) as part of their "SPOT skin cancer" campaign; patients are advised to examine their extremities, torso and to use a hand mirror to check the neck and scalp [134]. In reality, SSEs are likely to be variable in their thoroughness [135] and accuracy. A low proportion of individuals actually practice SSE (estimated between 9 and 18% [136]). Even in high-risk patients, such as families with CDKN2A mutation, the rates of SSE are low [137].

- *What evidence is there that the practice of SSE is effective?*
- A large case control study was the first to cite a reduction in the risk for advanced melanoma (63%) in patients who had a previous diagnosis of primary cutaneous melanoma, compared to general population controls [138]. Further study of the same cohort 5.4 years later showed a lower risk of death from melanoma in patients with higher "skin screening practices," assessed from a combination of SSE with other factors such as skin awareness. This effect was not seen with SSE alone [139]. An Italian study found that self-reported SSE was associated with thinner melanomas. The adjusted mean thickness of melanomas was 0.77 mm for participants who performed SSE compared to 0.95 mm for those that did not [140].
- *What efforts can be made to increase the rates of SSE in the population?*
- A combination of computer-aided learning, hands-on tutorials, and monthly reminders was found to be effective at increasing compliance in one randomized controlled trial [141]. A study in men above 50 years found both written and video media to be effective in increasing SSE behavior [142].

1.3.2.3 Mobile Applications

The Role of Apps in Melanoma Prevention

Mobile phone applications or "apps" have a number of potential roles in melanoma prevention. For patient-targeted apps this includes software to track skin lesions and aid self-surveillance, and to facilitate teledermatology. Some more controversial apps purport to detect melanomas; however, no app can currently diagnose melanoma.

Several Apps, such as "UVI Mate," give the UVI forecast and sun protection recommendations depending on the user's GPS location. Apps may act as an adjunct to other melanoma prevention methods and even promote compliance. For example, Marek et al. found that an App which held digital total body photographs increased the rate of patient self-skin examination [143].

Apps can also be used to train medical professionals; it has been shown that apps can improve the ability of medical students to visually diagnose melanoma compared to more traditional teaching methods [144].

Mobile apps may also aid participants' engagement in medical research. The Mole Mapper iPhone app allows individuals to track images of their nevi and self-monitor their skin, without providing medical advice. The app provides a platform for crowdsourcing recruitment of research participants and curation of mole images in efforts to advance melanoma research. Users can consent for their images, nevi measurements and self-reported demographic information to be shared in research to develop melanoma diagnostic algorithms [145]. To date, more than 5500 participants from across the United States have contributed images to this effort.

The Challenges Facing Users and Designers of Mobile Apps

Dermatology smartphone apps encompass a broad range of capabilities and are under constant revision and turnover [146]. App features may include education, dermatology referral, teledermatology, lesion photography and monitoring, image analysis, advice, or combinations

of these features. Some apps work in conjunction with personal dermoscopy devices. Apps can be targeted toward the general public or physicians, and several offerings include pairs of apps aimed at each audience, such as VisualDx and Aysa or DermEngine and MoleScope. Content-based Image Retrieval (CBIR) is a sufficiently low-risk level of advice that it typically avoids the need for regulatory approval. This method presents images, clinically confirmed diagnoses, and recommendations for images similar to the one photographed by the end user, thereby letting the user decide on the appropriate action [147]. While many apps claim to include some form of artificial intelligence (AI), to our knowledge only one app, SkinVision based in the Netherlands, appears to offer a clinically validated AI-based analysis of risk and provides users with a recommendation. Like teledermatology apps, SkinVision charges users for assessments. This app has varying levels of regulatory approvals in Europe but does not have FDA approval in the United States. Some controversy exists over accuracy claims for this app [148]. A concern with this and other apps which assess the risk of skin lesions being cancerous is that they might lead patients to forego medical attention. A recent Cochrane review has concluded that apps that rely on AI detection of skin cancer have yet to demonstrate sufficient accuracy and "are associated with a high likelihood of missing melanomas" [149].

Machine Learning

The majority of modern algorithms used for classification of dermatological images are based on a type of Deep Learning architecture called Convolutional Neural Networks (CNNs). Since 2017, these have shown performance on par with or exceeding dermatologists on very specific tasks, usually the classification of single images [150–152]. Despite some promising successes, there remains healthy skepticism regarding premature adoption of these algorithms as primary diagnostic tools, especially in the context of smartphone apps [149, 153, 154]. Use of apps in clinical decision support or so-called Augmented Intelligence in clinical settings is less controversial [147, 155].

Teledermatology

Teledermatology has benefited from the global pandemic in that it has been much more widely adopted since in-person clinic visits have been restricted. Teledermatology has also improved access of rural patients to specialists. There are three different types of teledermatology visits. The first, known as store and forward, is where the patient uploads a photograph of the lesion of interest and sends it to a provider; then the provider evaluates the photograph and sends a message to the patient giving a diagnosis and providing recommendations. The second type is the virtual visit, which takes place in real time. The provider may inspect the skin using the computer's camera, or a patient can upload a higher resolution photo during the session. Because photos are frequently not good enough to make a diagnosis of melanoma, home dermoscopy is being explored as a potential solution. Finally, a primary care provider or hospitalist can request a teleconsult with a dermatologist when presented with a difficult case.

1.3.2.4 PCP Screening

A population-based study in France found that general practitioners who had had specific training on melanoma were more likely to detect melanoma among their patients [156]. The INFORMED (Internet Curriculum for Melanoma Early Detection) online training program is one such teaching effort that has been shown to improve the melanoma diagnostic skills of PCPs [157].

Primary Care Providers (PCPs) offer many patients their main or only point of contact with the healthcare system. They are often in a position to examine the skin and perform opportunistic screening during the process of providing care for conditions unrelated to melanoma. However, time is a limited resource in primary care; the median visit time for older patients is 15.7 min [158]. Medical teaching surrounding skin cancer examination is variable, with most physicians

receiving little dermatologic training during medical school or residency. Almost a quarter of medical students leave medical school without having seen a skin cancer examination [159]. In fact, rates of TBSE administration by PCPs are thought to have fallen [160]. There is no endorsement from the USPSTF for routine skin screening in primary care and therefore no systematized incentive or reminder to perform TBSE or other melanoma screening, although providers may encounter suspicious skin lesions during routine examinations of other systems.

1.3.3 Interventions in Individuals at Moderate Risk

In addition to measures mentioned above for low-risk individuals, moderate-risk individuals (Table 1.1) benefit from regular in-person skin screening including total body skin examination (TBSE) with their PCP or dermatologist. Clinicians may or may not use dermoscopy as a diagnostic aid. Dermoscopy will be considered elsewhere (*Detection and Diagnosis of Melanoma).*

1.3.3.1 Total Body Skin Examination

A total body skin examination includes a review of the whole skin surface, including the scalp, genitalia, palmoplantar surfaces, and nails. It is safe, technically simple, inexpensive, and completely non-invasive. A TBSE also offers an opportunity to screen for melanoma risk factors, such as the presence of atypical nevi.

TBSE screening rates are very low compared to other screening tests; in one study, 16% of men and 13% of women reported having a TBSE in 1 year, compared to 51% of the surveyed population undertaking colorectal cancer screening and 54% having breast cancer screening [161].

There are numerous observational studies that support the use of TBSE in melanoma prevention. A large case control study, based in Queensland, of individuals with a primary invasive melanoma, found that the risk of having a melanoma >2 mm in thickness was significantly increased in those who had not had a clinical skin examination in the preceding 3 years compared to controls [162]. Similarly, Swetter et al. found an association between having a thinner melanoma of <1 mm (compared to >1 mm) and having had a physician skin examination in the year before diagnosis [163]. Berwick et al. found that skin cancer awareness was associated with lower risk of death from melanoma (HR-0.5, $p = 0.022$) [139].

1.3.4 Interventions in High and Ultra-High-Risk Individuals

In addition to the measures recommended for low- and moderate-risk individuals, high-risk individuals should undergo regular clinical assessment with TBSE by a dermatologist. This can be supplemented with longitudinal photography and dermoscopy. These are discussed in detail in *Detection and Diagnosis of Melanoma*.

Ultra-high-risk individuals include those with a single, highly penetrant genetic risk factor such as the CDKN2A mutation, or multiple cumulative melanoma risk factors (Table 1.1). Regular clinical examination is known to benefit patients who have had multiple primary melanomas; it is associated with thinner subsequent melanomas [164]. The care of these patients is most suited to dermatologists with a special interest in melanoma, preferably at a center where there is multidisciplinary support from specialized plastic and oncological surgeons, medical oncologists, radiation oncologists, and dermatopathologists. They may also benefit from newer imaging techniques such as total body photography, longitudinal digital dermoscopy, and in vivo confocal microscopy with targeted biopsy. These adjuncts may increase the diagnostic yield of melanomas and reduce the number of unnecessary biopsies.

Hereditary Melanoma; Pre-Screening and the "Rule of Threes"

The diagnosis of genetic melanoma syndromes can help the provider tailor screening recommendations to individual patients. However, genetic testing for mutations in melanoma predisposition

genes carries significant risk including increased biopsies and surveillance. Genetic testing is also a significant source of uncertainty and anxiety for the patient and for untested family members. Therefore a "pre-screening" process is needed to identify those with a reasonable probability of carrying an actionable mutation. It is equally important to provide accurate risk statistics to patients who undergo genetic testing, and this includes an acknowledgment that some data is incomplete and thus no change in management is yet recommended.

The "rule of threes" is a simple pre-screening tool that can be used to decide whether patients should be offered genetic testing. It was originally developed to give a 10% pretest probability of finding a CDKN2A mutation [165] but has subsequently been widened to include screening for mutations in genes associated with other melanoma dominant and subordinate syndromes (Table 1.3). Mutations in *CDKN2A, CDK4, MITF, BAP1*, and *POT1*, where melanoma is the predominant cancer type, are associated with "melanoma dominant syndromes." Mutations in *PTEN* and *BRCA1/2* give rise to "melanoma subordinate syndromes" where melanoma has lower penetrance compared to other solid organ tumors.

If a genetic mutation associated with inherited risk for melanoma is confirmed, individuals should be counselled on the importance of photoprotection and monthly self-skin examinations. They should undergo TBSEs every 3–12 months. The interval should be determined by their own past medical history of melanoma, as per the NCCN (National Comprehensive Cancer Network) guidelines [166]. A large number of atypical nevi should also increase the frequency with which TBSEs are scheduled. Even in ultra-

Table 1.3 "Rule of Threes" Cancer syndrome Pre-assessment tool. Used with permission from Leachman (2017) [165]

Cancer type	Criteria	Points per occurrence
Melanoma	Occurrence in melanoma proband, first- or second-degree relative	1 or 1.5[a]
Astrocytoma	Occurrence in melanoma proband, first- or second-degree relative	1.5
Breast	Occurrence in proband, first- or second-degree relative under 45 years	1[b]
	Occurrence of bilateral- or triple-negative breast cancer proband, first- or second-degree relative	1[b]
	Occurrence in male gender	1[b]
Colon	Occurrence in proband or first-degree relative that occurred under 50 years old	1[b]
	Proband has had 5 or more adenomatous polyps occurring under 50 years of age	1[b]
Ovarian	Occurrence in proband, first- or second-degree relative	1
Pancreatic	Occurrence in proband, first- or second-degree relative	1.5
Prostate	Proband has had metastatic prostate cancer and/or had a Gleason score of >7 at diagnosis	1[b]
High frequency	At least two occurrences of breast, colon, or prostate cancer in melanoma proband, first- or second-degree relatives that do not meet the criteria above	1
BAP1 cancer syndrome	Occurrence in proband or first-degree relative of uveal melanoma, paraganglioma, mesothelioma, atypical Spitz tumors, or clear cell renal carcinoma	1.5/cancer type
Perform genetic testing		3 or more

[a]1 point in moderate or high melanoma incidence areas and 1.5 in low incidence areas

[b]The criteria listed suggest a hereditary pattern that may fulfill standard criteria for single-gene or cancer-specific panels without association with melanoma. Anyone or any family with these findings should be considered for genetic testing regardless of their melanoma status. However, if the criteria are met in the context of melanoma, we test additionally for melanoma genes

high-risk hereditary melanoma family members, compliance with photoprotection and melanoma screening recommendations is low. However, counselling and genetic test reporting increases compliance with these prevention recommendations [137].

Another important consideration in the management of hereditary melanoma is the extent and frequency of screening for other cancers. Although these cancer predisposed patients may be under the care of other medical specialties, frequently dermatologists are best positioned to help coordinate these additional screenings. For example, *BAP1* carriers should be offered regular skin screening as well as screening for uveal melanoma, mesothelioma, and renal carcinoma [167].

1.3.5 Population and Public Health

Schleswig-Holstein

The SCREEN project, which aimed to provide evidence for the effectiveness of melanoma screening in the state of Schleswig-Holstein in northern Germany, took place between 2003 and 2004. Between 1998–1999 and 2008–2009, Schleswig-Holstein witnessed a reduction in age-standardized melanoma mortality of 47% in men and 49% in women [168].

Based on the favorable results of this study, Germany became the first country in the world to introduce a nationwide melanoma screening program in 2008. Nineteen percent of the eligible population was screened with a total body skin examination (TBSE). The national health insurance plan covered individuals above 35 years of age for biannual skin cancer screening, but the public advertizing and systematic referrals to dermatology was discontinued. However, while the nationwide rate of diagnosis of melanoma increased, this did not translate into the anticipated reduction in mortality from melanoma. In fact, over the first 5 years of the screening program death rates were stable from pre-intervention levels [169].

Some have subsequently questioned the results of the SCREEN study. The reduction in mortality followed very closely behind the introduction of the screening, but reasonably there would be expected to be a lag period. The reduction in mortality was also very high when it is considered that a minority of the state's population underwent screening. Mortality data was not collected for SCREEN participants and the study relied on routine mortality data collection. Bias may have occurred in the certification of deaths by doctors who would have been likely to have taken part in the study, or at the very least been aware of the study. Notably, there was a corresponding peak in death from malignant neoplasms of ill-defined, secondary, and unspecified sites [170].

War on Melanoma

The "War on Melanoma" (WOM) is a melanoma prevention study based in Oregon. It has attempted to address some of the shortcomings of the German screening program by including features such as prospectively collected objective endpoints [27]. The WOM will collect outcome measures such as melanoma literacy, in addition to mortality data.

The study is multifaceted (Fig. 1.3). but aspects that are focused on secondary prevention include:

- *Skinny on Skin eLearning*: E-learning modules that promote early detection by increasing awareness among skin care professionals. These modules teach professionals such as hairstylists, tattoo artists, and massage therapists to identify skin lesions which "don't look right" and provide guidance for how to discuss the need to see a healthcare professional with clients.
- *Early detection training for Clinicians*: CME online training modules aimed at primary care providers and non-dermatologists. Training includes the recognition of suspicious lesions, identification of patients in need of screening by virtue of their risk for melanoma, and advice on when to refer for specialist treatment.
- *Public Screening Events*: Skincare festivals aimed at public education and offering TBSE

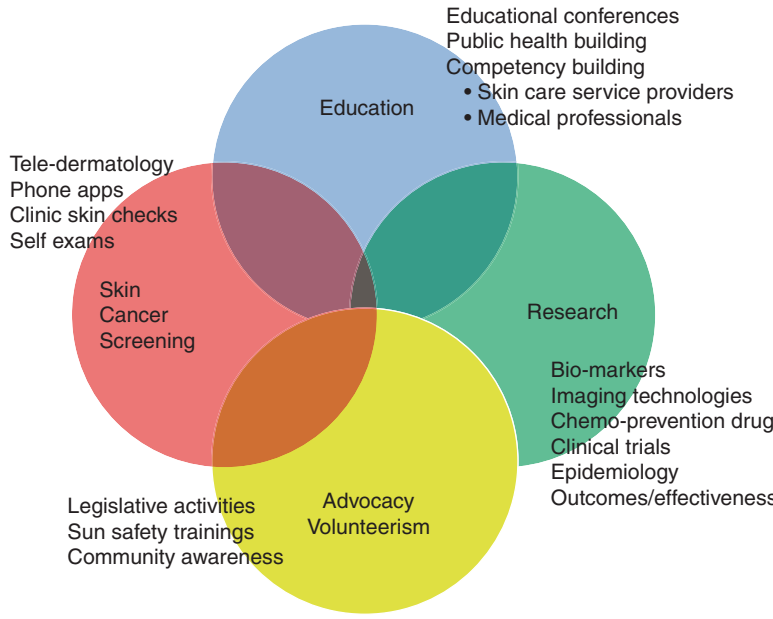

Fig. 1.3 A broad overview of the "War on melanoma" interventions. Figure provided courtesy of the War on Melanoma™

by dermatologists. Free TBSE events have also been extended to more rural areas of the state.

- *@Start Seeing Melanoma*: A public education campaign, which uses state-wide billboards, transit system adverts, and social media to communicate the importance of SSE (Fig. 1.4).

Fig. 1.4 Image used as part of the WOM social media campaign https://www.ohsu.edu/war-on-melanoma/social-media-toolkit. Figure provided courtesy of the War on Melanoma™

Pennsylvania

Overtreatment and increased skin surgery from melanoma screening has been cited as a cause for concern [124]. Weinstock et al. [171] specifically studied the adverse outcomes of a population screening program. The effort was launched in a large primary care population at the University of Pittsburgh Medical Center. PCPs were offered a modified form of the online training program, "INFORMED" (Internet course FOR Melanoma Early Detection). This is a tool that was designed to increase the melanoma detection rates among PCPs. Adverse downstream consequences such as number of skin surgeries and dermatology consultations were monitored. 16,472 individuals underwent a physical examination with their PCP, although not all PCPs had undergone INFORMED training. The team monitored for the number of skin surgeries and dermatology consultations; there was no increase in either metric. The number of melanomas detected

increased in the subgroup of patients assessed by PCPs with the highest rate of INFORMED training. This screening intervention was not randomized or blinded, nonetheless it does provide some reassurance that a large-scale screening program does not cause substantial iatrogenic harm and may be helpful.

1.4 Summary Points

- Clinicians need to provide clear advice to patients stating that simple primary preventive measures that reduce UV exposure, such as the use of sunscreen and protective clothing, are safe and efficacious.
- Risk stratification can improve the efficacy of screening. In the United States, a risk-stratified screening program may be more feasible than a broad-based program. Risk stratification methods now exist, but there is currently no widely accessible tool that recommends the most appropriate melanoma screening method for the individual patient.
- Assessment of the success of preventative strategies in reducing melanoma incidence and mortality is not straightforward, in part due to long latency between UV exposure and melanoma tumorigenesis. However, there is strong supportive evidence for the use of interventions such as SSE and TBSE for early detection of melanoma in the general population.
- Melanoma prevention has many different aspects and successful public health campaigns are often those that are multifaceted, such as the Australian SunSmart campaign.

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Epidemiology of Melanoma

2

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2.1 Melanoma Trends Worldwide

GLOBOCAN, an online database using data from the International Agency for Research on Cancer (IARC), provides estimates of incidence and mortality of various cancers from 185 countries. Using the GLOBOCAN database for the evaluation of global cancer incidence and mortality in 2018, it is estimated that there were 287,700 new cases of melanoma and 60,700 deaths from melanoma worldwide [1]. Among all cancer types captured worldwide in 2018, melanoma ranked 20th (1.6%) for the number of new cases, and 23rd (0.64%) for number of deaths [2]. Melanoma has a greater preponderance in light-skinned individuals, as reflected by a higher incidence in countries with a large proportion of these populations. Age-standardized world incidence and mortality rates (per 100,000) were highest in Australia and New Zealand (33.6) followed by Western Europe (18.8), Northern Europe (17.0), North America (12.6), Southern Europe (9.1), and Central and Eastern Europe (5.3). This is in comparison to Africa and Asia, where age-standardized incidence rates range from 2.2 in Southern Africa to 0.30 in South-Central Asia [3].

2.2 Melanoma Incidence Worldwide

In countries with predominantly fair-skinned individuals, incidence rates of melanoma have progressively increased over the past several decades [3]. One study analyzed population-based cancer registries from 39 countries studying time trends and incidence rates of melanoma. It demonstrated that while incidence rates of melanoma continued to rise in most southern and eastern European countries, a stabilization or decline of incidence rates was seen in Australia, New Zealand, North America, Israel and Norway, which was even more noticeable in the younger age groups (25–44 years). Factors that likely fueled an increase in melanoma incidence in the last century can be attributed to changes in various socioeconomic related attitudes such as: a shift to "sun-seeking" instead of "sun-protective" behavior, more vacations spent in sunny climates, a trend in more

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exposed clothing styles such as shorter skirts, sleeveless tops and bikinis. Another significant influence is the popularity of tanning booths from the 1960s onwards. The stabilization of incidence rates in more recent cohorts has been hypothesized to be partly related to the improved knowledge and public awareness of skin cancer and its risk factors. This has led to a gradual shift in attitude and behavior of the public to UV exposure [4].

Another study analyzed current trends in melanoma incidence rates with a view to projecting incidence rates for the future in six populations where melanoma incidence is high, namely: US whites, the UK, Sweden, Norway, Australia, and New Zealand. In these first four countries between 1982 and 2011, melanoma rates increased more than 3% per year, with projections suggesting a persistence of this rate increase until at least 2022. This persistence may partly be attributed to the high prevalence of tanning lamps in the 1980s and 1990s. In contrast to these countries, there was a decrease in melanoma incidence of 0.7% per year since 2005 in Australia. New Zealand, though in the midst of an increase in melanoma incidence rate, was projected to turn the corner and start to decline in the near future. Between 2012 and 2031, the study projected an increase in the crude numbers of invasive melanomas diagnosed in all populations. This was thought to be due to the increase in age-specific melanoma rates in the elderly in an ever-growing and aging population. Melanoma rates, however, are stabilizing and perhaps even declining in the young. It is theorized that younger people now have reduced sun exposure compared to prior generations; however, reduced exposure was unlikely to be fully explained by sun prevention activities alone, given that recent surveys among Australian youths suggest only a modest change in attitude to sun-seeking behavior. It was hypothesized that other factors related to trends in behavior among the young might be contributing to the decrease in incidence rates in youths, as national surveys have confirmed greater screen time among the young, leading to less time spent outdoors and hence UV exposure [5].

2.3 Incidence of Melanoma in the USA

A study of the US population by the Center for Disease Control and Prevention (CDC) showed a doubling of melanoma incidence rates between 1982 and 2011, while the annual cost of melanoma treatment was projected to triple by 2030, and strongly supported the use of evidence-based, comprehensive skin cancer programs to help reduce the projected significant health burden posed by melanoma [6].

In 2019, it was estimated there were 96,480 new cases of melanoma which represented 5.5% of all new cancer cases in the USA. There were also 7,230 melanoma-associated deaths during that time, which comprised 1.2% of all cancer deaths [7], and melanoma was ranked the fifth most common cancer overall in the USA [8]. In 2018 melanoma was ranked fifth most common cancer in men and sixth in women [9]. Age-adjusted SEER incidence rates for melanoma were 22.2 per 100,000 per year based on data from 2012–2016 [7]. Several reports showed that although the overall incidence of melanoma is increasing in the USA, there has also been a slowing or decline in rates in certain age groups. From 1973–1997, incidence rates of melanoma overall increased for men and women but slowed after 1981 [10]. Others have shown that from 1973 to 1994, melanoma incidence rates increased, most notably for men [11]. From 1990 to 1994, melanoma incidence rates continued to increase in men but slowed from previous analyses, and had actually declined in women [11], while during 1992–2004, overall melanoma incidence increased by 3.1% annually [12]. Analysts predict an overall continued increase in the incidence of melanoma in the USA, and it is estimated that in 2030 there will be 112,000 new cases of melanoma [6]. Similarly, it is projected that 116,000 cases of invasive melanomas will be diagnosed per year in 2026–2031 in US whites, compared to about 70,000 per year in 2007–2011 [5].

2.4 Melanoma Incidence by Race, Sex, and Age in the USA

The incidence of melanoma is by far the highest among light-skinned individuals. Data from the American Cancer Society reveals that in 2019, melanoma had the highest incidence among non-Hispanic whites at 27 per 100,000, followed by Hispanics at 5 per 100,000, and Blacks and Asians/Pacific Islanders at 1 per 100,000 [13]. In one study, whites comprised 95% of patients diagnosed with invasive melanomas from 1999–2006, followed by Hispanics (2%), African Americans (0.5%), Asians/Pacific Islanders (0.3%), American Indians/Alaskan Natives (0.2%) [14].

There is also a higher incidence of melanoma among males in the USA; out of the 96,480 new melanoma cases diagnosed in 2019, the incidence in males was 57,220, which accounts for 59.3% of all new melanoma cases that year, compared to 39,260 new cases in females which account for 40.7% of new melanoma cases. The differences in mortality follow a similar trend between sexes [15]; however, it is important to consider age when looking at the difference in melanoma incidence between men and women, as the rate of melanoma is higher among young women compared to young men, but this trend is reversed in the elderly population [16]. In one study, an age-related bimodal distribution pattern was observed among males and females. The incidence rates in women for melanoma were higher than males from birth until age 44. For women 20–24 years of age, age-specific incidence rates were double those of males. After age 44, males had a higher incidence of melanoma than females [17]. A population-based study using cancer registry data from the CDC and the SEER program found that incidence rates of melanoma among females were higher than males in non-Hispanic whites age 15–49, in every age group, from 1992 to 2012. Age distribution was mostly younger in women than in men. Earlier in the study period between 1992 and 2012, melanoma increased in incidence in all groups. However, after 2004–2005 a decline of ~3.0% annually was noted particularly in the younger age groups suggesting a possible cohort effect. The most common sites of melanoma in women were the trunk and lower extremities in contrast to men, where the most common sites were the trunk and the upper extremities. This is likely to reflect variations in the pattern of UV exposure [18]. Over time the incidence of melanoma in young females has been increasing more than for young males age 15–39 years. Purdue and colleagues noted that age-adjusted annual incidence for melanoma in males increased from 4.7 in 1973 to 7.7 in 2004, while in females the incidence was 5.5 in 1973 and increased to 13.9 in 2004. In the 1980s melanoma incidence for young males started to level off; however, in young females, incidence declined and then stabilized but started to increase again in 1992 [19]. Linos and colleagues found that men 65 years and older had the fastest growing incidence rate for melanoma during the years 1992–2004 [12].

The median age of diagnosis for melanoma is 65 years of age [20]. While the overall incidence of melanoma has been increasing in the USA, there are different trends observed between different age groups. There is recent evidence to suggest a decline in melanoma incidence among younger populations. In one study, in non-Hispanic whites 15 years or older in the US from 2005–2014 in men and women combined, there was a significant decrease in the incidence of melanoma for age groups 15–24, 25–34, and 35–44 vs. a significant increase in melanoma in age groups 55–64, 65–74, 75–84, >85 [21]. A study by Paulson and colleagues showed that from 2001–2015 melanoma incidence remained low and stable among children aged 0–9 years old, while the incidence of melanoma in adolescents aged 10–19 has been slowly declining since 2006. Specifically, from 2006–2015, incidence rates decreased in adolescents by an annual percent change of −4.4% in males and −5.4% in females. A similar trend was observed among young adults (age 20–29), where the annual percent change decreased by −3.7% and −3.6% for males and females, respectively. This decrease in incidence in the young population is in contrast to the increase in incidence among

adults over the age of 40, where a significant increase of 1.8% is seen in both adult men and women [16]. In one study of pediatric patients <20 years old from 2004–2010, investigators found a significant decreasing trend in melanoma incidence by 11.58% per year [22], in contrast to earlier studies which demonstrated a rise in incidence of pediatric melanoma, including a study using SEER data from 1973–2009, where overall pediatric melanoma increased by 2% per year and annual percent changes were especially significant in 10–14 year-olds (APC, 2.9%) and 15–19 years old (APC 1.9%) [23, 24].

2.5 Factors Contributing to the Rise and Fall in Incidence of Melanoma

The reason for the rise in melanoma incidence worldwide continues to be a topic of debate since it was first observed in the 1960s and it is likely to be multifactorial. Some experts do not believe that the increased melanoma incidence represents a rise in disease burden and attribute it instead to improved screening programs and the detection of thinner, slow-growing melanomas, or biologically indolent behaving atypical pigmented lesions that are being inadvertently categorized as melanoma [25]. Support for this argument comes from the observed rise in thin melanomas as screening intensity increased [26, 27]. One study showed that between 1986 and 2001, when the average biopsy rate increased by 2.5-fold among people over the age of 65, the incidence of thin melanomas in that group increased by 2.4-fold. Over that time period, 1000 extra biopsies resulted in 6.9 extra cases of in situ melanomas and 2.3 extra cases of early-stage melanomas without changes in the incidence of advanced melanomas or melanoma mortality [27]. Some experts believe that since the change in the incidence of melanoma mortality and thick melanomas has been minimal compared to that of thin melanomas, this would not be compatible with an aggressive malignant behavior of thin melanomas [28] and that such trends could represent melanoma cases that are histologically but not functionally malignant [25, 29]. Interobserver variability in melanoma diagnosis between pathologists is illustrated well in a study where, following a review of 37 specimens of classic melanocytic tumors, a panel of 11 dermatopathologists unanimously agreed on a diagnosis of benign vs. malignant in only 35% of cases [30]. Another study suggested a shift over time in the threshold of diagnosing melanomas; specimens that were initially diagnosed as benign in the 1980s and 1990s were more likely to be called malignant when reexamined in 2012 [31]. The liability of misdiagnosing melanomas and the increasing pressure on dermatopathologists in calling borderline specimens malignant have been cited as potential factors contributing to that shift [32]. Another factor thought to contribute to the rising incidence of melanoma is increased reporting to melanoma registries. Early localized melanomas managed in outpatient offices were initially less likely to be reported to cancer registries compared to hospital cases. However, as funding increased for the national program of cancer registries (NPCR), a program that provides cancer information and prevention at the local level, there was a dramatic rise in melanoma incidence in a short amount of time with an average annual increase of 2.8%. Such a large increase is unlikely to represent true disease, especially when the reported rise was larger in NPCR registries compared to national registries like SEER [33]. Experts have also pointed to inconsistencies in SEER registries resulting from inaccuracies in reporting tumor thickness. A study comparing SEER Detroit data to pathologist reports revealed a significant (26%) miscoding in tumors thickness which had originally been classified as ultrathin melanomas (≤0.25 mm Breslow). This led to a higher than usual incidence of ultrathin melanomas, which is normally uncommon. After reexamining the pathology reports, it turned out that only ~4% of the original number remained as being ultrathin. Most of the errors were due to decimal point misplacement. This highlights how patient outcomes may be mischaracterized if data from registries are not validated [34]. The debate regarding the issue of increasing melanoma

incidence has been well summarized by Gardner and colleagues [35].

While some experts are able to rationalize the rising incidence of melanoma through issues of enhanced screening and histological overdiagnosis, others believe that the observed rise in melanoma incidence worldwide represents a true pandemic. Explanations put forward include increased UV exposure with survey data supporting an increase in sunburn and the use of tanning beds between the years 1986 and 1996 [36]. Climate change and the resulting increase in UV radiation reaching the earth have also been proposed as an explanation for the rising incidence of melanoma [37, 38]. As melanoma risk increases with age, the increase in life expectancy in the developed world is also thought to contribute to the rising melanoma incidence [39, 40]. Supporting this argument is the observation of a rise in melanomas of all histologic subtypes and thicknesses. A large meta-analysis in 2009 of over 300 million person-years covering 70,000 new cases of melanomas revealed a significant 3.86% annual increase in melanomas thicker than 4 mm. The authors concluded that the increase in melanoma incidence could not be adequately explained by increased screening and detection of thin melanomas alone [41]. It is notable that the rise in the incidence of melanomas thicker than 4 mm was steepest among people in the lowest quartiles of socioeconomic status. Since this patient population has limited access to healthcare and regular screening, the increased incidence seen in this subgroup could lend further support to the notion that the true disease burden of melanoma is rising and cannot solely be the result of improved detection and screening [42].

2.6 Trends in Melanoma Tumor Thickness

Tumor thickness is the most important prognostic factor for primary cutaneous melanoma [43]. Decreased tumor thickness at diagnosis in recent years has been reported worldwide. The efforts that led to the decline in tumor thickness are thought to also contribute to the stabilization of melanoma mortality. Analysis of the central melanoma registry in Germany, for example, revealed a decrease in average tumor thickness from 1.81 mm in 1976 to 0.53 mm in 2000. In the USA, mean tumor thickness decreased from 0.73 to 0.58 mm from 1986 to 2009 [44, 45]. An increased proportion of thin melanomas at the time of diagnosis has also been seen in several different countries, including Scotland [46], France [47], central Europe, parts of Australia [48] and Spain [49]. These observations have been attributed, at least in part, to the implementation of public education campaigns such as the introduction and expansion of the ABCDE rule from 1985 through 2004 [50], the Stockholm cancer prevention program in Sweden, and the Sunsmart health promotion campaign in Australia [51, 52], in addition to improved screening and associated earlier detection of melanoma.

From 1988–2006, the distribution of melanoma in the USA among all tumor categories remained stable; however, the proportion of melanoma in situ increased, and the proportion of fatal melanomas with >4 mm thickness also increased, suggesting that screening and early detection had not resulted in a reduction of thicker melanomas with poorer prognosis [53]. There is significant evidence for an increased incidence of in situ melanoma, which has been growing in parallel with that of invasive disease. Analysis of data obtained from the US Surveillance Epidemiology End Results (SEER) in 2011 showed an increased incidence of in situ melanoma at 9.5% and an increase in the incidence of invasive melanoma at 3.6% [54]. This trend has been observed in several different countries, including France [47], Scotland [46], Spain [55], parts of Australia, and central Europe [48].

Age has also been associated with increased tumor thickness and a worse prognosis of melanoma. Individuals over the age of 65 are significantly more likely to have a tumor thickness of >2 mm at the time of diagnosis compared to younger individuals; 13.2% of males and 10.2% of females <65 years old had a tumor thickness of 2 mm or more at the time of diagnosis, compared to 20.2% and 20.5% for males and females over the age of 65, respectively [56]. There have been

many proposed hypotheses to explain the increase in tumor thickness with age. One hypothesis stems from data suggesting that individuals over the age of 65 are less likely to perform skin self-exams, allowing for a longer time for the tumor to advance to a more invasive stage before detection [57]. Older individuals are also less likely to report symptoms associated with early melanoma such as itching, changes in color and evolution compared to their younger counterparts, and more likely to report signs of more advanced disease such as ulceration [58]. Others have suggested that the increased thickness of melanoma with age may be explained by deteriorating vision, increased development of seborrheic keratoses, which may mimic melanoma and be a source of confusion, and loss of a partner resulting in an inability to check spots that are in areas difficult to access, such as the upper back, a common site for melanoma in this subgroup [59]. The gradual deterioration of the immune system with aging, a phenomenon termed immunosenescence, is also thought to contribute to increased susceptibility and worse prognosis of melanoma seen in the aging population [60] as this is associated with age-related changes in immune cells in the skin, increased susceptibility to solid tumors [61] as well as age-associated subgroups of advanced melanoma patients responding poorly to immunotherapy [62].

2.7 Site of Melanoma and Associations with Sun Exposure

The anatomic site of cutaneous melanoma is of clinical importance as it is associated with particular pathologic characteristics and has been identified as an independent prognostic factor in melanoma [63–65]. Associations between the anatomic site of melanoma with sex, age, patterns of sun exposure and histologic type have been reported. Overall, areas with higher sun exposure tend to have a higher incidence of melanoma per unit area; the upper back has a higher incidence of melanoma than the lower back and buttock, the upper chest has a higher incidence of melanoma than the abdomen, and the lower legs have a higher incidence of melanoma than the thighs [66]. The predilection for particular sites to develop melanoma also varies by sex, reflecting different patterns of sun exposure. When looking at head and neck melanomas, for example, nearly 80% of cases in women occur over the central area of the face, namely the nose, cheeks, chin, and around the mouth. In men, however, most head and neck melanomas (57%) occur over the temple, scalp, forehead, ears, and neck. This difference in incidence reflects the sun-protective effect of hair and the difference in hair styling between men and women [67]. Clothing pattern differences between sexes have also been associated with the difference in the anatomic location of melanoma. Men tend to have a higher incidence of melanoma on the chest, abdomen, and back, while women tend to have a higher incidence of melanoma on the lower legs and dorsal feet [68].

Differences in the site of melanoma vary between age groups. Specifically, individuals over the age of 60 have a higher incidence of melanoma on the scalp, ears, and forehead and a lower incidence on the back and limbs, and nearly 80% of new melanoma cases diagnosed in patients over the age of 80 are found in the head and neck regardless of sex [66, 69]. This variation in the site of melanoma between age groups is thought to reflect different patterns of sun exposure; older individuals are more likely to develop melanoma in areas of chronic sun exposure, while younger individuals have a higher incidence of melanoma on areas of intermittent, intensive sun exposure. Anatomic distribution has also been associated with certain histopathologic types of melanoma; for example, lentigo maligna melanoma tends to occur in areas of chronic sun exposure, such as the face, head, and neck of older individuals. Nodular melanoma tends to be more common over the head and neck areas as well, while superficial spreading melanoma is more common on areas of intermittent sun exposure such as the trunk, limbs, and upper back [66, 70].

Of note, the prevalent anatomic sites for melanoma have been changing over time, according to

the Surveillance, Epidemiology, and End Results (SEER) program in the USA, as age-adjusted melanoma incidence on the arms and trunk has increased by 45 to 57 percent for each subsequent 5 year birth cohort among men born between 1890 and 1919. Age-adjusted melanoma incidence on other body sites (arm, leg, trunk, and head) only increased by 14% to 20%. For the most recent cohorts, the trunk has become the most common site for melanoma per square meter of body surface area [71].

2.8 Major Melanoma Histopathological Subtypes

There are four main histologic subtypes of invasive melanoma: superficial spreading melanoma (SSM), nodular melanoma, lentigo maligna melanoma (LMM) and acral lentiginous melanoma (ALM). SSM is the most common histopathologic subtype, accounting for about 70% of malignant melanomas. Such lesions typically arise in areas of intermittent sun exposure, such as the back for males and the legs for females [8]. About 30% of SSM arise from a preexisting nevus, while the majority arise de novo [72]. Clinically, SSM can have a variety of colors, including red, tan, brown, blue, gray, and black, and the surface can have palpable papules or nodules [73]. Nodular melanoma is defined as melanoma with a predominant vertical growth phase and accounts for 15–30% of melanoma diagnoses. Such lesions appear as spheroidal red, gray, or black nodules and are most commonly found on the lower limbs or head and neck [74, 75]. LMM accounts for about 11% of new melanoma cases and appears as an irregular, tan, freckle-like macule on sun-damaged skin, which occurs most commonly on the face of elderly patients [76, 77]. ALM accounts for 2–8% of melanoma cases in whites but represents the most common subtype of melanoma in African Americans, where it accounts for 60–72% of melanoma cases, and Asians, where it accounts for 29–46% of melanoma cases. Even though ALM represents a higher proportion of melanoma cases in darker individuals, it has a similar incidence in whites and other ethnicities [78]. Clinically, ALM appears as a black to brown irregularly pigmented macule or patch most commonly found on the palm, sole, or subungual locations [78]. The four major histological subtypes differ in terms of age distribution, with SSM tending to affect younger patients with a peak incidence at 54 years. The peak age for nodular melanoma is 59 years, for ALM it is 65 years, and the peak age for LMM is 69 years [79].

Other melanoma subtypes include amelanotic melanoma, which is mostly observed with nodular and desmoplastic melanomas. Amelanotic melanoma is used to describe melanomas lacking pigment clinically, either due to no eumelanin production (pure amelanotic) or hypomelanotic melanomas that produce low levels of eumelanin but may still appear to lack pigmentation clinically. These melanomas account for 2–8% of melanomas and represent a diagnostic challenge, especially if they are not of the nodular subtype [80]. Desmoplastic melanoma is another rare subtype that represents approximately 1% of all melanoma cases, appears as a plaque or nodule clinically and is often amelanotic. There is frequently a delay in the diagnosis of desmoplastic melanoma because it can mimic the appearance of other benign lesions such as a scar or be confused as a non-melanotic skin cancer [81].

2.9 Melanoma Mortality Trends Worldwide

According to GLOBOCAN 2018, it is estimated that the number of deaths from melanoma worldwide will total 60,712 [1]. Age-standardized mortality rates (per 100,000) are highest in Australia and New Zealand (3.4), followed by Northern Europe (2.0), Western, Central, and Eastern Europe (1.7), Southern Europe (1.5) and North America (1.4) [3]. Mortality from melanoma of the skin was found to be higher among Asian countries compared to the rest of the world. Global surveillance of trends in cancer survival from 2000–2014 showed age-standardized 5-year net melanoma survival rates ranged from 60–90% in most countries. 5-year survival exceeded 90%

in 11 countries, including the USA, Denmark, Sweden, the UK, Belgium, France, Germany, the Netherlands, Switzerland, Australia, and New Zealand. Survival was <60% in Ecuador, China, and Taiwan. Trends between 2000–2004 and 2010–2014 were stable in North America, Oceania, Japan, and several European countries, while survival increased by 5–10% in Korea and 12 other European countries [82].

Mortality rates for melanoma generally increased in the 1970s and 1980s and stabilized in the 1990s in most European countries, Australia, and the USA. A study of melanoma mortality rates in 22 different countries (18 in Europe, Canada, USA, Australia, and New Zealand) from 1955–1984, showed increased mortality rates in men from all countries evaluated and increased rates in females, in all countries except Australia and Portugal. From 1985–1995, mortality declined in many of these countries, particularly in middle-aged women in central and northern Europe and North America, and in men and women age 20–44 years in northern Europe [83, 84].

In Australia, melanoma mortality rates increased from 1931–1985, and more steeply from 1945–1959, followed by a plateau for both men and women. When looking at age cohorts, mortality rates increased in men born before 1930, were stable in those born between 1930–1950, and declined in those born after 1950, with similar trends in women. An Australian study analyzing median birth year (cohort) and year of death provided convincing evidence that the increase in mortality observed in the last century was drawing to a close with the effect being seen earlier in women. As referred to earlier in this chapter, during this period an increase in the incidence of melanoma had also been noted, particularly of thin melanomas. Thus some of the decreases in mortality were attributed to better and earlier detection of melanoma. However, another likely more significant cause was felt to be a "cohort effect." Points of inflection on the mortality rate charts corresponded to birth year rather than the year of death. This pattern is more compatible with a change of exposure to a cause of melanoma from one generation to the next [85]. A population-based study looking at reported death statistics in Australia and New Zealand, the two countries with the highest incidence of melanoma, demonstrated discrepant mortality trends in the two countries. The age-standardized mortality rates had both increased over the period 1968–2007 in both countries, though this was greater in New Zealand than Australia and more pronounced in New Zealand women. Despite the overall mortality increase, more recent years have demonstrated a downturn in mortality rates in young men and women in Australia, but to a lesser degree in New Zealand women <45 years. Both countries have similar certification and coding of melanoma, so a systematic difference between the two countries is less likely to occur and be a cause of the difference. It is therefore unclear if these results demonstrate a delayed response to screening and detection in New Zealand compared to Australia; if so, a downward trend is to be expected in New Zealand soon after Australia [86].

2.10 Melanoma Mortality Trends in the USA

An estimated 7,230 deaths were attributed to melanoma in the USA in 2019, of which males account for 4640 (65.6%) melanoma deaths, compared to 2490 (34.4%) deaths in females [15]. From 1973 to 1994, melanoma mortality rates in the USA increased by 38.9%, from 1.8 to 2.5 per 100,000. The statistics were worse for men vs. women and older vs. younger people with the greatest rise in mortality for men 50 years or older; mortality rates for women younger than 50 years of age were stable, and an increase in mortality was seen only in women 50 years or older. From 1990–1994, mortality rates stabilized or decreased overall, with age-specific increases seen in men 70 years or older and women 60–69 years of age [11]. Similar results were seen in another study based on data from the SEER program of the National Cancer Institute from 1969–1999. The greatest contributor to melanoma mortality rate increases from 1969–1999 were men aged 65 and older (7.5 to

19.3 per 100,000). This was calculated as a 157% rate increase and a greater than threefold increase compared to women of the same age. Mortality rates in men and women 20–44 years of age decreased during this same time period [87]. A study of mortality data from SEER between 1992 and 2006 showed a continuation of this trend. Death rates increased in older populations >65 years, but not in the younger groups. In addition, between 1998–1999 and 2004–2005 there was an increase in melanoma deaths secondary to thin lesions, contributing to 30% of all melanoma deaths. These mortality data for the older age group and the increase in death from both thin and thick melanomas was felt to be, at least in part, a reflection of increased UV exposure [12, 88]. In a similar fashion to young adults, the mortality rate from melanoma in the pediatric population decreased steadily between 1968 and 2004. There was a strong association of age in this population, with the mortality rate being 8–18 times higher in the 15–19 year-old age group vs. the youngest children. Sex and race comparisons showed 25% higher mortality in males vs. females, and twice the mortality rate in white vs. Black children. The overall age-adjusted mortality in the pediatric population was calculated to be 2.25 deaths per year per ten million at-risk individuals. The study authors pointed out that, despite the low mortality rate in children, the public health burden from a disease that is essentially preventable was significant [89].

With melanoma incidence on the rise, yet mortality appearing to stabilize, some have questioned whether there is a true melanoma epidemic and that perhaps the increase in melanoma incidence could be explained by increased detection of thinner melanomas due to better awareness and screening. Melanoma survival is complex and, most importantly, dictated by stage, though other influences also contribute to patients' survival. A study looking at SEER data from 1989–2009 found that the incidence of melanoma increased across all thickness groups, including in T3/T4 groups, that thickness increased in all age and sex categories, in whites and non-Hispanics and at all body sites. This suggests that the burden of melanoma is truly rising and the increased incidence cannot be simply attributed to an artifact of increased T1/T2 melanomas from increased detection. Melanoma-specific survival was shown to improve every 3 years in multivariate analysis across all subgroups barring non-black minority groups, acral lentiginous and nodular melanoma subtypes. While it is possible that this survival is related to early detection of thin but potentially fatal melanomas, an explanation felt more plausible was the increased detection of indolent vs. clinically relevant melanomas [44].

There is a significant effect of socioeconomic status on treatment and outcomes for low-income populations. The National Cancer Database (NCDB) which records 70% of all newly diagnosed cancers in the USA, was utilized in a study to investigate the effect of socioeconomic status on melanoma outcomes between the period 2004 to 2012. The results showed that lower socioeconomic status correlated with a statistically significant decrease in median survival in all stages of melanoma, together with greater mortality rates compared to the national average at every stage [90]. This corroborated earlier studies, including one which showed that patients aged 18–64 with Medicaid or those who were uninsured were more likely to die from melanoma than those with non-Medicaid insurance between 2007 and 2012 [91]. Another study showed that while overall mortality rates from melanoma declined in men and women from 1993–2007, this decrease in mortality was associated with higher education levels [92], while others found that melanoma patients living in lower income areas and areas with greater non-white populations, as well as residents who did not complete a high school education had a worse prognosis [93].

Although melanoma is most commonly seen in the white population, it also occurs in other racial groups. Melanoma in ethnic minorities is less commonly studied given the reduced incidence; it often presents in unusual locations in this group with a more atypical appearance, which can lead to diagnostic delay. With ethnic minority groups projected to grow over the next several decades, understanding the risks and

disease outcomes in this population is essential. A study using the SEER database studied a cohort of over 95,000 patients from 1992–2009 with melanoma and found profound disparities in survival among races. The survival in non-whites was significantly lower despite whites having a higher incidence of melanoma. White individuals had the longest survival time ($p < 0.05$) followed by Hispanic ($p < 0.05$), Asian American/Native American/Pacific Islander ($p < 0.05$) and then Blacks ($p < 0.05$). Minority races were also noted to present at a later stage compared to white individuals [94]. The disparity between the races has been attributed to a number of possible explanations. There is a common misconception among the general public that minority groups are not at risk of melanoma, which leads to suboptimal screening. The anatomical location of melanoma in minority groups tends to be in non-sun exposed sites, which makes them easily overlooked and likely to present late, with a delay in diagnosis. Socioeconomic status and health insurance are additional factors likely to play a role in disease outcome in these individuals with suboptimal screening and worse survival outcomes. These data highlight the need for improved screening and awareness in non-white populations to help improve melanoma survival, and mirror earlier studies showing improved survival rates in whites of 82% in 1975–77 to 94% from 2008–2014, vs. African Americans with a 57% relative 5-year survival rate in 1975–77, which increased to 79% from 1987–89 but subsequently declined to 66% from 2008–2014 [95].

2.11 Factors Contributing to the Stabilization of Melanoma Mortality Worldwide

The reasons for stabilization of melanoma mortality in the US and around the world are likely to be multifactorial and include improved primary and secondary prevention, educational outreach, and increased skin cancer screening among the highest risk group for melanoma, men >50 years old [35, 96–100].

Several studies have shown that melanoma screening may lead to the detection of thinner melanomas which is likely to affect mortality. A Lawrence Livermore National Laboratory study revealed that the incidence of melanomas thicker than 0.75 mm decreased during an educational and screening program, which also resulted in decreased melanoma-specific mortality [101]. A case-control study of patients who underwent a whole-body skin exam 3 years prior to diagnosis with invasive melanoma in Queensland, Australia, was associated with a 14% lower risk of being diagnosed with a thick melanoma (>0.75 mm). In this study, the risk of diagnosis decreased with increasing thickness of melanoma with a 40% risk reduction of being diagnosed with a ≥3 mm melanoma [45].

The quality of the skin exam also appears to contribute to the effect on mortality. Swetter and colleagues carried out a questionnaire-based study looking at self-skin exam vs. physician skin exam practices in the year before melanoma diagnosis. They found that melanoma screening by trained professionals was effective in identifying disease at earlier stages as tumors detected by a physician were significantly thinner than those detected by the patient or his/her spouse/partner (odds ratio [OR] 2.66; 95%CI 1.48–4.80). Those who received skin exams by a physician were more likely to have thinner melanomas than those who did not, and this was largely due to the significant effect a physician exam had on men >60 years old (OR 4.09; 95%CI, 1.88–8.89) This subgroup is also the one with the highest mortality, suggesting a regular physician skin exam may be the best approach to successfully detect melanoma early in this population [102].

There is important prospective data from a German screening study suggesting that melanoma screening may have a positive effect on mortality following implementation of the SCREEN project in the German state of Schleswig-Holstein in 2003. During this project, patients with health insurance who were ≥20 years were eligible for a standardized full-body skin exam during a 12-month period. Five years after it was implemented, a decrease in melanoma mortality was seen in women

(0.66/100,000, expected 1.30/100,000) and men (0.79/100,000, expected 2.0/100,000). During this time, melanoma incidence increased by 34% [103]. Additionally, a study found melanoma mortality declined significantly by 47% in men and 49% in women in Schleswig-Holstein from 2008–2009, while melanoma mortality remained stable in the surrounding German territories where the screening program was not taking place. The authors concluded that though this was not absolute proof, the data provided strong evidence that the reduction in melanoma mortality in Schleswig-Holstein was linked to the skin cancer screening program [104]. Further analysis of mortality trends in Schleswig-Holstein and Germany showed that the original decline in melanoma mortality rates during the SCREEN project reverted to pre-screening rates after the study period; moreover, the mortality rate in Schleswig-Holstein resembled the rest of Germany. This cast doubts on the initial benefit in mortality from skin screening exams; however, a more plausible explanation for the post SCREEN data reversion is likely due to changes in the screening methods following the pilot study, since it was found that the screening methods were less thorough after the study compared to those used during the pilot study. This may better explain the reversion to higher mortality in Schleswig-Holstein, and an absence of reduced melanoma mortality in Germany overall, in the period 2008 to 2013 [105, 106].

There is mixed data on national primary prevention strategies. In 2018, a systematic review in the USA was conducted to inform the US Preventive Services Task Force on behavioral counseling for skin cancer prevention so they could update their recommendations to the public. The study concluded that while behavior interventions can increase sun-protective behaviors, there is minimal evidence to support that such interventions reduce sunburns or have an impact on skin cancer outcomes. Behavioral intervention was found to increase self-skin exams in adults but was also associated with a number of potential drawbacks, including the development of vitamin D deficiency, reduced physical activity, a sense of false reassurance leading to paradoxical overexposure to UV radiation and anxiety from excess concern for skin cancer. Intervention had a positive effect on compliance with self-skin exams, but data suggests this leads to overtreatment with increased skin interventions without detecting atypical nevi, precancerous lesions or skin cancer [107]. Conversely, data from Australia suggests that primary prevention strategies may help to prevent the development of melanoma. In the 10-year follow-up of a randomized trial in Queensland, investigators found that daily sunscreen use was associated with a decreased risk of melanoma vs. sunscreen use which was applied on a discretionary basis. Notably there was a sizeable reduction in invasive melanomas ($n = 3$ in active vs. 11 in control group; HR, 0.27; 95% CI, 0.08–0.97) compared to preinvasive melanomas (HR, 0.73; 95% CI, 0.29–1.81) [108]. The results of this randomized trial were corroborated by a recent population-based case-control study in Australia, showing that both self-reported childhood sunscreen use and lifetime sunscreen use were protective against melanoma in young adults <40 years of age. Characteristics associated with less regular use of sunscreen included male sex, lower levels of education, perception of a reduced risk of skin cancer such as dark-skinned individuals and those with resistance to sunburn [109]. The authors suggested that education on best practices with sunscreen (i.e., frequency, reapplication, broad spectrum) needed to be emphasized in all population subgroups.

Finally, melanoma treatment itself may, for the first time, be having a positive and significant effect on mortality. Advances made early this century in melanoma therapy have been unparalleled. Prior to 2011, the standard of care for advanced melanoma was chemotherapy and IL-2, with limited impact on overall survival. Since 2011 there has been an explosion in approved therapies for advanced melanoma. Notably, for all the approved therapies, the primary endpoint from the phase III trials was met. Both targeted therapy and immunotherapy drugs showed significantly improved overall survival compared to standard therapy for the first time in decades. This has led to a paradigm shift in the management

of advanced melanoma from one that was universally palliative to one that can produce a durable clinical response in a significant minority of individuals and effective disease control and palliation in the remaining majority of patients [110]. The future prospect of melanoma drug development and currently ongoing clinical trials look promising and is expected to improve management and outcome in these individuals further. While the widespread use of new and effective therapies may impact melanoma mortality in advanced stage disease, such interventions alone cannot fully explain the leveling off in mortality in the USA and many other countries around the world over the past few decades. It is expected that the use of novel targeted and immunotherapies, in combination with early detection strategies, will continue to lead to improvements in melanoma mortality rates worldwide.

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Pathogenesis of Melanoma

3

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3.1 Introduction and Overview of Melanoma Pathogenesis

Cutaneous melanoma is a malignant neoplasm arising from neural crest-derived melanocytes, which are normally located within the stratum basale of the epidermis [1]. Physiologically, melanocytes are responsible for the production of the pigment melanin, which gives the skin color, and plays an important protective role, shielding epidermal keratinocytes from DNA damage induced by carcinogenic ultraviolet (UV) radiation [2, 3]. Melanocytes commonly form harmless nested lesions within the skin, known as benign melanocytic nevi. These lesions can, however, progress to malignancy, with 30% of melanomas arising from existing nevi [4]. The pathogenesis of melanoma is complex and multifactorial, involving an interplay between inherited susceptibility, environmental risk factors, and genetic and epigenetic changes.

Inherited susceptibility to melanoma includes rare germline mutations that lead to familial melanoma syndromes, the most prevalent of which are mutations in the cyclin-dependent kinase inhibitor 2A (CDKN2A) cell cycle regulatory gene [5] and common variants in genes that modulate melanoma risk; most notably, the melanocortin-1 receptor (MC1R) which is involved in pigment production [5–7]. Environmental risk factors implicated in melanomagenesis are varied [8, 9]; however, the most significant environmental risk factor is exposure to UV radiation [9]. UV light is well known to promote genetic alterations in the skin, affecting both keratinocytes and melanocytes and is a significant carcinogen and risk factor for both melanoma and non-melanoma skin cancers [10]. The effects of UV radiation on the skin include direct DNA mutations, the production of DNA-damaging reactive oxygen species and free radicals, induced expression of hormonal growth factors, and stimulation of localized cutaneous immunosuppression [7, 10, 11]. In addition to exposures, which are influenced by geographical, occupational, behavioral, and lifestyle factors, there is clear evidence of gene-environment interactions in melanoma as risk is further modulated by ethnicity, phenotype, and genetic polymorphisms.

During the development of melanoma, somatic mutations arise in melanocytes which enable neoplastic growth through the overactivity of oncogenic signaling pathways, and loss of tumor suppressor, cell cycle regulation, and apoptotic pathways, which ordinarily control growth. As melanoma progresses, dysplastic melanocytes acquire gain-of-function mutations, which facilitate tumor invasion and metastasis to distant sites [7, 12, 13]. The mutational burden of melanoma, in addition to the key genetic drivers,

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is dependent upon the subtype of melanoma, the anatomical location, and the history of chronic versus intermittent sun exposure [1].

3.1.1 Histopathological and Biological Model of Melanoma Initiation and Progression

The histopathological progression of melanoma was first described by Clark et al. in 1984. Eponymously named the Clark Model, it charts the stepwise progression of melanocytes from benign nevi to the development of metastatic melanoma (Fig. 3.1) [14]. While this model is useful as a theoretical outline, its use for prognostication in modern clinical practice has been replaced by more precise measures, such as the Breslow depth [15]. The first event in the Clark Model is the proliferation of functionally normal melanocytes in a nested formation at the stratum basale, forming a benign nevus with a flat or mildly raised appearance, with uniform color and pigment [7]. The proliferation of melanocytes within the nevus is triggered by somatic mutations within key oncogenic pathways. The most well-described mutations are within the mitogen-activated protein kinase (MAPK) pathway, which triggers constitutive expression of transcription factors responsible for regulating various cellular functions, including cell survival, growth, and differentiation [16]. Well-described somatic mutations, including in codon 600 of the serine/threonine protein kinase BRAF, which is present in 60–80% of benign nevi [17], lead to constitutive hyperactivation of this oncogenic pathway [3]. Although nevic melanocytes with constitutive MAPK activation are under constant growth stimulation, the melanocytes within such benign nevi rarely progress to malignancy, likely as a consequence of oncogene-induced cell senescence [18].

The second step of the Clark Model is the formation of the dysplastic nevus, which is characterized by aberrant growth and cellular atypia. Dysplastic nevi can arise from pre-existing benign nevi, or de novo. Clinically, the dysplastic nevus appears asymmetric, with an irregular border, increasing diameter, and variation of color. On dermoscopic examination, the appearance can be heterogeneous, but common features include an irregular pigment network, scalloped borders, areas of depigmentation, white veils, and brown globules [19]. Histologically, the melanocytes within such lesions show discontinuous and disorganized atypia [7]. At the molecular level, aberrant growth is mediated by somatic or germline loss of key tumor suppressor genes, including the cell cycle regulator CDKN2A [13, 20], and key proteins involved in apoptosis, such as phosphatase and tensin homolog (PTEN), amongst others [3, 7, 16, 20–22]. Dysplastic nevi are generally termed pre-malignant, and epidemiological studies have estimated that 20% of melanomas arise from dysplastic nevi [23].

The third stage of the Clark Model is the radial growth phase, where the previously described oncogenic pathways paired with the loss of critical growth regulatory mechanisms lead to the expanded growth of the cells within the epidermis. The radial growth phase is marked by malignant cells with decreased differentiation, hyperplasia, and clonal proliferation. The cellular atypia of the melanocytes is continuous and can penetrate the dermis to some degree, but without the formation of malignant dermal colonies. Clinically, the lesion may present as raised [7].

Following the radial growth phase of the Clark Model, malignant cells enter the vertical growth phase, acquiring the ability to penetrate the basement membrane leading to dermal invasion. The tumor cells form an expansile nodule that primarily demonstrates downward migration [7]. Molecularly, this stage is associated with the acquisition of key tumor functions needed for tissue invasion and continued cell growth. The functional gains include changes in cell-cell adhesion and the expression of communication proteins such as cadherins, which normally act to prevent cellular overgrowth [3, 7]. There is also increased expression of integrins and production of matrix metalloproteinases (MMPs) which are needed to degrade collagen in the basement

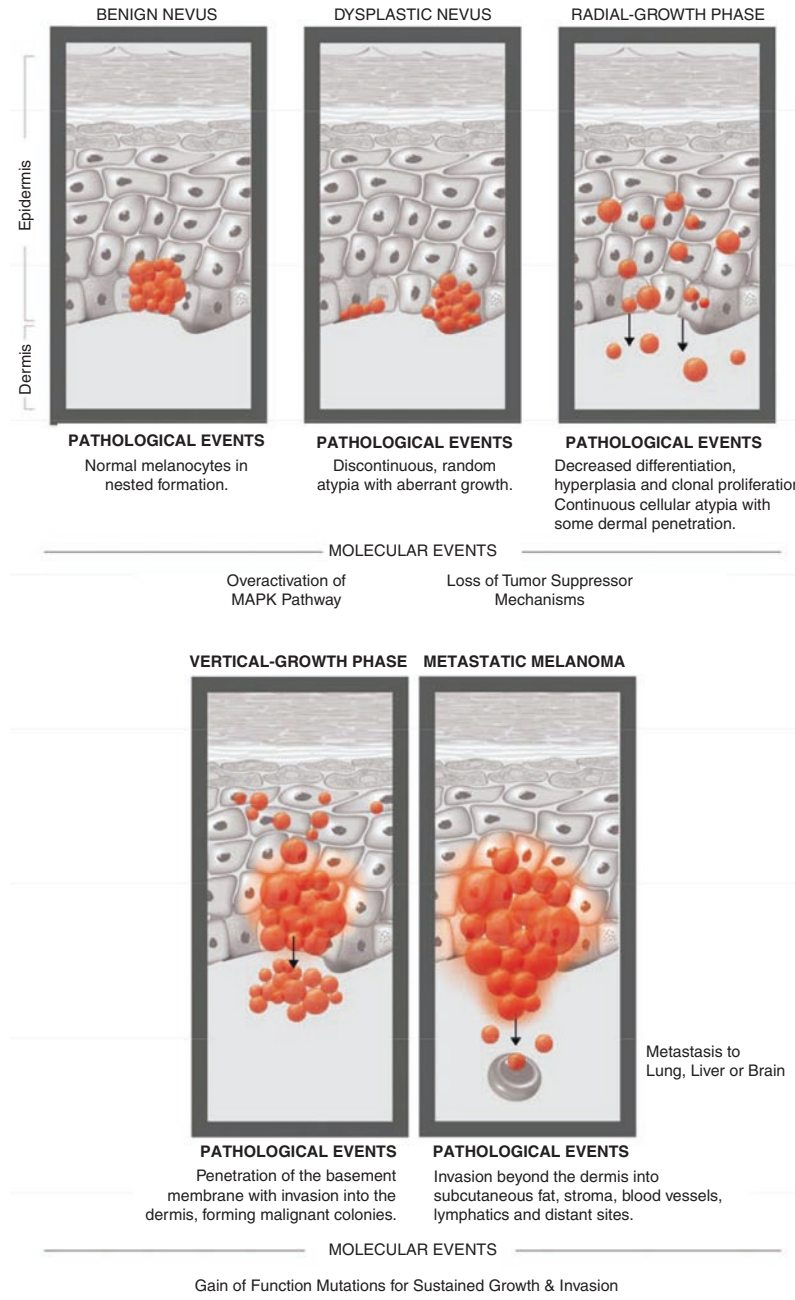

Fig. 3.1 The Clark Model of histopathological progression of melanoma from benign nevus to metastatic malignancy, with associated pathological and molecular changes

membrane and allow invasion [1, 7, 24]. Angiogenic growth factors are produced to facilitate growth as the highly metabolically active cells expand [24], and the melanocytes lose their normal physiological functions [7]. The depth of vertical growth, known as the Breslow thickness, can be used clinically for risk stratification and prognostication [15].

The final phase of the Clark Model is metastatic spread, where malignant cells leave the dermis and enter the subcutaneous fat, stroma, blood vessels, and lymphatics, eventually culminating in the growth of tumor(s) at distant sites [7]. The metastatic phase of melanoma represents the end stage of development and has a five-year survival rate of 25–32% [25, 26].

3.2 Risk Factors for Melanoma Development and their Proposed Pathophysiological Mechanisms

Through epidemiological research, a number of modifiable and non-modifiable risk factors have been implicated in the development of melanoma, alongside many proposed risk factors [8, 9]. Many of these risk factors involve lifestyle and behavioral influences which contribute to melanomagenesis through modulation of exposure to UV radiation [10]. Other risk factors include demographic factors such as age, gender, and ethnicity, in addition to phenotypic traits and personal and family history of melanoma [9].

3.2.1 Age, Gender, and Socioeconomic Status

The incidence of melanoma is known to increase with age [27, 28]. This is confirmed by national data from the Surveillance, Epidemiology, and End Results (SEER) database in the United States from the period 2012 to 2016, which demonstrates an increasing incidence of melanoma with age, with a peak in the 80–84 year-old age group, where the incidence of melanoma was 106.6 per 100,000 individuals. While the incidence of melanoma is highest in the elderly, unlike most solid organ malignancies, there is still a significant disease burden in young and middle-aged people, with an incidence of 13.1 per 100,000 between the ages of 25–49 [29]. U.S. data from 2006 to 2015 suggests that the overall incidence of melanoma continues to increase over time, with the incidence rate per million person-years rising from 200.1 in 2006 to 229.1 in 2015. Interestingly, when stratified by age, the majority of this increase is seen in adults over the age of 40, with incidence rates decreasing for adolescents and young adults, stable in the middle-aged, and significantly increasing in older adults. For those over 40, the annual percentage change (APC) was 1.8% for men (95% CI 1.4%–2.1%) and the same for women (95% CI 1.4%–2.2%). This included a greater incidence of both localized (APC 1.9%; 95% CI 1.4%–2.4%) and distant metastatic disease (APC 4.8%; 95% CI 3.9%–5.8%). For young adults aged 20–29, the APC was −3.7% for men (95% CI −2.5% to −4.8%) and −3.6% for women (95% CI −2.8% to −4.5%) [30]. It has been hypothesized that the decreasing incidence of melanoma in the young adult age group may be due to changes in sun-protection behaviors and public health initiatives, such as restrictions on indoor tanning and increased awareness of the association between UV exposure and skin cancer. However, the national registry data does not include information on other cofounding risk variables; therefore, this hypothesis has not been proven [8].

Incidence rates of melanoma within the United States also vary by gender, and this relationship is modulated by age. National data from 2015 has demonstrated that below the age of 50, the melanoma incidence rate is greater in women compared to men, but over the age of 50, men are more likely to develop melanoma. In the 20–29 age group, melanoma incidence in women is more than twice that of men, while the opposite is true in the 70–79 age group. Changes in incidence rates from 2006 to 2015 by age group, however, reflect similar trends in both males and females [30]. The reasons for the differences in gender incidence rates are unclear but may be accounted for, in part, by differences in lifestyle factors, alongside intrinsic gender-specific biological differences. The use of indoor tanning beds, for instance, is known to be more prevalent amongst young women compared to their male peers [31]. Occupational factors, such as greater outdoor working among men leading to higher chronic sun exposure, may also play a role in the greater incidence of melanoma in older men.

Socioeconomic status has been reported to correlate with melanoma outcomes in epidemiological studies in the United States, likely due to inequities in healthcare. Individuals with lower socioeconomic status, including those without private health insurance, a high school diploma, or who live in an area with a lower-than-average

income, are more likely to have advanced disease at diagnosis, including metastatic spread, in addition to higher mortality rates [32, 33].

3.2.2 Race and Ethnicity

Race and ethnicity are important factors that affect melanoma risk, in part due to the protective role of skin pigmentation. Epidemiological data from the SEER database between 1992 to 2011 in the United States shows that, for all subtypes of melanoma other than acral lentiginous melanoma, age-adjusted and gender-stratified incidence rates are highest in non-Hispanic whites (NHW), followed by Hispanic whites (HW), while they are lowest in Blacks. In the case of the most common melanoma subtype, superficial spreading melanoma, the incidence rate in NHWs per 100,000 person-years was reported as 9.05, compared to 1.12 in HWs, 0.31 in Asian/Pacific Islanders (API) and 0.15 in Blacks. For acral lentiginous melanoma, the subtype least associated with UV exposure, HWs have the highest incidence rate (0.24), followed by NHWs (0.21) and Blacks (0.19), while the lowest rate was reported in APIs (0.17) [34]. Cause-specific mortality for melanoma has also been analyzed from SEER data. After controlling for anatomical location, stage at diagnosis, age, and gender, Black patients were found to have a 30% reduced hazard of melanoma death compared to NHWs (HR 0.7; 95% CI 0.6–0.8); however, when analyzed by all-cause mortality, after adjustment for covariates, the protective effect of Black ethnicity was lost, with no significant differences in hazard ratios found [35]. Previous studies of melanoma in the United States have also shown that non-Caucasian patients presented with more advanced stage melanoma than Caucasian patients and had worse overall outcomes [36]. These disparities may be partly associated with race-related socioeconomic inequities.

The differences in melanoma incidence between ethnicities are largely explained by the role of melanin in protection from the damaging effects of UV radiation. The production of melanin in response to UV exposure is an important physiological defense mechanism. UV radiation stimulates the production of α-MSH, which signals to melanocytes via MC1R. Activation of this receptor leads to an intracellular signaling cascade involving cAMP, upregulating key enzymes needed for the synthesis of melanin and its transfer to adjacent keratinocytes via the dendritic processes of the melanocytes. Melanin is able to absorb and dissipate the radiation, as well as acting as a cutaneous thermoregulator, antioxidant and chelator [3, 7, 17]. There are key differences in the chemical structure and quantity of melanin between ethnicities, alongside phenotype-associated polymorphisms of MC1R that reduce its signaling capabilities. Melanin is the key pigment responsible for darker skin tones. In these patients, a greater ratio of dark brown eumelanin to red-yellow pheomelanin can be found, in addition to a greater overall quantity of melanin [3]. The role of ethnicity in modulating the risk of melanoma from UV has been demonstrated by epidemiological evidence. In NHWs, lower geographical latitude and increased UV index are associated strongly with greater melanoma incidence, while the same relationship has not been demonstrated in people of other ethnicities [37].

3.2.3 UV Radiation: Mechanisms of DNA Damage and Associated Lifestyle Factors

As previously mentioned, exposure to UV radiation is the most well-studied risk factor for the development of melanoma, and the epidemiological evidence for the association is significant [8]. The UV spectrum is comprised of two major bands which reach the earth's surface; UVA, which has low-energy wavelengths between 315 and 400 nm and is able to penetrate cloud cover, and UVB, which is higher-energy with wavelengths between 280 and 315 nm, and has less penetrance. A third UV band, UVC, does not reach the earth's surface. UVB is primarily absorbed by the keratinocytes of the stratum corneum, whereas UVA is able to penetrate into the dermis and stroma [11]. UVA and UVB have dis-

tinct mutagenic properties contributing to melanomagenesis as a result of their differential penetrance and absorption [10, 11].

UVB is associated with direct, rapid, melanin-independent DNA damage leading to the formation of cyclobutene pyrimidine dimers (CPDs) and pyrimidine 6-4 pyrimidine photoproducts (6-4 PPs) [8, 10]. 6-4 PPs are formed when UVB interacts with the carbonyl group and the carbon bond of adjacent pyrimidines, while CPDs form when an additional single or double covalent bond is induced between pyrimidine bases, leading to greater DNA disruption. 6-4 PPs are efficiently removed and the DNA repaired by excision endonucleases, meaning that these lesions are less mutagenic than CPDs, which are more likely to leave lasting mutations [11, 38].

UVA has traditionally been considered less mutagenic than UVB [10]; however, it has been proposed that UVA contributes indirectly to DNA damage through the generation of reactive oxygen species (ROS) [8]. UVA-generated ROS can damage DNA through the creation of single- and double-strand breaks, oxidation of purines and pyrimidines, and inactivation of DNA repair proteins [2]. UVA has also been implicated in the formation of CPDs, but through a melanin-dependent pathway that has been termed the "dark CPD" process. Interestingly, this pathway allows for the formation of DNA mutations several hours after sunlight exposure and is more common in melanocytes containing pheomelanin. This suggests that the lighter pigment of pheomelanin compared to darker eumelanin is more prone to photoexcitation and dark CPDs, while also being a poor UV shield that increases susceptibility to direct CPDs [2, 8].

The dark CPD process (outlined in Fig. 3.2) leads to the generation of nitric oxide and super oxide free radicals through UVA-induced upregulation of the enzyme NADPH oxidase and nitric oxide synthase, in addition to increased melanin synthesis through the previously outlined physiological tanning response. These free radicals generate the oxidant peroxynitrite, which is capable of depolymerizing melanin to its monomer form that is able to enter the melanocyte's nucleus. Peroxynitrite further induces melanin

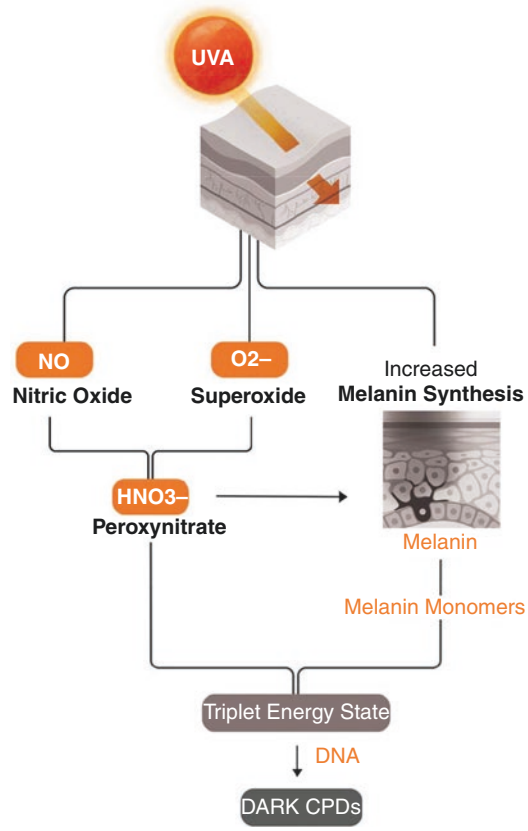

Fig. 3.2 Formation of dark CPDs by UVA radiation: UVA leads to the formation of CPDs, through a melanin-dependent pathway that allows for the formation of DNA mutations several hours after sunlight exposure and is more common in melanocytes containing pheomelanin. Pheomelanin is more prone to photoexcitation and dark CPDs than eumelanin, while also being a poor UV shield

monomers into a triplet energy state through electron excitation, forming high energy, labile dioxetane that is able to transfer energy to DNA bases in a radiation-independent manner triggering dimerization, and thus CPD formation [2, 39]. In addition to CPD formation, the ROS induced by UVA radiation also damage other key cellular components, including DNA repair. It has been found that CPDs generated by UVA are more mutagenic and cytotoxic than those induced by UVB, while also requiring greater time for repair. It has been postulated that the increased DNA damage potency of UVA-associated CPDs is a result of UVA-mediated oxidative damage to nucleotide excision repair

genes, eliminating the melanocyte's ability to correct dimerization [2].

Host immunity is important for cancer prevention, and UV radiation has been implicated in suppressing immune function through damage to DNA and lipids within the skin [2]. UV radiation has also been shown to alter the immune cell populations within the skin, alongside changes to cytokine production which include increased release of interferon-gamma, which has been shown to promote tumorigenesis in mice through the induced expression of genes associated with tumor evasion [40]. Some authors have therefore speculated that the interplay of UV radiation and the immune system may play a significant role in melanomagenesis, particularly in chronically UV-exposed skin [11]. Paracrine hormonal signaling pathways have additionally been implicated in modulating the response of melanocytes to UV-induced DNA damage. These pathways, including melanocortin/MC1R, endothelin/ETBR, insulin-like growth factor-1/IGF-1R, and circadian clock systems, are thought to be involved in the regulation of melanoma development, with dysfunction contributing to carcinogenesis [2, 41].

The role of UV exposure in melanoma pathogenesis is modulated by important lifestyle and behavioral factors. One of the important associations reported in the literature is the effect of the pattern of sun exposure on the risk of melanoma in comparison to non-melanocytic cancers. Melanoma is most strongly associated with intermittent, intense UV exposure and sunburn, particularly on regions of the body that are intermittently exposed to the sun, such as the skin of the back or the lower extremities [42–45]. For melanomas on chronically sun-exposed sites, for example the head and neck, a distinct subgroup of melanomas called lentigo maligna melanoma arise which are associated with advancing age, higher mutational burden, and a distinct pattern of UV-induced signature DNA mutations [11]. Non-melanocytic skin cancers are additionally more associated with chronic, suberythemogenic sun exposure, particularly on the face, dorsum of the hands, and the forearms [8]. The association of sunburn with melanocytic and non-melanocytic skin cancers was investigated using data from two large prospective cohort studies of healthcare professionals in the United States. After adjustment for confounding variables, a hazard ratio for melanoma of 2.41 (95% CI 1.32–4.41) was reported in males with a baseline history of severe sunburn. Non-melanocytic skin cancers had less association with severe sunburn; for SCC, the hazard ratio was 1.48 (95% CI 1.08–2.03), and for BCC it was 1.18 (95% CI 1.06–1.32). Interestingly, the difference in risk between melanocytic and non-melanocytic cancers was less pronounced in females. Sunburn on the trunk in men was also more associated with the risk of melanoma when compared to other body sites [42].

One hypothesis that has been proposed to explain the differential relationship between intermittent, intense UV exposure versus chronic exposure and melanoma risk is that keratinocytes are more prone to apoptosis following severe, UV-induced DNA damage. Melanocytes are likely to be more resistant to intense UV radiation, given the protective role of melanin, present in larger quantities than within keratinocytes. The consequence of this protection is that melanocytes are resistant to the physiological protective cellular mechanisms of programmed cell death following irreversible DNA damage, suggesting that melanocytes are able to survive with potentially deleterious oncogenic mutations [8].

Childhood exposure to UV is another significant risk factor for the development of melanoma [44]. Large prospective cohort studies in the United States have reported a relative risk of 1.80 (95% CI 1.42–2.28) for melanoma in individuals with at least five blistering sunburns before the age of 20 [46]. Furthermore, migration during childhood from northern countries to equatorial regions is also associated with a greater risk of melanoma [47].

Certain high-risk sun exposure activities carry an associated increased risk of melanoma. Indoor tanning, via the use of UVA-emitting tanning beds, has been the focus of public health initiatives worldwide. A 2014 meta-analysis of 31

observational studies reported that the odds ratio for melanoma in people who had ever used a tanning bed, versus those who had never, was 1.16 (95% CI 1.05—1.28), representing a 16% increased risk (subject to the rare disease assumption where the odds ratio approximates the relative risk). Significantly higher risk was reported in people with more frequent tanning bed use; for more than 10 tanning sessions, the odds ratio was 1.34 (95% CI 1.05—1.71) [48]. A large prospective cohort study of Norwegian women validated these findings, with an adjusted relative risk of 1.32 (95% CI 1.08—1.63) for the heaviest users of tanning beds compared to those who never used them [49]. It must be noted, however, that some of the increased risks in this population may be accounted for by other confounding negative sun health behaviors. In a cross-sectional study of 7200 French adults, tanning bed users were more likely to engage in sunbathing and other activities involving sun exposure. Within the tanning bed group, knowledge of the risks of skin cancer and photoaging alone was not sufficient to motivate change in behavior [50]. While tanning bed use in the United States remains common among adolescents and young adults, there is evidence to suggest that use is declining, possibly driven by public health measures including education and age restrictions [51].

Geographical location is another important consideration for melanoma risk. The incidence of melanoma, with adjustment for skin phototype, is highest in equatorial regions where UV exposure is greatest, and decreases proportionally with distance from the equator [52]. The incidence of melanoma is highest in Queensland, Australia, where melanoma is the most common cancer and cause of cancer mortality in young adults [9]. Occupational UV exposure can also increase melanoma risk. This is the case particularly in those occupations involving outdoor work, such as construction, in addition to welders exposed to radiation from their torches [9]. Medical UV exposure, for instance in patients receiving psoralen-UVA (PUVA) therapy for skin dermatoses such as psoriasis, has also been linked to a greater risk of melanocytic and non-melanocytic skin cancers [8, 9].

3.2.4 Phenotypic Traits

As previously noted, phenotypic traits related to skin pigmentation are important in determining melanoma risk. Darker skin tones decrease melanoma risk by modulating the effect of UV exposure, due to the protective role of melanin as a shield against DNA damage. Individuals with lighter skin tones, blonde or red hair, propensity for freckling, and inability to tan belong to a well-described phenotype that has significantly higher melanoma incidence [8]. This phenotype is associated with common germline polymorphisms, including mutations in the MC1R gene, which reduce the ability of the receptor to induce melanin production in response to UV radiation [53]. Phenotypic traits, including lighter skin phototype, high-density freckling, fair skin color, blue eye color, and red hair color have all been found to carry a two to four-fold increased risk of melanoma in a meta-analysis of 60 observational studies [54].

The presence of both benign and atypical nevi, including atypical nevus syndromes, is also known to be associated with increased risk for melanoma. While approximately 30% of melanomas arise from preexisting nevi [4], the presence of increased numbers of benign nevi alone is a strong risk factor for melanoma. In individuals with 11–25 nevi, the risk is 1.5 times higher than in individuals with fewer than 10. For every increase in 25 nevi, the risk likely doubles in a dose-dependent fashion. The presence of more than 100 nevi was found in a meta-analysis to have a relative risk of 6.89 (95% CI 4.63–10.25) compared to people with fewer than 15. Larger nevi are also associated with significantly increased risk [27, 54]. It has been proposed that the anatomical location of melanoma in patients with multiple nevi is important, determined under a hypothesis termed the “divergent pathway” model. Whereas melanomas arising on the head and neck are generally associated with chronic sun exposure, advancing age and other features of chronic UV-induced skin damage, the melanomas in patients with multiple nevi have a tendency to arise on the trunk. These patients do not require the same cumulative UV exposure to

develop malignancy versus patients with fewer nevi; instead, it is hypothesized that following an initial dose of UV radiation, the melanocytes of nevi-prone individuals undergo proliferation and malignant transformation without further UV exposure required [54]. Epidemiological data support this model, as patients with multiple nevi have a greater risk for melanoma of the trunk or lower extremities than the head and neck [55].

In addition to benign nevi, people with congenital or atypical nevi are also at increased melanoma risk. Congenital melanocytic nevi are nevi present at birth or within the initial months of life. Large congenital nevi, generally classified as those greater than 20 cm in diameter by adulthood, occur in at least 1 in 20,000 births and carry a lifetime risk of melanoma of up to 5% [56]. Atypical, or dysplastic nevi, are those which contain cytological atypia, and as previously discussed, are the second stage of the Clark Model of melanoma pathogenesis. The role of dysplastic nevi as melanoma precursors has been disputed; it is generally agreed that about 20% of melanomas arise from existing dysplastic nevi, hence the majority of melanomas arise de novo [23]. The presence of a dysplastic nevus, however, is a marker of increased risk for both melanomas and for the development of multiple primary melanomas [27]. The presence of a single dysplastic nevus has an associated relative risk of melanoma of 1.5 (95% CI 1.3—1.6), while the presence of five dysplastic nevi is associated with a relative melanoma risk of 6.36 (95% CI 3.80—10.33) [57]. Finally, a syndrome known as familial atypical multiple mole and melanoma (FAMMM) has also been recognized, where 50% of patients develop melanoma by middle age [27].

3.2.5 Personal History of Melanoma and Non-melanoma Skin Cancers

A personal history of a previous melanoma is an identified risk factor for the subsequent development of an additional melanoma. The risk is greatest during the first 12 months from diagnosis, and at 5 years, the risk of a second melanoma has been estimated to be between 2 and 11% [7–9] and is influenced by a number of other factors. Patients with a history of dysplastic nevi or multiple benign nevi, younger age at diagnosis, head or neck location of the first tumor, NHW ethnicity, female gender, or strong family history, are all at increased risk of a second melanoma. The risk is also greater with certain melanoma subtypes for the initial tumor, notably lentigo maligna or nodular melanoma [8].

3.2.6 Family History of Melanoma

Family history is an important consideration in melanoma patients, with approximately 8–12% of melanomas being familial. A number of inherited germline mutations have been discovered in familial melanomas, including a number of melanoma-predominant genetic syndromes. Melanoma may also be a feature of other inherited cancer syndromes that are not melanoma-predominant (discussed further in the genetics of melanoma, below) [5]. Considerable heterogeneity in risk for melanoma exists in patients with a family history of melanoma. This risk is modulated by environmental factors, and as previously discussed, multifactorial inheritance of genes related to ethnicity and phenotype is an important component of risk [5]. A large study of mono and dizygotic twins in Scandinavia reported high levels of melanoma concordance, particularly in monozygotic twins. They estimated that the proportion of melanoma risk that can be attributed to genetic variation is 58% (95% CI 43–73%) [58].

3.2.7 Immunosuppression

Chronic immunosuppression is a well-known risk factor for the development of both melanocytic and non-melanocytic skin cancers. This increased risk is in part due to the important role of the immune system in tumor suppression. A two to fourfold increased risk of melanoma has been reported in solid organ transplant recipients, while increased risk has also been found in association with immunosuppressant medications

including sirolimus, cyclosporine, azathioprine, and tumor necrosis factor (TNF) inhibitors [8, 9]. An association with HIV is less clear, as these patients have a greater risk for non-melanocytic cancers, but the same has not been demonstrated for melanoma [9]. The immune system has also been used as a target for melanoma therapies, which we will discuss further at the end of this chapter.

3.2.8 Other Proposed Risk Factors

A diverse range of other potential risk factors for melanoma have been proposed in the literature, but the data for these factors is inconsistent. Occupational exposure to industrial chemicals, including heavy metals, benzene, polyvinylchloride, selenium, pesticides, and polycyclic aromatic hydrocarbons have been associated with a small increase in melanoma incidence, but UV exposure remains the most significant occupational risk factor [8, 27, 59, 60].

A number of studies have explored dietary factors for possible melanoma risk involvement [27]. Certain dietary factors, such as moderate or heavy consumption of alcohol or daily consumption of citrus fruits or juice, have been associated with modest increases in risk. It has been suggested that the latter is due to psoralens contained within the fruit, which act as photosensitizers. Other dietary factors may be protective against melanoma, including consumption of antioxidants, including vitamins C and E, vitamin D, retinoids, and caffeine [8]. A meta-analysis of eight case-control studies and two prospective studies evaluated dietary retinoids, including retinol, beta-carotene, and total vitamin A consumption. Retinol was found to be the most protective against melanoma, with the least heterogeneity between studies, with a summary odds ratio of 0.80 (95% CI 0.69—0.92) [61]. A linear dose-dependent protective effect of caffeinated coffee has been reported in a meta-analysis, while non-caffeinated coffee was not found to have the same benefit. A number of biological mechanisms demonstrated in animal models may explain this protective effect, including that caffeine inhibits UVB-induced CPD formation, enhances apoptosis through upregulation of tumor suppressor proteins, and may also inhibit oncogenic pathways in melanoma such as UV-mediated nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) activation [62]. The relationship between smoking and melanoma risk has also been examined, but the evidence is inconsistent [8, 27].

Hormonal factors may affect melanoma risk, as estrogen and progesterone are believed to stimulate melanocyte growth and proliferation. Age at menarche, menopausal status, number of pregnancies carried to term, breast cancer and endometriosis may all have some association with increased risk [8, 27]. The use of oral contraceptives and hormone replacement therapy are more controversial; while some individual studies have reported an increased risk, a meta-analysis of 36 observational studies did not support any increased risk with exogenous female hormone use [63].

Comorbidities, including Parkinson's disease and prostate cancer, in addition to medications including sildenafil, voriconazole, and BRAF inhibitors have additionally been proposed as potential risk factors for melanoma [8], while non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, have been suggested to be chemoprotective agents against melanoma. This hypothesis is based on the known anti-carcinogenic properties of NSAIDs in vitro, both through cyclooxygenase (COX) dependent and independent mechanisms. Prostaglandin E2, a product of COX isozyme 2, is involved in tumor proliferation, angiogenesis, invasion, and metastasis, which in theory should be suppressed by NSAID COX-2 inhibition. The COX-2 enzyme has been shown to be highly expressed in malignant melanocytes but is rarely expressed in benign nevi. Other proposed anti-melanoma properties of NSAIDs have also been postulated; however, clinical and epidemiological studies have not reliably supported a protective effect of NSAIDs on melanoma development [64].

3.3 The Genetics of Melanoma: Germline and Somatic Mutations and their Molecular Pathways

As outlined in the introduction to this chapter, melanoma pathogenesis is the result of a complex interplay of inherited genetic susceptibility and environmental factors, which result in a series of somatic mutations. These DNA alterations lead to oncogenic growth signaling, loss of protective tumor suppression mechanisms, and gain of function mutations which enable the tumor to proliferate, become immortalized, and develop invasive properties. In this section, we will first discuss the commonly identified familial, germline mutations which have been implicated in inherited melanoma susceptibility. This will be followed by a discussion of the key somatic mutations involved in melanomagenesis. Finally, the genetics of melanoma subtypes will be briefly touched upon.

3.3.1 Germline Mutations and Familial Melanoma Syndromes

We have already discussed the role of MC1R in melanin synthesis in response to UV radiation and the presence of polymorphisms associated with certain phenotypes that result in a decreased melanin response to UV in these individuals. Studies have revealed that 72% of melanoma patients have MC1R polymorphisms, compared to 56% in healthy controls. More than 60 MC1R polymorphisms have been identified to date, each increasing the risk of melanoma by approximately two-fold [65]. It is believed that MC1R mutations do not act to directly initiate melanomagenesis; rather, MC1R variants increase the propensity of individuals to acquire further melanoma-inducing mutations as a consequence of attenuated UV-induced signaling to melanocytes. Research has validated that MC1R polymorphisms compared to the wild type are highly associated with pathogenic mutations, including in the important BRAF and NRAS oncogenes [3, 66]. A high level of concordance between MC1R variants and germline mutations in CDKN2A, discussed further below, has also been reported [3]. It has been proposed that MC1R variants may increase the penetrance of CDKN2A mutations, leading to significantly greater rates of melanoma in patients with both germline mutations. In an Australian case-control study, 83% of individuals with both MC1R and CDKN2A mutations developed melanoma, compared to 50% of those with mutant CDKN2A and wild-type MC1R [67].

CDKN2A germline mutations are frequently implicated in familial melanoma, involving 25–40% of cases [7]. CDKN2A is an important cell-cycle regulatory gene, involved in both the cyclin-dependent kinase/retinoblastoma checkpoint pathway controlling the transition of the melanocyte from the G1 growth phase of the cell cycle to the DNA synthesis/S phase and the regulation of apoptosis (Fig. 3.3) [17]. The CDKN2A gene, located at chromosome 9p21, is able to code for two separate proteins through alternative splicing of exons: $p16^{INK4A}$ and $p14^{ARF}$. $p16^{INK4A}$ is an inhibitor of cyclin-dependent kinase 4 (CDK4), an enzyme responsible for the phosphorylation of the retinoblastoma (RB) protein, which is its dephosphorylated state binds to the E2F transcription factor, rendering it inactive. E2F transcriptional targets include cyclins, CDKs, cell cycle checkpoints regulators, and DNA repair and replication proteins; thus, E2F function is required for progression through the G1-S phase checkpoint. Loss of $p16^{INK4A}$, therefore, permits increased activation of CDK4, leading to RB phosphorylation/activation and subsequent activation of E2F and oncogenic growth [7, 17]. The second protein coded within the CDKN2A gene locus is $p14^{ARF}$, named to denote the *a*lternative *r*eading *f*rame required for its translation. Within familial melanoma, missense or nonsense mutations affecting $p16^{INK4A}$ have been reported in 25–60% of cases, whereas familial mutations affecting $p14^{ARF}$ are less com-

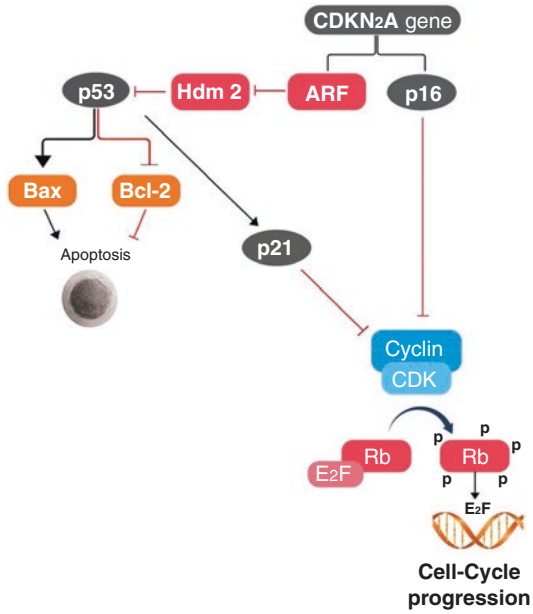

Fig. 3.3 The CDKN2A cell-cycle regulatory pathway: Germline variants of CDKN2A are the most commonly detected mutations in familial melanoma and CDKN2A germline mutations involve 25–40% of familial melanoma cases. CDKN2A regulates cell cycle transitions in tumor cells through direct regulation of the cyclin-dependent kinase/retinoblastoma/p53 checkpoint pathways and G1- to S-phase transitions as well as apoptosis. Notably, the CDKN2A gene encodes two tumor suppressor proteins, $p16^{INK4A}$ and $p14^{ARF,}$ through alternative splicing of exons. E2F transcriptional targets include cyclins, CDKs, cell cycle checkpoints regulators, and DNA repair and replication proteins, all critical mediators of cell cycle progression

mon, suggesting that its role in melanomagenesis is likely less significant [3, 5]. Interestingly, $p14^{ARF}$ plays a critical role as a tumor suppressor protein within the context of p53, the common tumor suppressor implicated in many human cancers, which does not demonstrate a high mutation rate in early melanoma [17]. Despite a lack of primary mutations of p53 in human melanoma, p53 may be inactivated through targeted ubiquitination and proteasomal degradation mediated by the human double minute 2 (HDM2) protein [20]. $p14^{ARF}$ allows for stabilization of p53 by functionally inhibiting HDM2. As p53 normally suppresses tumor formation through transcriptional activation of the CDK inhibitor p21 and promoting cellular apoptosis through regulation of BCL2/BAX (see Box 3.1 for explanation) [20], reduced function of $p14^{ARF}$leads to increased destruction of p53, leading to cell cycle activation and subsequent unregulated melanocyte growth [7, 17].

Box 3.1: Review of Apoptosis [20, 72]

Apoptosis is an essential mechanism whereby cells that are damaged can self-induce a sequence of programmed cell death, therefore preventing the proliferation of cells with deleterious mutations. This process helps to avoid the development of malignancy, by preventing cells from developing a high mutational burden. Apoptosis is mediated by caspases, enzymes that can be activated to destroy the cell. There are two essential apoptosis pathways; the *intrinsic pathway*, triggered by intrinsic recognition of DNA damage or the loss of trophic growth signal, and the *extrinsic pathway*, activated by receptors on the cell membrane by cytotoxic immune cells, including the FAS receptor, TNF-alpha, and perforin/granzyme.

The intrinsic pathway commonly fails in malignancy due to somatic mutations or germline loss. This pathway is activated when the DNA repair proteins, ATM and CHK2, detect double-strand breaks within cellular DNA. These proteins stimulate p53, which at low concentrations induces DNA repair, and at high concentrations triggers apoptosis. p53 activates the latter by stimulating the dimerization of the protein BAX, which in its dimerized form acts as a channel within the plasma membrane of the mitochondria. This channel allows cytochrome C, the protein normally used for the electron transport chain during cellular respiration, to escape the mitochondria. Once in the cytoplasm, cytochrome C activates numerous caspases, primarily caspase 9, alongside the apoptotic agent Apaf-1. In addition to stimulating BAX, p53 is also an inhibitor of the anti-apoptotic protein BCL2, which functions to sequester BAX, preventing its dimerization.

Loss of the trophic growth signal to the cell can also trigger apoptosis. AKT, a survival protein, acts in the presence of a growth signal to sequester the protein BCL2 antagonist of cell death (BAD). Without this sequestration, BAD is able to itself sequester BCL2, therefore enabling BAX dimerization and encouraging apoptosis.

Germline variants of CDKN2A are the most commonly detected mutations in familial melanoma. Patient characteristics that have been reported to be predictors of CDKN2A mutation include earlier age at diagnosis, multiple family members with melanoma, and family members with multiple primary melanomas. Germline mutations in CDKN2A are also associated with pancreatic cancer. Within melanoma families, the prevalence of CDKN2A mutations has been reported to be on average 39%, with lower rates in Australia (20%), and higher rates in North America (45%) and Europe (57%) [68]. It has also been suggested that carriers of CDKN2A inactivating mutations have between a 50–90% risk of melanoma by the age of 80 [69]. Somatic mutations in CDKN2A have also been reported to arise, but these appear to be less frequent than germline mutations [3, 13].

As previously noted, CDK4 is an important mediator of cell-cycle progression through its effects on the retinoblastoma tumor suppressor protein, RB. Germline mutations within CDK4 have been reported, and while these mutations are uncommon, when they do arise, they tend to be in patients with a normal CDKN2A gene. These mutations affect arginine 24 of CDK4, resulting in the protein being insensitive to inhibition by $p16^{INK4A}$ leading to loss of cell-cycle regulation [5, 17].

The melanocyte-inducing transcription factor (MITF) is an important regulator of melanocyte differentiation and maintenance. It plays a role in the α-MSH–MC1R pathway, where activation of MC1R increases MITF expression, resulting in the transcription of key genes needed for melanin synthesis, including tyrosinase. MITF is also implicated in numerous other functions, including induction of cell-cycle arrest, through increased expression of $p16^{INK4A}$ and p21, and promotion of melanocyte survival by increasing production of BCL2 [7, 16]. A variant of MITF, the E318K variant, has been identified in some familial cases of melanoma. It has been estimated that this variant is present in 1% of individuals of European ancestry, and confers a two-fold increased melanoma risk, alongside the increased risk of renal cell carcinoma. The E318K variant is a moderate-penetrance, missense mutation which deletes a site for a small ubiquitin-like modifier (SUMO) modification which affects the transcriptional function of MITF [70, 71].

Alterations in the function of telomerase are important in melanomagenesis. Telomeres are regions of long, repetitive nucleotide sequences at the ends of each chromosome, which act as a protective buffer for the genome. In normal cellular replication, telomeres progressively shorten after each division, as a result of the discontinuous nature of replication of the DNA lagging strand, which requires an upstream RNA primer

for each new Okazaki fragment. Eventually, once the telomeres become truncated, the coding genes of the chromosome are affected, which triggers cell senescence and apoptosis [73]. Aberrant expression of the enzyme telomerase reverse transcriptase (TERT), which functions to extend telomere length resulting in unlimited cellular replication, has been implicated in more than 90% of invasive malignancies [16]. A familial mutation in the promotor region of the TERT gene which leads to greater transcription factor affinity and increased TERT expression has been identified in a small number of families with multiple melanomas [5]. Regulation of the interaction between telomerase and the telomeres is the function of the shelterin complex, and familial mutations of multiple genes within this complex, including POT1, ACD, and TERF2IP, have also been reported [5].

Xeroderma Pigmentosum (XP) is a rare autosomal recessive condition that significantly increases the risk of melanoma and non-melanoma skin cancers up to several thousand-fold [2]. XP can be caused by a mutation in one of eight genes coding for proteins involved in nucleotide excision repair (NER). As previously noted, one of the major forms of UV-induced DNA damage is the formation of pyrimidine dimers, where adjacent thymine nucleotides become covalently bonded, disrupting the shape of the DNA strand. These dimers are repaired by NER endonucleases (outlined in Fig. 3.4). In XP, this process was disrupted resulting in a significantly increased UV-induced mutational burden. Patients with XP develop melanoma at a significantly younger age, with an average age of onset of 22. Strict lifelong avoidance of UV is necessary for the prevention of cancer in affected patients [74].

A number of other familial cancer syndromes have been described that are associated with increased melanoma risk. These melanoma-subordinate syndromes include those associated with breast cancer risk BRCA 1 and 2 mutations, Li–Fraumeni syndrome (an autosomal dominant condition involving heterozygous germline mutations in the p53 tumor suppressor), mutations in the BRCA1 associated protein-1 (BAP1),

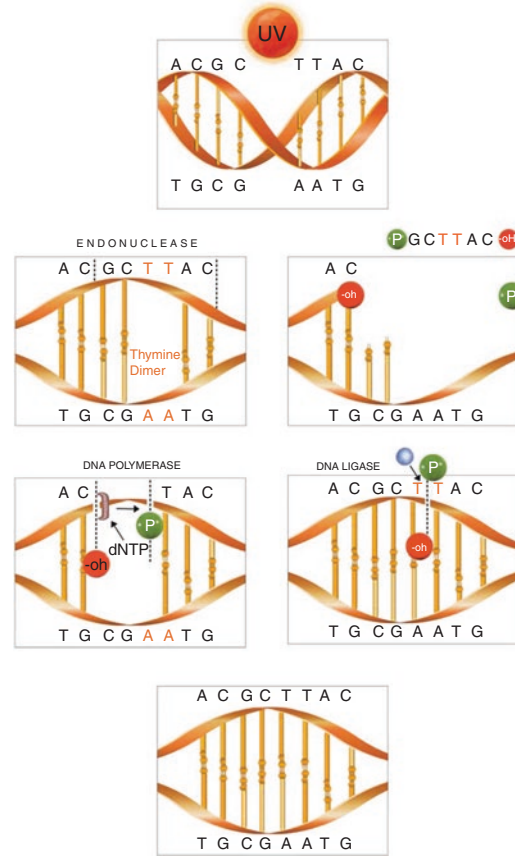

Fig. 3.4 Overview of nucleotide excision repair: UV light induces the formation of covalent bonds between adjacent thymine nucleotides, resulting in the formation of thymine dimers which disrupt the shape of the DNA strand and which can be removed by NER endonucleases and repaired by DNA polymerase and DNA ligase. This process is defective in patients with xeroderma pigmentosum leading to increased DNA mutational events and significantly increased risks of both melanoma and non-melanoma skin cancers

Cowden syndrome (with germline mutations in the PTEN tumor suppressor) and retinoblastoma (RB1) [5].

3.3.2 Somatic Mutations in Melanoma

While some of the genetic mutations associated with melanoma can be inherited through the germline, the vast majority appear to acquire somatically, either spontaneously or as a result of

UV exposure and other environmental factors. Melanoma is associated with the highest somatic mutational burdens of any human cancer, with a median burden in excess of 10 mutations per megabase [75]. The key driver mutations, however, and the degree of mutational burden, are dependent on a number of elements, including the subtype of melanoma, and the association with either intermittent, high-intensity sun exposure or chronic, cumulative UV exposure [1].

Somatic mutations that can contribute to the development of melanoma can be divided into three main groups based on the functions of the affected genes; oncogenes, which drive excessive cellular growth and proliferation, tumor suppressor genes, where the loss of function mutations prevent the melanocyte from activating protective growth regulatory pathways, and finally gain of function mutations, where atypical melanocytes acquire additional genetic mutations leading to new molecular functions or patterns of gene expression promoting unlimited cell growth and invasion. We will discuss each of these groups in turn, alongside the key pathways and somatic mutations that have been identified.

3.3.2.1 Oncogene Activation in Melanoma

The MAP Kinase Pathway

A major breakthrough in our understanding of the fundamental molecular basis for melanoma development and progression came in 2002 with the discovery that approximately 50% of all melanomas harbor driver mutations in the BRAF kinase gene [76]. Subsequent discoveries have further informed the significance of the MAP kinase pathway in melanoma (Fig. 3.5), and it is now known that roughly 90% of cutaneous melanomas demonstrate hyperactivation of the MAP kinase pathway, which is central to melanomagenesis [1]. Under normal cellular conditions, the MAPK pathway is responsible for signal transduction from extracellular growth factors and hormones to the cell nucleus, where it induces transcription of genes needed for cell growth, proliferation, and survival. This pathway is activated through ligand binding to a transmembrane receptor tyrosine kinase, such as KIT, which in turn phosphorylates the membrane-bound G protein-coupled NRAS GTPase. Phosphorylation by the receptor tyrosine kinase converts bound GDP to guanosine triphosphate (GTP), activating NRAS, which acts as a switch to activate the BRAF protein, as well as another oncogenic pathway associated with PI3K-AKT signaling (see discussion on PTEN, below). BRAF, the key downstream effector of NRAS in melanoma, is a serine/threonine kinase, which dimerizes, either with itself, or another RAF protein in response to growth signals from NRAS. Homo- or hetero-dimerized BRAF is able to phosphorylate the protein MAPK/extracellular signal-regulated kinase (ERK) kinase (MEK), which in turn phosphorylates its downstream substrate, ERK. Upon phosphorylation, ERK induces expression of transcription factors, such as C-MYC, which promote the expression of key growth and proliferation genes. ERK is also able to induce cell-cycle progression, mediated by cyclin D1, and additionally inhibits tumor suppressor proteins and prevents apoptosis [1, 3, 12, 16, 20].

NRAS and BRAF are the two components of the MAPK pathway that are commonly affected by somatic mutation in melanoma, resulting in the constitutive overactivation of the pathway. Mutations in these proteins are generally mutually exclusive, which is to be expected given their overlapping functions [3]. Mutations in the BRAF gene are the most frequent driver mutations seen in melanoma and are present in about 50% of melanoma cases. BRAF mutations, in addition to NRAS mutations, are particularly associated with intermittent sun exposure and are much less common in melanomas from sites of chronic UV exposure [1, 3, 12, 20]. Eighty to ninety percent of BRAF mutations are missense mutations leading to valine to glutamic acid substitution at codon 600, known as $BRAF^{V600E}$. This mutation affects the catalytic binding site of BRAF, which normally forms a hydrophobic interaction between a glycine-rich loop and the activation site, making it inaccessible to ATP, the phosphate donor for BRAF-mediated phosphorylation of MEK. Replacement of hydrophobic valine with hydrophilic glutamic acid in

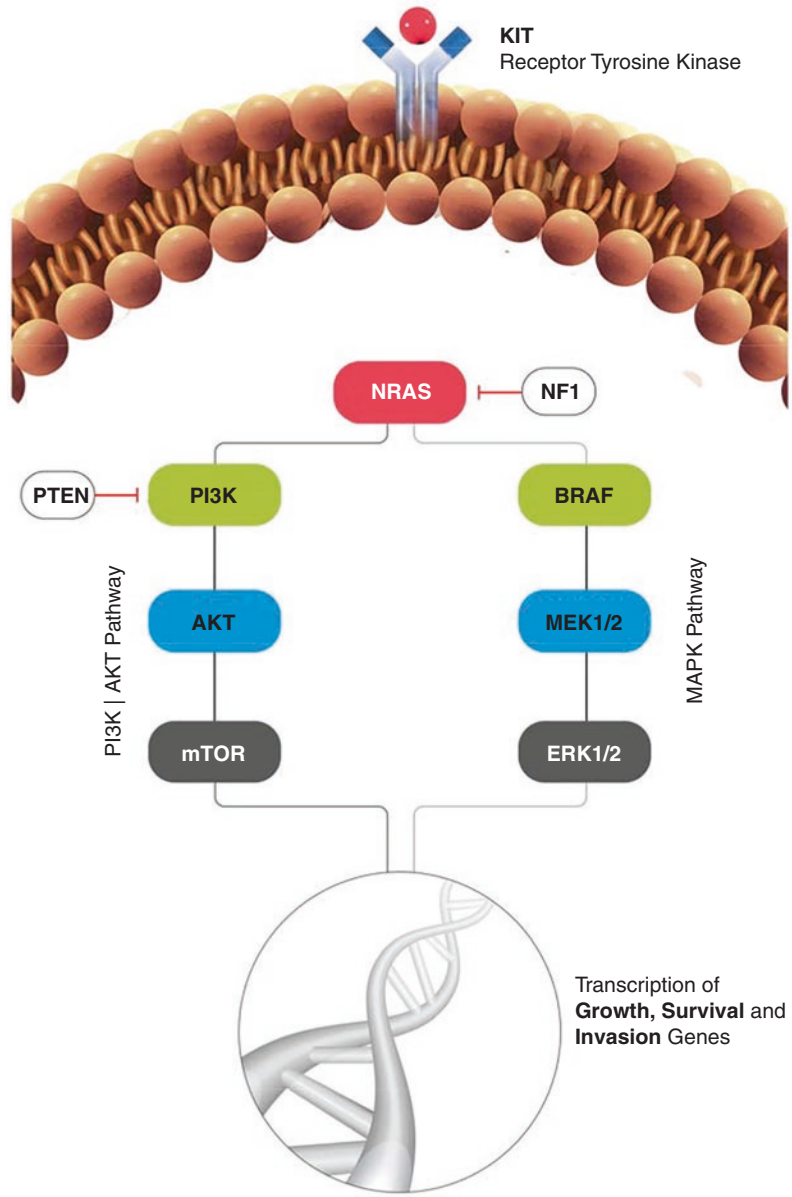

Fig. 3.5 Key oncogenic pathways in melanomagenesis: The MAP kinase pathway, illustrated below, is responsible for signal transduction from extracellular growth factors and hormones to the cell nucleus, where it induces transcription of genes needed for cell growth, proliferation, and survival. Several genes associated with this pathway are altered during melanoma development and progression in a mutually exclusive fashion including activating mutations of BRAF kinase 40–50% of cases, activating mutations of NRAS (20–30% of cases), and inactivating mutations of the NF1 tumor suppressor (10–15% of cases). The PI3K/AKT pathway is also activated in melanoma; however, this pathway does not appear to be a major driver event for disease development

$BRAF^{V600E}$ facilitates ATP binding, increasing BRAF's kinase activity 500-fold compared to the wild-type form of BRAF [1]. Interestingly, BRAF mutations are also present in 60–80% of benign melanocytic nevi, suggesting that BRAF mutation alone is not sufficient to promote melanoma development. Rather, BRAF activation in human melanocytes promoted limited melanocyte proliferation which is ultimately held in check by oncogene-induced cellular senescence [1, 7, 17]. Sustained expression of $BRAF^{V600E}$ in primary human melanocytes in vitro results in cell-cycle arrest through the oncogene-driven expression of $p16^{INK4A}$ and subsequent development of a senescence phenotype, and similar senescence-associated changes have been seen in nevi from patients [18].

Mutations in NRAS at codons 12, 13, and 61 represent the second most common somatic driver mutations implicated in melanoma patho-

genesis [3, 16]. As previously noted, NRAS mutations lead to constitutive activation of cell growth-promoting pathways, resulting in downstream effects on cell growth both through the MAPK pathway via BRAF, and through the PI3K-AKT pathway. NRAS mutations are found in roughly 20–30% of melanomas and have been found to be associated with more aggressive diseases including tumors with greater thickness and mitotic rate, and poorer survival [16]. NRAS mutations are also highly associated with congenital nevi, where mutations in BRAF are rare [77]. Similar to BRAF, NRAS mutations are commonly found in benign nevi, supporting that these oncogenic mutations are not sufficient to induce malignancy alone [3]. Somatic mutations within the transmembrane receptor tyrosine kinase KIT have also been implicated in constitutive activation of the MAPK and PI3K-AKT pathways. KIT mutations are less common in cutaneous melanoma and are associated with chronic sun exposure and advanced age where mutations are present in 15–30% of cases compared to less than 1% of cases of intermittent UV exposure-related cutaneous melanomas in Caucasians. KIT mutations are also more common in acral lentiginous melanoma and mucosal melanoma (see genetics of melanoma subtypes, below) [12].

MITF

The MITF transcription factor may be overexpressed in melanoma through acquired somatic events which contribute to melanocyte invasion and survival. MITF gene amplification has been reported in 20% of metastatic melanomas and is associated with increased mortality and resistance to chemotherapy [7, 12, 16]. MITF has also been implicated in mechanisms of resistance to melanoma targeted therapies involving inhibition of the MAPK pathway, including BRAF and MEK inhibitors. This relationship is complex and will be discussed in subsequent chapters dedicated to melanoma treatment. One mechanism of proposed MITF functions in MAPK therapeutic resistance suggests that the tumorigenic effects of MITF include increased expression of the anti-apoptotic factor BCL2 in this setting [16].

3.3.2.2 Other Oncogenic Mutations in Melanoma

Two other somatic oncogenic mutations that have been reported in melanoma include RAC1 and ribosomal protein S27. RAC1 codes for an RHO GTPase, which is a small monomeric protein that functions as a molecular switch for signal transduction pathways involved in actin reorganization. Exome sequencing studies have identified a proline to serine mutation at codon 29 of RAC1 in 5–9% of melanomas, likely the consequence of UV-induced base transition. This mutation results in a persistent GTP-bound state of the RHO protein, which accelerates signaling leading to cellular proliferation. Melanomas with this mutation have increased thickness, mitotic rate, and ulceration, and are more likely to present with metastatic spread at diagnosis [16]. A recurrent mutation in the 5′ untranslated region, upstream of the AUG start codon, has also been identified in the gene for ribosomal protein S27. Sequencing data from a cohort of 489 melanomas revealed a prevalence of 10%. Activation of S27 is believed to act through mTOR, a component of the PI3K-AKT oncogenic pathway [16, 78].

3.3.2.3 Tumor Suppressor Gene Inactivation in Melanoma

PTEN

Activation of oncogenic growth signaling alone in human melanocytes is insufficient for malignant transformation. Loss of tumor suppressor gene functions plays an important, synergistic role in melanomagenesis. Phosphate and tensin homolog (PTEN) inactivation is frequently implicated in melanoma, with mutations in 8% of cases and focal deletions in 6%, and the prevalence is likely much greater in invasive and metastatic disease [16]. PTEN is a key suppressor of the PI3K-AKT pathway (Fig. 3.5), functioning to dephosphorylate the product of PI3K, phosphatidylinositol (3,4,5)-trisphosphate (PIP_3), leading to pathway inactivation [3]. Mutations in PTEN often coexist with mutations of BRAF, but not with NRAS as the latter is able to activate the PI3K-AKT pathway independently [16]. Activation of the PI3K-AKT pathway, either through loss of PTEN suppression or activation

of NRAS, leads to a competitive growth advantage to the melanocyte, leading to proliferation and metastatic spread. The pathway functions through PI3K, which functions to increase levels of PIP_3. Rising levels of PIP_3 triggers the phosphorylation, and thus activation, of protein kinase B, also known as AKT. This latter protein works to stabilize the melanocyte against apoptosis. As explained in Box 3.1, AKT inactivates the protein BAD, which releases BCL2, stabilizing the mitochondrial membrane. Other functions of AKT include increase cell proliferation through induction of cyclin D1, and activation of transcription factors [7, 20].

P53 Inactivation

As discussed previously, primary mutations in the central tumor suppressor p53 are less frequent in melanoma than in other human malignancies. Less than 20% of melanomas are reported to have primary p53 mutations. However, mutations in the regulators of p53, including hdm2 and hdm4, have been reported. Hdm2 is the target protein of the $p14^{ARF}$ tumor suppressor encoded by the CDKN2A gene that is frequently implicated in familial melanoma. Hdm2 and 4 act as negative regulators of p53, increasing its degradation via ubiquitination. Both have been reported to be overexpressed in melanoma, with mdm4 present in 65% of melanomas [16].

NF1 and Apaf1

There are two other tumor suppressors that have been identified as mutated in melanomas. The first is the neurofibromin 1 (NF1) gene. NF1 is a negative regulator of NRAS, upregulating the activity of RAS GTPase, which converts the GTP bound to NRAS to GDP, switching off the signaling. As a consequence, loss of NF1, seen in 10–15% of melanomas, results in constitutive activation of NRAS, and hence both the MAPK and PI3K-AKT pathways (see Fig. 3.5). NF1 mutations are associated with melanomas on chronically sun-exposed skin, advancing age, and increased mutational burden. Loss of NF1 is also highly prevalent in the desmoplastic melanoma subtype [16, 79]. Another tumor suppressor implicated in melanomagenesis is Apaf1. This is an effector agent of apoptosis, activated by p53, which triggers cell death through caspase enzymes. Some studies have reported the inactivation of Apaf1 through deletion or methylation [20].

3.3.2.4 Gain-of-Function Pathways in Melanoma

The last category of somatic mutations in melanoma is the gain-of-function mutations. In order to become invasive, melanocytes need to acquire the ability to sustain independent cell growth and invade the dermis and subcutaneous tissues. Cell migration is typically regulated through cellular adhesion proteins, which mediate cell processes involving cellular movement, organization, and organogenesis. Cadherins are one group of proteins that become altered in melanoma. Cadherins are transmembrane glycoproteins located within the zona adherens; they bind to nearby cells via cell autonomous cadherins which enable intercellular signaling and growth regulation. The epithelial (E-cadherin) subclass of cadherins is expressed by normal human melanocytes, which facilitate communication with adjacent keratinocytes. Progression from the radial growth phase to the vertical growth phase of melanoma, however, is characterized by a shift from a predominant expression of E-cadherin to the neural (N-cadherin) subclass in melanoma. This shift in expression of cell adhesion molecules is significant as N-cadherin is a marker of invasive carcinoma which permits interaction between the melanocyte and other N-cadherin expressing cells, such as fibroblasts within the dermis and vascular endothelial cells, which is a key function needed for metastatic spread [3, 7]. Cadherins also play a role in cell survival, through the β-catenin wingless-type mammary tumor virus family (WNT) pathway. β-catenin is a large protein complex that interacts with the intracellular domain of cadherin and the bundles of actin filaments within the cell that form the cytoskeleton. β-catenin is capable of dissociating from cadherin and migrating to the nucleus, where it increases the expression of genes including MITF

and CCND1 (the gene for cyclin D1), promoting melanocyte survival and proliferation. Altered expression of cadherins, primary mutations in β-catenin which occur in 2–4% of melanomas via the CTNNB1 gene, or increased secretion of the WNT protein which stabilizes β-catenin, can enhance signaling through this pathway [1, 7].

In addition to changes to cadherins, the transition from the radial to the growth phase of melanoma is also marked by altered expression of integrins and MMPs. Integrins mediate cell adhesion to components of the surrounding extracellular matrix, including collagen, laminin, and fibronectin. Vertical growth phase melanomas demonstrate increased expression of αVβ3 integrin, which has three proliferative functions including induction of MMP2, which degrades the collagen of the basement membrane, permitting tumor invasion into the dermis and infiltration into the vasculature. αVβ3 integrin also induces expression of BCL2, preventing apoptosis, and stimulates melanocyte motility [7]. Increased expression of MMP9 is also found in melanoma, mediated by dysregulation of NF-κβ [1].

Angiogenesis is important for melanoma survival since large tumors will quickly outgrow their original blood supply as a function of increases in cell mass and metabolic rate. Melanoma is known to produce a number of angiogenic growth factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), neuropilins, platelet-derived growth factor (PDGF), and angiopoietin. Production of these factors increases significantly during the transition to the vertical growth phase. Additionally, the production of MMPs is important for facilitating angiogenesis [24].

As previously mentioned, a critical characteristic of tumor cell growth is the ability to sustain continued self-renewal, which is significantly regulated by the enzyme, telomerase. Somatic mutations of the telomerase reverse transcriptase gene, TERT, have been reported, with the most frequent mutations occurring in the promoter region of the gene at specific transcription factor binding sites. These mutations increase the affinity of the critical transcription factor, GA-binding protein, leading to increased transcription of TERT. These mutations are likely to be UV-induced and have been identified in 33% of sporadic melanomas and, most significantly, in *85%* of metastatic melanomas [16, 80].

3.3.3 Genetics of Melanoma Subtypes

While many of the same somatic mutations are shared between melanoma subtypes, the propensity for particular mutations is dependent on specific melanoma subtypes and associated with distinct patterns of UV exposure, as illustrated in Fig. 3.6. The mutations commonly reported in uveal melanoma are particularly distinct from the other subtypes; mutations in BRAF, NRAS, and KIT are rarely reported. Instead, somatic mutations in the G-proteins GNAQ and GNA11 are found in more than 80% of these melanomas. These mutations result in the upregulation of protein kinase C, which can activate the MAPK pathway [81]. Other mutations in uveal melanoma include BRCA1-associated protein (BAP1), splicing factor 3B subunit 1 (SF3B1), and eukaryotic translation initiation factor (EIFAX) [12].

The BAP1 gene, located at the 3p21 locus, is susceptible to high rates of somatic mutation in uveal melanoma, undergoing mutation in greater than 80% of cases. In addition, uveal melanomas with BAP1 mutations are at greater risk of metastatic spread. Inactivating mutations, most commonly leading to premature stop codons, result in loss of the tumor suppressor functions of BAP1 or ubiquitin carboxyl-terminal hydrolase. This protein normally functions as a deubiquitinase, playing a role in cell cycle regulation [82]. Germline alterations in BAP1 can also lead to a BAP1 cancer predisposition syndrome, which is characterized by an increased incidence of uveal melanoma, cutaneous melanoma, mesothelioma, and renal cell carcinoma [12, 83].

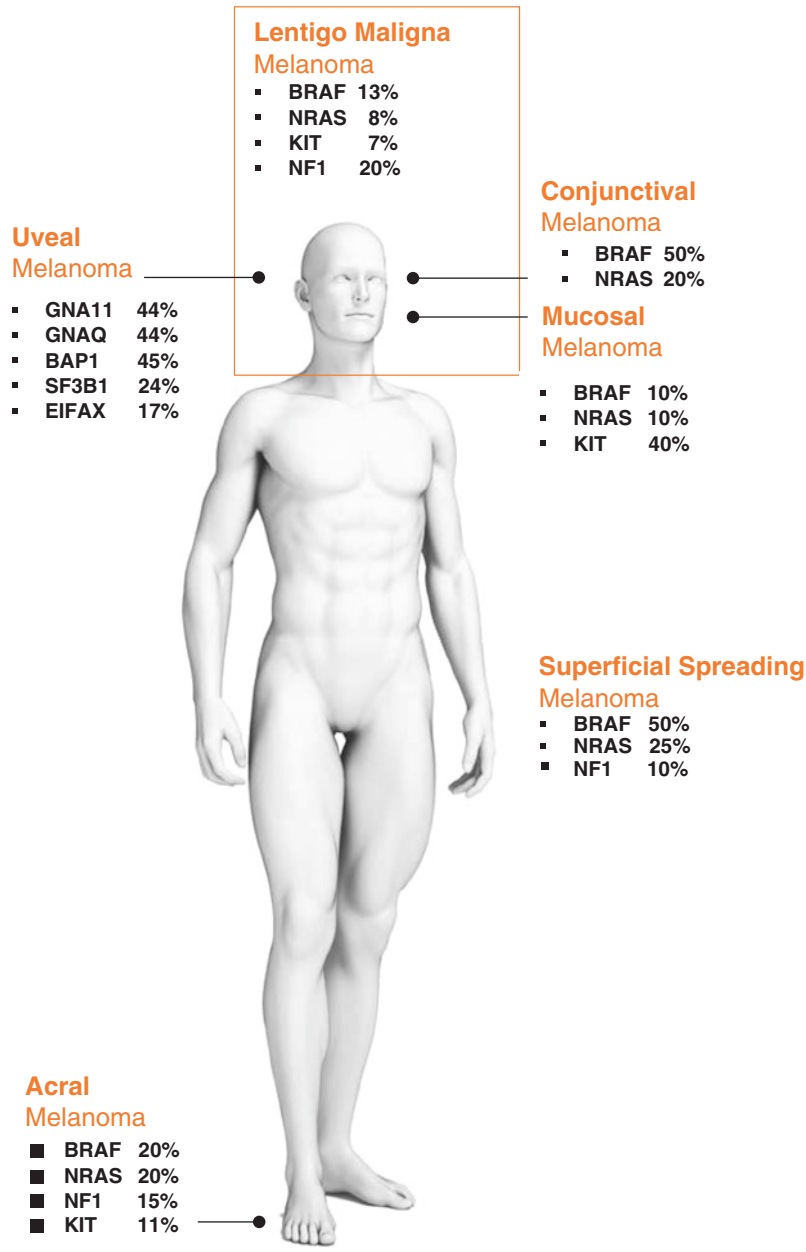

Fig. 3.6 Melanoma subtypes and their associated somatic mutations

3.4 Melanoma Pathogenesis: Outlook for the 2020s

Over the past decade, advances in high-throughput molecular and genetic studies have enabled the discovery of key pathways (Fig. 3.7) involved in the pathogenesis of melanoma. Our improved understanding of this disease over the past decade has revolutionized our approach to the treatment of advanced disease and led to the development of novel and effective therapies for melanoma which are unprecedented. Looking forward to the next decade, we expect that continued improvements in precision medicine will

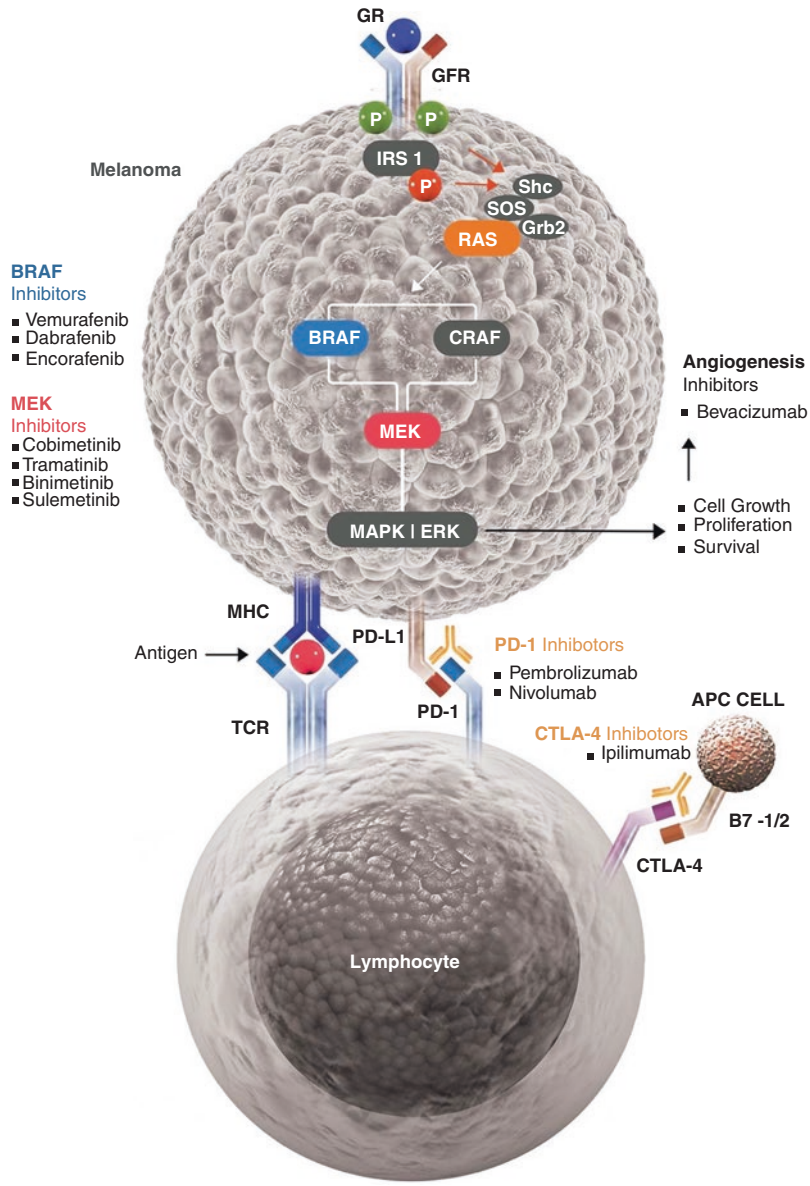

Fig. 3.7 Critical pathways involved in immune checkpoint therapy and targeted therapies in melanoma. Targeted therapies such as BRAF inhibitors and MEK inhibitors act on the mitogen-activated protein kinase (MAPK) pathway. This pathway is critical for cell growth and survival. The MAPK pathway is constitutively activated by driver mutations (such as V600E in BRAF) in a significant number of melanoma cells providing a survival advantage to the cell. Targeted therapies inhibit the activity of the mutated protein and switch off the constitutive activation. T cell activation is normally regulated via signaling molecules called immune checkpoints (CTLA-4 and PD-1) to prevent collateral damage to normal tissue and prevent autoimmunity. Immune checkpoint inhibitors (ICIs) block signaling by these molecules and potentiate the immune response against tumor cells

build on this knowledge and allow for further advancements in the diagnosis and treatment of this aggressive form of skin cancer.

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4 The Histopathology of Melanocytic Nevi and Malignant Melanoma

Zena Willsmore and Alistair Robson

4.1 Introduction

Melanocytic lesions are one of the most common samples submitted for dermatopathology assessment. Whilst most are uncomplicated the distinction between various nevi and malignant melanoma is at times very challenging. The dominance of misdiagnosed melanocytic lesions in dermatopathology lawsuits [1] underscores the medical and financial penalties attached to diagnostic error. This chapter therefore details the histopathology of the melanocytic nevi and the various types of melanoma to clarify diagnostic recognition and facilitate distinction between banal lesions and those that pose greater risk to patients with attendant consequences for appropriate management. In addition, the role of histopathology in providing a guide to prognosis and a brief summary of ancillary investigations as aids to diagnosis are considered.

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4.2 A Comment on Nomenclature and Classification

Most melanocytic lesions are readily considered benign (nevus) or malignant (melanoma) though this is not always straightforward, and the ensuing terminology can be confusing. Thus, there are examples of certain nevi in which certain histological features raise concern for melanoma but are insufficient for a confident diagnosis of malignancy; these are consequently labelled "atypical," e.g. atypical blue nevus, or "borderline." Atypical Spitz tumor is an exception, representing a specific diagnostic category. An intermediate group designates morphologically reproducible neoplasms whose biological nature is believed to lie between benign or malignant, e.g. pigmented melanocytoma. Indeed, a number of tumor types have a propensity to involve local lymph nodes without subsequent patient fatality, militating against a simple benign or malignant dichotomy. Finally, dysplastic melanocytic nevus is an example of the intermediate group, in terms of molecular progression, but as the features of concern are intraepidermal it is a clinically benign lesion. Research into the genetics of melanocytic tumors, whilst enlightening our understanding, has simultaneously illustrated the shortcomings of histopathology, such that the current classification of melanocytic lesions is a farrago of morphology, molecular abnormalities,

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Table 4.1 Benign, intermediate, atypical, and malignant melanocytic lesions. The nosological status of intermediate and atypical lesions is unclear

Benign	Intermediate	Atypical	Malignant
Common acquired nevus	Deep penetrating nevus	Blue/cellular blue nevus	Superficial-spreading melanoma
Halo nevus	Combined nevus	Spitz tumor	Lentigo maligna melanoma
Special site nevi	Pigmented melanocytoma		Nodular melanoma
Congenital nevus			Acral lentiginous melanoma
Blue/cellular blue nevus			Nevoid melanoma
Spitz nevus			Desmoplastic melanoma
Reed nevus			Malignant blue nevus
Dysplastic nevus			Spitzoid melanoma

and anticipated prognosis. The melanocytic tumors discussed in this chapter (Table 4.1) are largely considered under the benign, intermediate, malignant subheadings and, where relevant, atypical examples are detailed.

4.3 Benign Melanocytic Nevi

A variety of melanocytic nevi are now described that differ clinically and histologically. These have importance both as mimics and as potential precursors to melanoma, and in the wider context of our evolving understanding of the differing genetic pathways that can eventuate in malignancy. Although benign, they may at times have histological features that cause diagnostic concern. Thus, any attempt at accurate diagnostic resolution between a benign and malignant melanocytic lesion requires a robust grasp of nevi morphologies.

4.3.1 Common Acquired Melanocytic Nevus

The common acquired melanocytic nevus is the most frequently encountered nevus in clinical practice. Most prevalent in fair skin types, a typical person will develop 15–40 during their lifetime, with subsequent regression [2–4]. During this evolution the nevus will pass through the histologically defined and clinically recognizable junctional, compound and intradermal

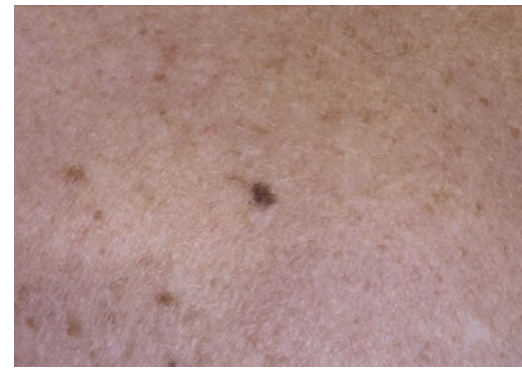


Fig. 4.1 A junctional melanocytic nevus on the back

stages. Melanocytic nevi are symmetrical, uniformly pigmented lesions, typically <5 mm diameter. An increased number of nevi correspond to a heightened risk of superficial-spreading and nodular melanomas [5], and approximately one third of melanomas arise within a pre-existing nevus. Nevertheless, the risk of a single nevus undergoing malignant transformation is very low [6]. Clinical change in a pre-existing nevus usually provokes the concern leading to removal and histopathological examination.

The junctional melanocytic nevus (see Fig. 4.1) is a well-circumscribed symmetrical lesion at scanning magnification. Regularly spaced nests of bland melanocytes lie at the dermoepidermal junction, located at the tips of rete ridges without bridging between rete, extension of melanocytes into the supra-papillary region or upward epidermal (pagetoid) spread. The con-

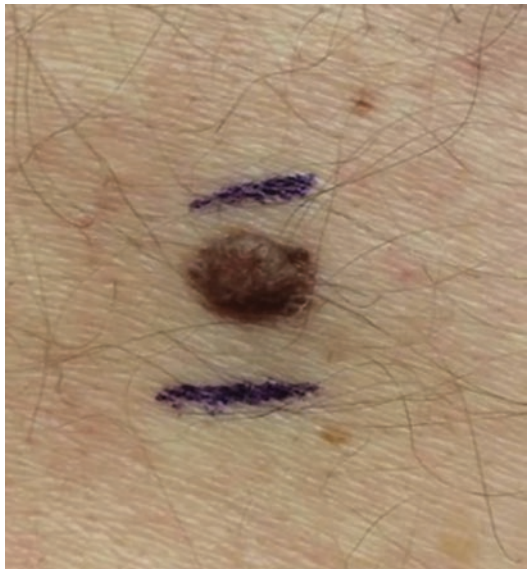


Fig. 4.2 A compound melanocytic nevus on the back

stituent (type A) epithelioid melanocytes have moderate amounts of clear cytoplasm containing variable amounts of melanin pigment, pale nuclei, and indistinct nucleoli. A sparse papillary dermal lymphocytic infiltrate may be present with delicate free melanin pigment. Additional (type A) melanocytes within the dermis define a compound melanocytic nevus (see Fig. 4.2). The dermal melanocytes typically lie in regular variably sized nests, sometimes with melanin pigment (Fig. 4.3a, b). Pseudovascular spaces are a common artifactual observation. Both the nests and individual dermal melanocytes become smaller with increasing depth, architectural and cytological maturation ("atrophy"), respectively. Toward the base of the lesion, the melanocytes often lie as individual cells and lack pigment. Subsequent disappearance of the junctional

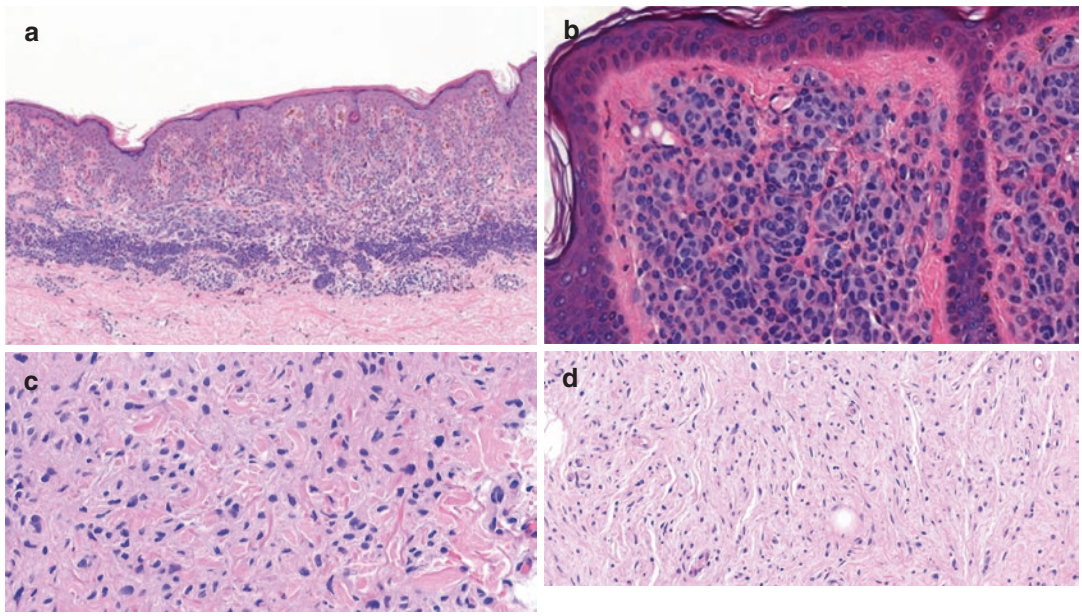


Fig. 4.3 (**a**) Scanning magnification of a compound melanocytic nevus. The lesion is symmetrical from left to right, and there is obvious maturation with depth. Superficial nested epithelioid type A nevocytes (**b**) typically give way to (**c**) smaller individually arranged type B nevocytes in the deeper dermis, in some cases eventuating in slender type C spindle cells (**d**)

melanocytes indicates an intradermal melanocytic nevus (see Fig. 4.4); in long-standing intradermal nevi, the constituent melanocytes may be small, resembling lymphocytes, and lack prominent nesting: type B nevocytes (Fig. 4.3c). Neurotization mimics nerve sheath differentiation, with type C nevus cells (Fig. 4.3d); spindled with a serpentine contour and may have Meissner corpuscle-like structures. In some nevi there remains a discrete group of larger epithelioid type A cells within the type B or C melanocytes, so-called clonal or inverted type A nevus (Fig. 4.5); these can mimic deep penetrating nevi or cause concern over malignant transformation.

Important consistent observations throughout this evolution include good circumscription and symmetry, and maturation. Junctional proliferations should not display significant numbers of melanocytes in the upper portions of the epidermis. Dermal populations of melanocytes might show some variation in size and shape, and an occasional mitosis can be found; older lesions can display cytological anisonucleosis mimicking pleomorphism. However, benign lesions should lack an expansile growth pattern, marked cytological atypia, or readily identified mitoses.

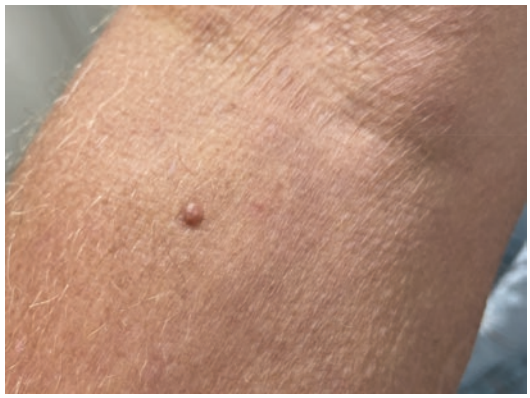


Fig. 4.4 An intradermal melanocytic nevus on the posterior leg

Balloon cell change reflects disruption in metabolism or processing of melanosomes [7]; the melanocytes have voluminous clear cytoplasm but central bland nuclei and inconspicuous nucleoli. If such cells constitute a majority, the tumor is designated a balloon cell nevus, although it has no clinical significance. Rarely this change is observed in other kinds of nevi [7, 8].

Adipocyte metaplasia, calcification, and bone formation are uncommon late events in some nevi. Nevi can darken ("reactivate") under the influence of the oral contraceptive pill or pregnancy, with histological pigmentation, and mitoses may be more prevalent, but other atypical features should not be observed. Meyerson's nevus has a superimposed clinical dermatitis, with histological parakeratosis, acanthosis, spongiotic change, and light dermal perivascular chronic inflammation. Usually a solitary finding, though there is sometimes widespread atopic dermatitis.

Specific situations or subtypes of common acquired melanocytic nevi often pose diagnostic

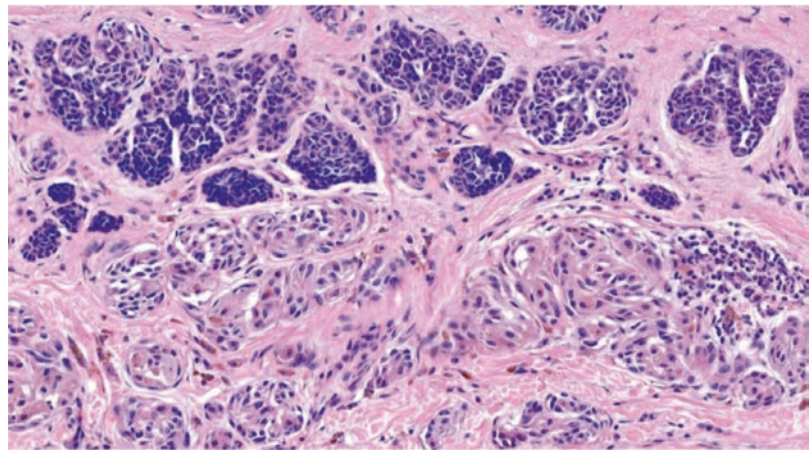


Fig. 4.5 An inverted or clonal nevus, in which the type A epithelioid melanocytes lie beneath type B nevocytes, should not be mistaken for malignancy

challenges and concern for dysplasia or malignancy. These are halo nevi, recurrent nevi, and special site nevi—including acral nevi.

4.3.2 Halo (Sutton's) Nevus

Halo nevi (see Fig. 4.6) present clinically with a pale depigmented area circumventing a pre-existing usually common acquired nevus, the "halo" [9]. These nevi are most commonly located on the trunk, particularly back, of young adults, and are solitary, although they can occasionally be displayed by several nevi concurrently [10]. The halo reflects a marked inflammatory cell response to the nevus and variable regression of the lesion. Histologically, the inflammation is lymphocytic, band-like, and may permeate the nevus such that extant nevocytes are difficult to discern without immunohistochemistry (Fig. 4.7). There can be variation in size of hyperchromatic melanocytes, "reactive atypia," and mitoses may be identified. Successful recognition of the benign nature of the tumor relies upon appreciation of the symmetry and peripheral circumscription of the lesion, lack of pagetoid spread, and cytological characteristics of residual nevocytes. Whilst melanocytes of halo nevi do disappear over time, the lymphocytes simultaneously peter out and there is no residual scarring. Rarely, a clinically observed halo is present in the absence of a histological lymphocytic infiltrate [11]. The halo phenomenon can affect other kinds of nevi.

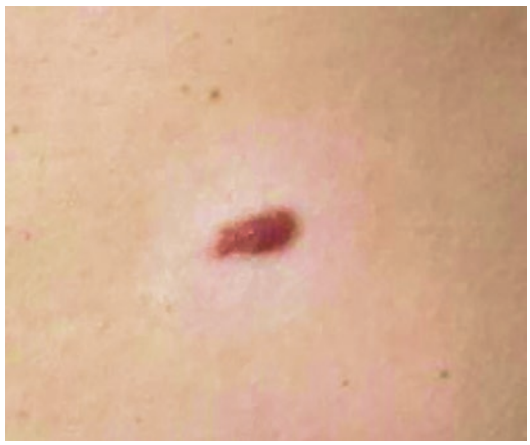


Fig. 4.6 A halo nevus on the abdomen

4.3.3 Recurrent Melanocytic Nevus

Common acquired melanocytic nevi that recur after partial excision often show irregular architecture, sometimes cytology, that can closely mimic dysplastic or malignant lesions; "pseudomelanoma" (Fig. 4.8) [12]. This is typically seen within several months of a partial shave excision of larger lesions but may be longer. Trauma to a banal nevus or incisional biopsy can elicit the same effect. Clinically, there is often concern as irregular pigmentation develops around the scar of the previous procedure. Histological features of alarm include lentiginous melanocytic hyperplasia, single and nests of melanocytes irregularly distributed within the epidermis sometimes with pagetoid spread, and mitoses. There may be cytological atypia. Inflammation—including dermal melanin and melanophages—and fibrosis, whilst helpful clues to prior surgery, can also be misinterpreted as regression of a sinister lesion. Reassuring features are the confinement of the atypical junctional proliferation to the area above the dermal scar—in most cases, flattened rete ridges, and maturation of any dermal component. Immunohistochemistry demonstrates a low Ki-67 index. Nevertheless, in situations where there is diagnostic doubt review of the initial partial excision is mandatory.

4.3.4 Special Site Nevi

Acquired melanocytic nevi arising at certain anatomic sites may present an irregular histological appearance that can particularly mimic dysplastic lesions, or even malignant melanoma. Anatomic locations include genitals, scalp, umbilicus, flexural areas, breast, mucosae, and ears [13–18]. Such nevi are usually clinically benign, but often present one or more of the following histological features: poor circumscription, focal suprabasal spread, confluence of junctional nests and discohesion, bridging of rete, lentiginous proliferation,

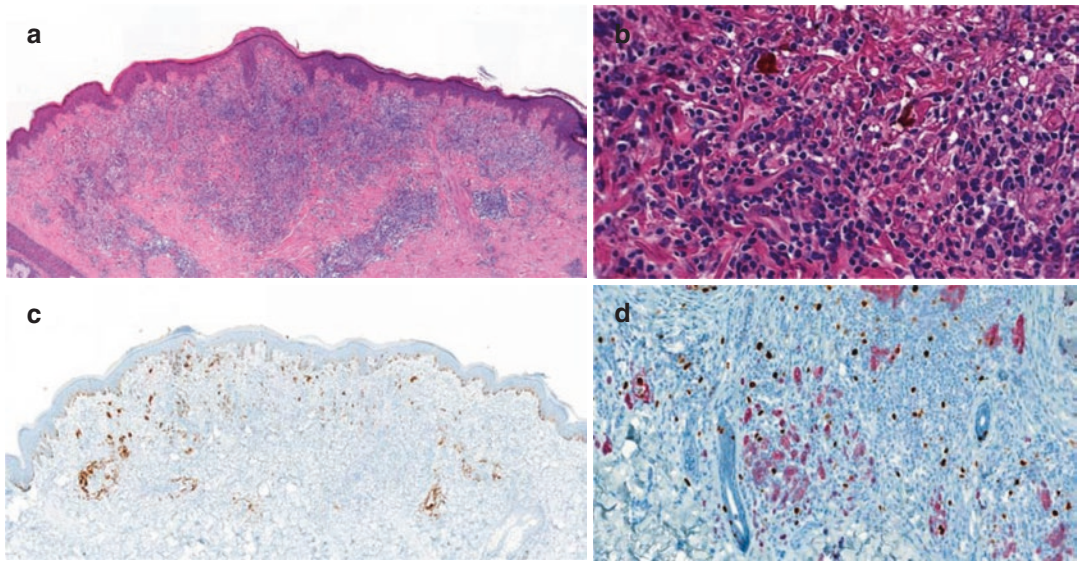
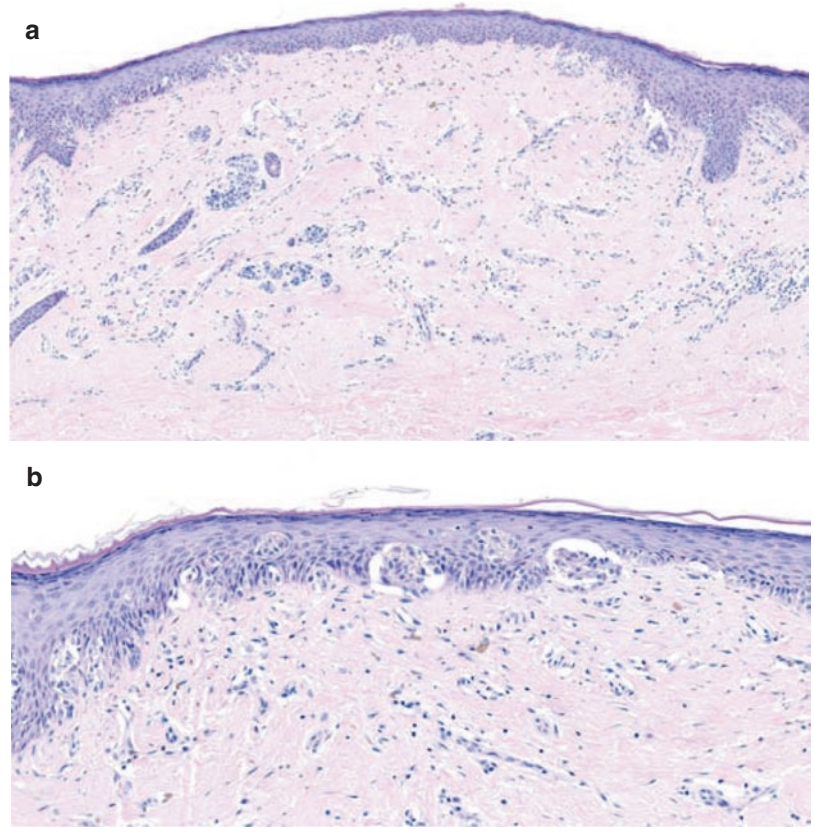


Fig. 4.7 (**a**) A late-stage halo nevus, a form of regression, dominated by lymphocytes (**b**) Nevocytes are difficult to identify. Immunohistochemistry (**c**, Melan A,) can be useful to demonstrate the residual melanocytes. (**d**) Dual staining for Melan A (red) and Ki67 (brown) provides reassurance that the melanocytes are not proliferating, militating against a regressing melanoma

Fig. 4.8 (**a**) Excision specimen of a previously partially shave excised compound melanocytic nevus. The scar is evident, within which lie residual non-mitotic melanocytes. (**b**) There is an irregular junctional proliferation, with suprabasal spread of melanocytes. Such lesions can closely mimic dysplastic or malignant tumors with regression



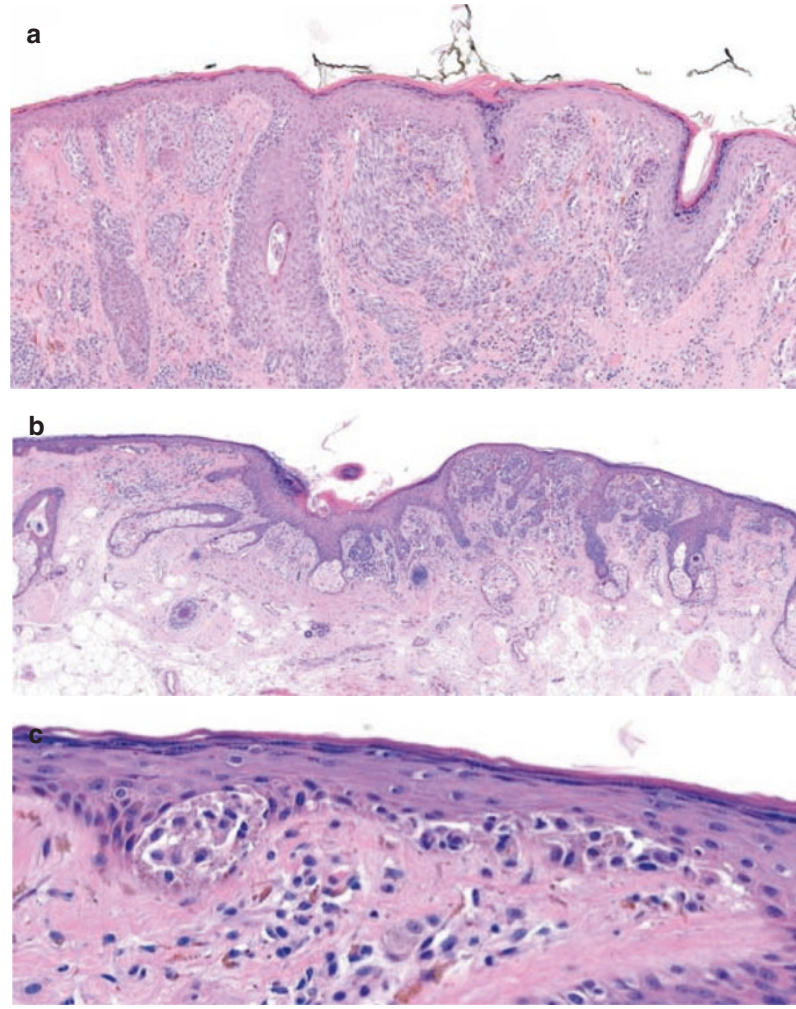


Fig. 4.9 (**a**) A compound melanocytic nevus removed from the ear, which has a lentiginous epidermal proliferation of melanocytes extending around adnexae. (**b**, **c**)

with variable cytological atypia, and dermal inflammation with fibrosis (Fig. 4.9). These lesions are wholly benign and important only insomuch as they risk being misdiagnosed as dysplastic or malignant.

4.3.5 Acral (Lentiginous) Melanocytic Nevus

Nevi on the hands and feet, particularly the palms and soles, including subungual lesions, frequently have a more irregular junctional architecture than is seen in nevi from non-acral sites, and essentially represent a specific example of special site nevus [19–21]. Clinically, acral nevi more commonly arise in pigmented skin as a brown-black macule. The histological irregularity can manifest as a greater lentiginous component, bridging of rete, central pagetoid scatter that in the case of palm or sole lesions may include large nests, and random cytological atypia (Fig. 4.10) [15, 21]. Nevertheless, lesions are usually well-circumscribed and symmetrical, there is often clefting between junctional nests and the epidermis, little atypia, and inflammation is characteristically absent. In compound lesions there will be dermal maturation.

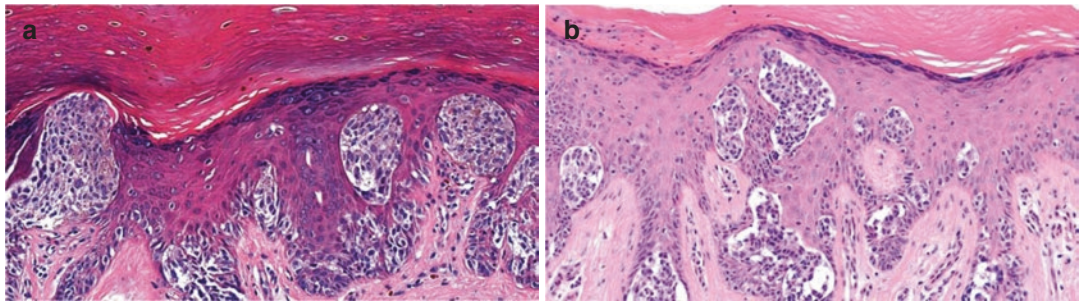


Fig. 4.10 (**a**, **b**) Two acral nevi, with large intraepidermal nests of melanocytes, including transepidermal elimination. Focal pagetoid scatter is also apparent

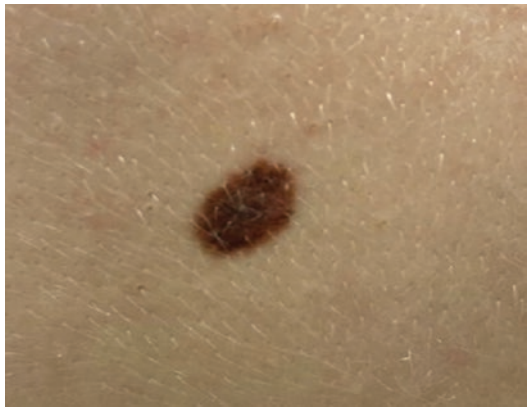


Fig. 4.11 A congenital nevus on the back

4.3.6 Congenital Nevus

Congenital melanocytic nevi (see Fig. 4.11) present at birth in 1% of individuals [22], or develop within the first year of life, commonly on the trunk and scalp. These are classified by size; small <1.5 cm, intermediate 1.5–20 cm, and giant >20 cm, the latter corresponding to the bathing trunk nevus. The risk of developing malignant melanoma is negligible in the smaller groups but ranges from 2 to 12% in the giant congenital nevi [23–27]. The nevus may be junctional, compound, or intradermal. In compound and intradermal tumors there is typically a widespread diffuse dermal population (Fig. 4.12a), with maturation, sometimes involving subcutaneous septae. Involvement of nerves, walls of blood vessels, arrector pili, and adnexae is common; perineural extension may be seen. Mitoses are absent or sparse. Proliferating nodules within congenital nevi form tumors of variable size that may be ulcerated, multifocal, and often worrisome [28, 29], although are far more numerous than malignant melanoma in this setting. Histologically, there is a circumscribed, apparently expansile population of dermal melanocytes (Fig. 4.12b), which may mimic blue nevi, melanocytoma, or even nevoid melanoma; reassuring features are the lack of cytological atypia, usually no or few mitoses, and no necrosis. The natural history of these nodules is one of regression [30], although locoregional nodal involvement may rarely occur. Neonatal tumors can be particularly alarming, with satellite lesions, ulceration, pagetoid spread, atypia and, in some cases, frequent mitoses [31, 32]. In such tumors, molecular analyses that demonstrate whole chromosome copy number changes can be reassuring [33, 34]. Bona fide melanoma, when it infrequently arises, does so in the dermis or subcutaneous tissue and is often aggressive [35].

4.3.7 Dysplastic Melanocytic Nevus

The existence of a histopathologically recognizable dysplastic melanocytic nevus (DMN) is accepted by a majority of dermatopathologists. A biologically intermediate category between benign acquired nevus and melanoma is supported by molecular studies, with DMN having a higher burden of mutations compared with benign lesions [36, 37]. One or more dysplastic nevi are found in 9–23% of the adult population [2, 38, 39], are usually >5 mm and variegated in

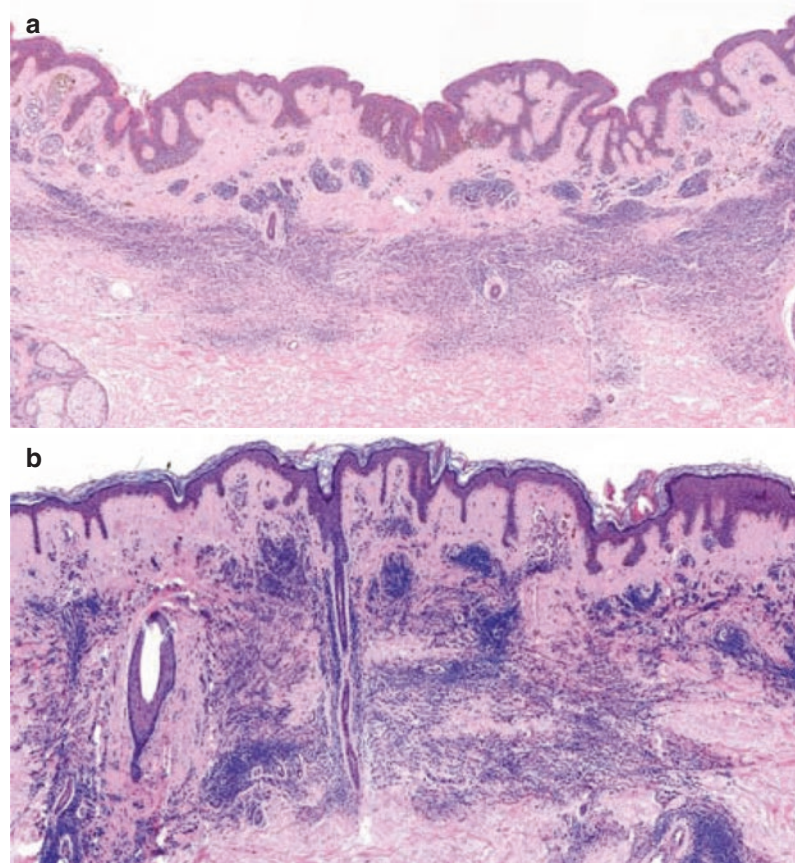


Fig. 4.12 Two congenital nevi. (**a**) A patchy irregular junctional component gives way to a widespread diffuse dermal population of melanocytes, also evident in (**b**). Melanocytes mature with depth but are irregularly distributed with intervening uninvolved dermal collagen

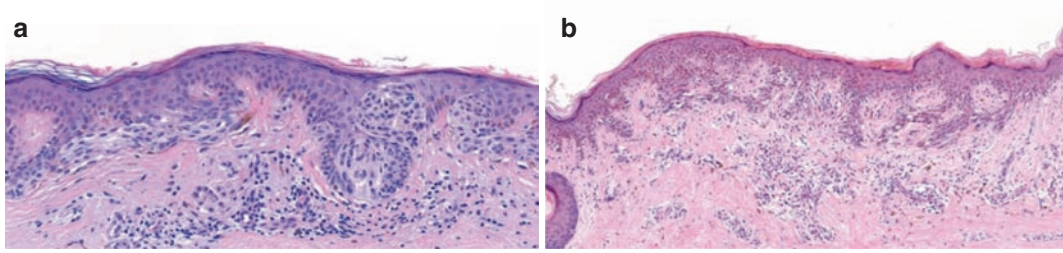


Fig. 4.13 Dysplastic melanocytic nevi should be >4 mm, and classified as (**a**) low or (**b**) high grade. In each case there are architectural and random cytological atypia, papillary dermal fibrosis, and light inflammation

color, often with a surrounding erythematous macule, the "shoulder" phenomenon.

Four principal histological features characterize DMN: architectural atypia; cytological atypia; lamellar fibrosis of the papillary dermis; and a perivascular inflammatory cell infiltrate (Fig. 4.13) [36, 40]. Architectural atypia denotes an irregular proliferation of nests and individual melanocytes with a lentiginous pattern; thus, in contrast to the regular melanocyte nests at the tips of rete ridges in common acquired nevi, there are also single melanocytes and variably sized nests at the sides of rete and tips of dermal papillae. Bridging of elongated rete ridges by often horizontally orientated spindle melanocytes is found. There may be "shouldering," the extension of the junctional portion beyond the dermal component. Cytological atypia manifests by

larger melanocyte nuclei, clumped chromatin, hyperchromasia, and variably prominent nucleoli; however, mitoses are usually absent. These cellular abnormalities are irregular in distribution and severity across the lesion, denoting "random cytological atypia." Lamellar and concentric fibroplasia is a characteristic pattern of stromal fibrosis within the papillary dermis around the rete ridges, surrounding melanocytes with wiry collagen. A variable perivascular lymphocytic infiltrate completes the criteria. As such changes are commonly found in small nevi [41–45], histological size >4 mm diameter is now a diagnostic requirement, corresponding to a clinical size of 5 mm or more [46].

The architectural and cytological atypia of DMN vary. At the less severe end of the spectrum distinction from common acquired melanocytic nevus, particularly if inflamed, traumatized, or located at a special site, may be challenging. Common acquired nevi may have some but not all of the diagnostic criteria. Conversely, DMN with more pronounced atypia need distinguishing from in-situ malignant melanoma. In general, DMN are <1 cm, do not show significant pagetoid spread or uniform cytological atypia, and junctional mitoses are usually absent. This variation gave rise to attempts to grade DMN, either using a three-tier—mild, moderate, and severe—or two-tier—low and high-grade—system. The significance of grading is supported by the observation that moderate-severe dysplasia more strongly associates with melanoma compared to mild dysplasia [47, 48]. Unfortunately, despite some reports concluding good reproducibility [49, 50] many attest to only poor-fair interobserver reproducibility of DMN recognition and grading [6, 51–53]. Attempts have been made in the past to combine dysplasia and in-situ melanoma into "melanocytic intraepithelial neoplasia" [39]. This was abandoned following criticism that inconsequential and significant lesions were categorized as equivalent, with inappropriate management. The Melanoma Pathology Study Group recommends a two-tier low- and high-grade system of classification as this is more reproducible (Fig. 4.13), reflecting meaningful variance with respect to the risk of melanoma [47, 48, 54]. Thus, the previous categories of moderate and severe dysplastic nevus are replaced with low-grade and high-grade dysplastic nevus, respectively; what was considered mild dysplastic nevus is no longer considered a dysplastic lesion.

4.3.8 Common and Cellular Blue Nevi

Proliferations of dendritic spindled melanocytes collectively form the dermal melanocytoses, believed to arise from latent dermal melanocytes arrested during neural crest development. These include the common blue nevus (BN), nevus of Ota and nevus of Ito, and congenital dermal melanocytosis. BN are located most often on the scalp, face, buttock, and distal extremities in young-middle aged adults, presenting as a blue-black macule or papule, ranging from 2 to 3 mm to 0.5 cm [55]. Histologically, beneath a grenz zone there is a poorly circumscribed proliferation of heavily pigmented spindled dendritic melanocytes in the mid-deep dermis parallel to the usually normal epidermis (Fig. 4.14a). Admixed melanophages are often conspicuous. Cells lie in loose fascicles, with intervening often fibrotic dermis; "sclerosing blue nevus" (Fig. 4.14b) designates those lesions in which this is prominent [16]. Such lesions can easily be mistaken for mesenchymal tumors, e.g. dermatofibroma. Atrophic or hypopigmented BN are paucicellular, closely resembling the usually more subtle nevi of Oto and Ito, and readily missed [56, 57]. Blue nevi can extend along appendages, show perineural extension (Fig. 4.14c), or involve blood vessel walls [55]; these do not indicate malignancy. Conversely, cytological atypia, mitoses, and inflammation are not found in most cases and if present invite consideration of atypical or malignant BN.

Cellular blue nevus (CBN) is most often found on the scalp, back, and buttocks of adults, with a modest predilection for females, as slow-growing pigmented blue-black nodules usually 1–2 cm [55]. Histologically, well-circumscribed nodular proliferation of melanocytes "bulge" into the

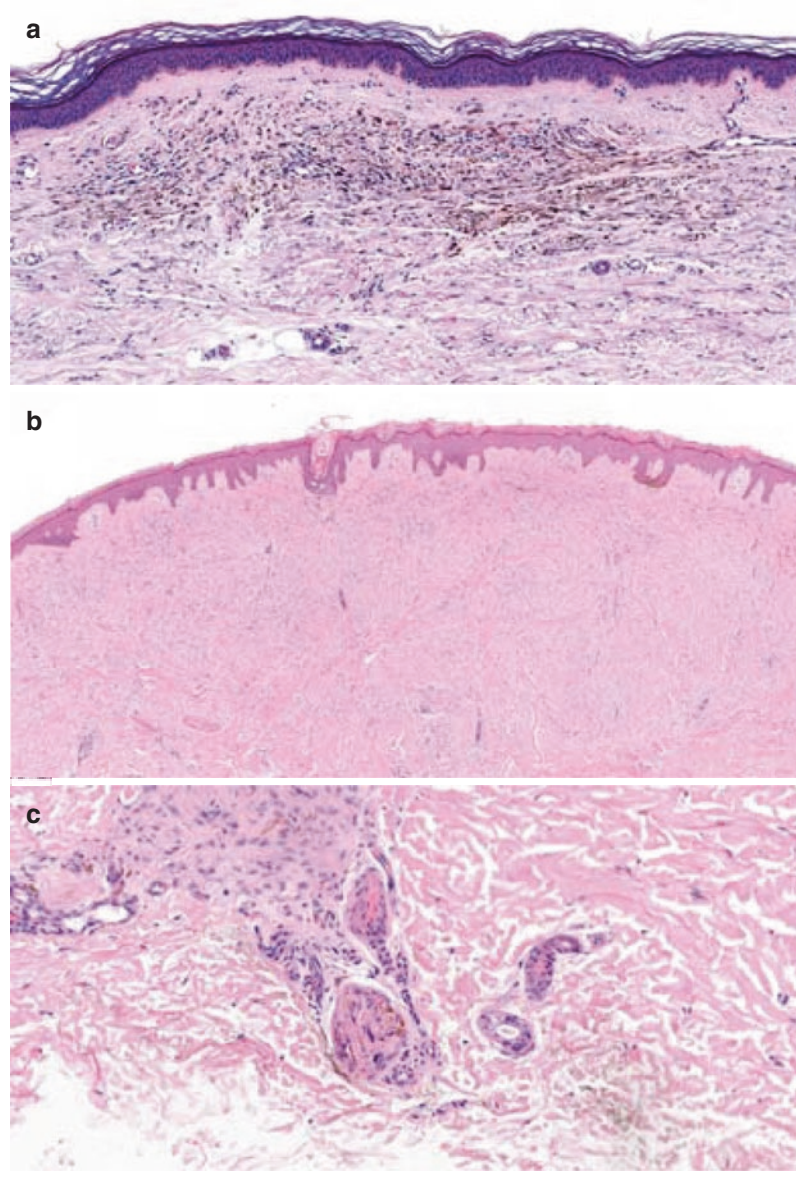


Fig. 4.14 (**a**) Common blue nevus, heavily pigmented dendritic melanocytes parallel to the epidermis. Infiltrative growth, atypia, and inflammation are absent. (**b**) Sclerosing blue nevi are easily mistaken for mesenchymal tumors. (**c**) Perineural extension should not be taken to portend a malignant diagnosis

deep dermis and the fascial planes of subcutaneous tissue taking on a characteristic vertically orientated "dumbbell-shaped" architecture (Fig. 4.15). There are admixed epithelioid and plump spindled cells, having abundant pale cytoplasm, inconspicuous nucleoli and little pigment, in diffuse sheets. The cells are arranged parallel to the long axis of the nests and fascicles. Maturation is not present although mitoses are sparse; perineural extension may be found [55]. Nevertheless, there is no atypia, pleomorphism, or necrosis. Admixed features of a common BN are discernible. The majority of the pigment lies within melanophages, which can be numerous. Sclerotic (desmoplastic), hypomelanotic, and myxoid variants are recognized [55, 56, 58, 59]. BN and CBN are genetically characterized by GNAQ and GNA11 activating mutations.

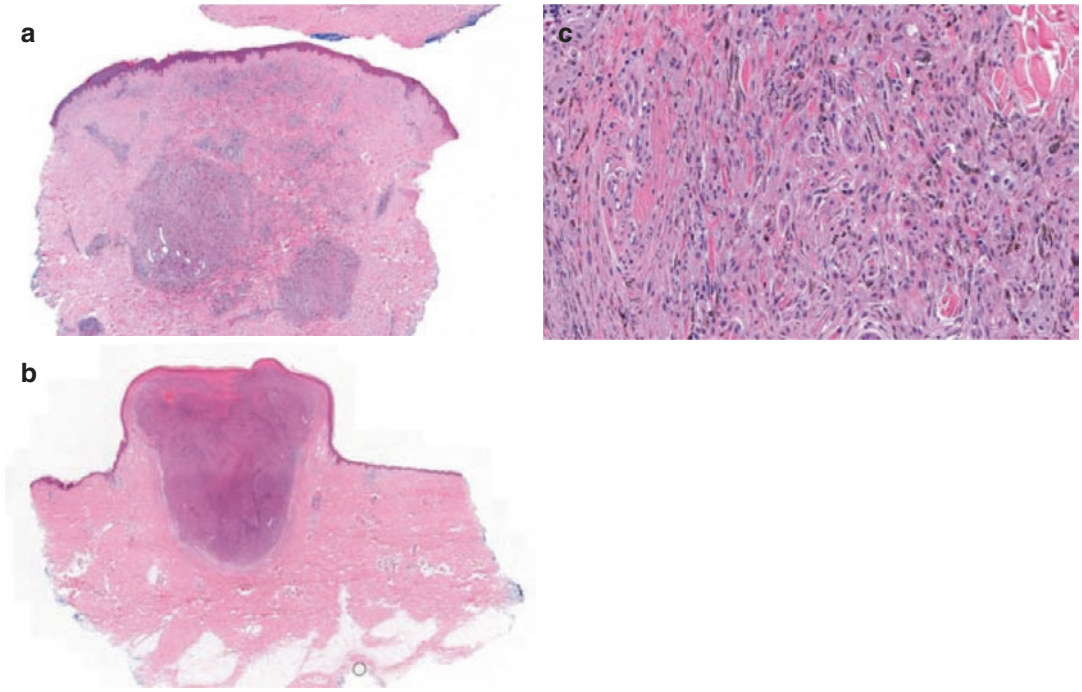


Fig. 4.15 (**a**, **b**) Two cellular blue nevi, which often comprise large nodules throughout the dermis, formed of (**c**) fusiform spindled and some epithelioid cells with admixed pigmented macrophages, and often a focally fibrotic stroma

4.3.9 Spitz Nevus

In 1948, Sophie Spitz described a distinct melanocytic proliferation in children, histologically resembling melanoma, but with a favorable prognosis [60]. Spitz nevus (see Fig. 4.16) represents around 7% of surgically removed pigmented lesions in children [61], although it not uncommonly arises in adults [62]. It presents as a symmetrical, <5 mm smooth pink-red papule or polypoid nodule, often mistaken for a vascular tumor or dermatofibroma, on the face, trunk, or proximal limb. An initial period of rapid growth and traumatic ulceration can occur. Clinical variants include multiple or agminate and pigmented lesions [63]. Histologically, most are well-demarcated symmetrical compound nevi extending into the reticular dermis (Figs. 4.17a and 4.39a). Epidermal hyperplasia, sometimes marked, is common, overlying telangiectatic blood vessels in the papillary dermis. Kamino bodies (PAS+ amorphous eosinophilic globules) often lie at the dermoepidermal junction but are not pathognomonic [62, 64]. The junctional component is composed of nests of spindled and epithelioid melanocytes, in vertical orientation to the epidermis imparting a "raining down" architecture; clefting between the melanocytic nests

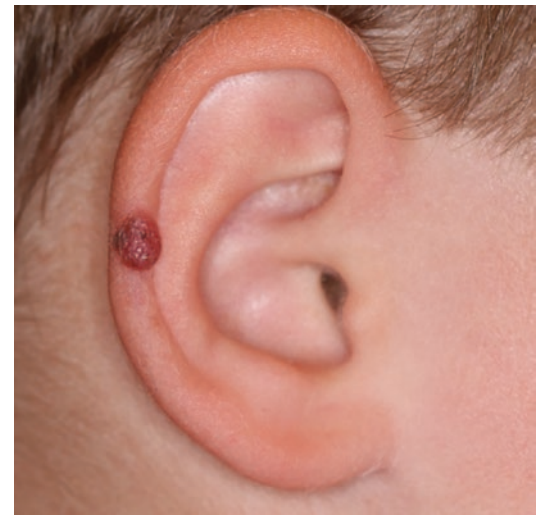


Fig. 4.16 A Spitz nevus on the right ear

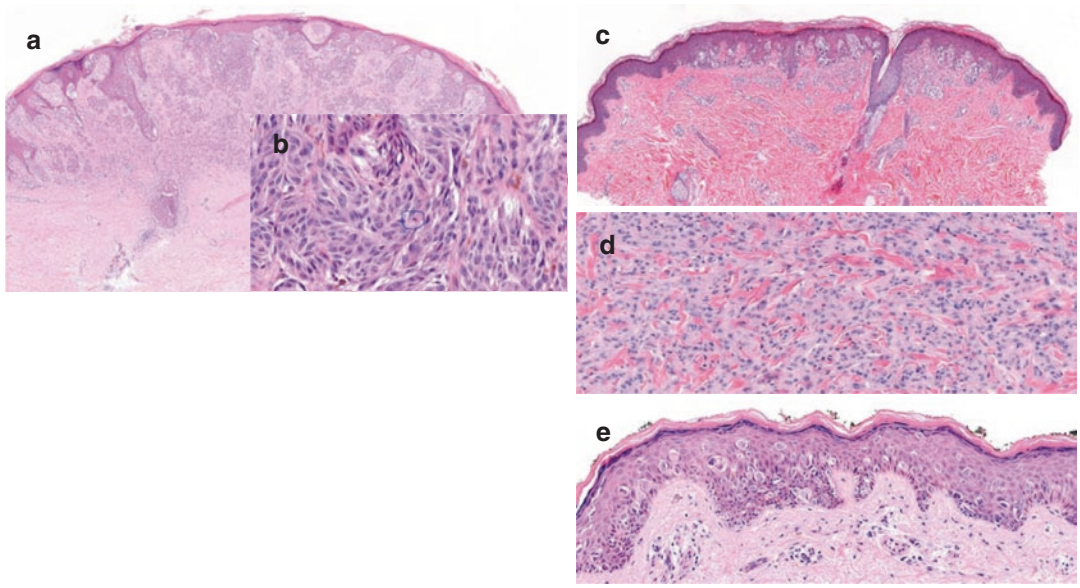


Fig. 4.17 (**a**) Prototypic Spitz nevus in a child; a compound lesion, with raining down of spindle cells into the dermis; maturation is present, although a few mitoses (**b**) are not uncommonly found. Junctional (**c**) and intradermal (**d**) Spitz nevi. Some junctional Spitz can have florid intraepidermal growth (**e**)

and the epidermis is characteristic. Pagetoid spread of melanocytes, usually limited to the lower half of the epidermis and the central portion of the lesion, is not uncommon [62]. There is maturation of melanocytes with depth; at the base of the lesion, individual small cells intersect dermal collagen. Mitoses can sometimes be found (Fig. 4.17b), particularly superficially, but are not numerous. The characteristic Spitz cytology is of large cells with voluminous eosinophilic cytoplasm, vesicular nuclei, and prominent basophilic nucleoli. A patchy dermal perivascular lymphocytic infiltrate is common [62]. Halo reactions, similar to those seen in common acquired nevus, are described [65].

Intraepidermal Spitz nevi (Fig. 4.17c) most commonly arise on the leg as circumscribed pigmented small macules [66]. Histologically, these are readily mistaken for melanoma in-situ, having large individual melanocytes, with characteristic Spitzoid cytology, arranged irregularly within the epidermis, with suprabasal spread (Fig. 4.17e). Usually, however, the latter does not involve the higher epidermis and, despite this irregularity, there is an organized appearance to the proliferation, which is circumscribed and symmetrical within a uniformly mildly acanthotic epidermis and absence of cytological atypia [66]. Purely intradermal Spitz nevus is often desmoplastic, with a wedge-shaped population of pleomorphic individual cells having conspicuous nucleoli, embedded within a densely fibrotic stroma. Intranuclear pseudoinclusions are common but mitoses are rare [67, 68] (Fig. 4.17d). Considerable molecular data have accrued concerning Spitz nevus and, interestingly, molecular events can have correlates with specific recognizable subtypes of Spitz lesions. Thus, 11p amplifications, with HRAS mutations, are common in desmoplastic Spitz nevus. Angiomatoid desmoplastic Spitz designates a subtype in which melanocytes are admixed with a prominent proliferation of small blood vessels [69].

Classical Spitz nevus is an overwhelmingly benign lesion that has a very low recurrence rate if completely excised. Partial excisions are not advised, and recurrent Spitz can present similar diagnostic challenges as recurrent common acquired nevus.

4.3.10 Reed Nevus

The pigmented spindle and epithelioid nevus of Reed most commonly presents as a deeply but uniformly pigmented 2–5 mm well-demarcated papule on the thigh (75%), arm, or trunk, in young adult females [70–72]. The nevus is mainly junctional and sharp lateral circumscription is a characteristic feature at scanning magnification (Fig. 4.18a). There are heavily pigmented large junctional fascicular nests of spindled melanocytes, in a moderately acanthotic epidermis with elongated rete; pagetoid spread is common, although it is usually concentrated toward the center of the lesion (Fig. 4.18b). Clefting between junctional nests and the epidermis, and occasional Kamino bodies [73], underlines the similarity to pigmented Spitz nevus with which it may form a spectrum. The cells are spindled and fusiform, sometimes with mitoses. Nuclei are delicate and nucleoli, whilst often identifiable, are small. The usually limited dermal component is restricted to the upper dermis and consists of similar cells [71, 74–76]. Some lesions are larger, e.g. >5 mm, display less conspicuous lateral circumscription, and may have more pronounced pagetoid spread and/or toward the edge of the lesion; such examples of "atypical" Reed's nevus need distinction from radial growth phase malignant melanoma, superficial-spreading variant [71, 76]. FISH molecular analysis may be useful in such cases [77].

4.4 Intermediate Nevi

These nevi are less well characterized or understood than the previous group. Thus, there is uncertainty regarding the true nature of the class of lesions, and the biological potential of any individual tumor. In general, there should be some caution regarding prognostication, and complete removal is prudent.

4.4.1 Deep Penetrating Nevus

Described in 1989 deep penetrating nevus (DPN), closely related to plexiform spindle cell nevus [78, 79], accounts for approximately 0.01–0.05% of melanocytic lesions [79]. Most commonly found in younger adults, on the face, trunk, proximal limb, as a single symmetrical deeply pigmented dome-shaped polypoid nodule, 0.5–1 cm, it is not infrequently mistaken clinically for melanoma [80, 81]. Histologically, there is a normal epidermis and a well-demarcated striking wedge or V-shaped bulbous architecture on scanning magnification, with the broad base uppermost, extending into the deep dermis or subcutis (Fig. 4.19a, b). The tumor is comprised of fascicles of spindled and plump fusiform cells (Fig. 4.19c) and variable numbers of admixed epithelioid cells. Permeation of arrector pili, hair follicles, and nerves is characteristic (Fig. 4.19d, e). Melanophages are frequently present. Cytologically, the cells are moderate in size,

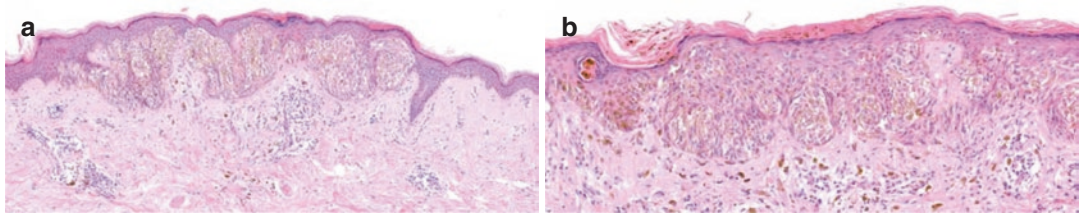


Fig. 4.18 (**a**) The typical sharp peripheral circumscription and heavy pigmentation of the spindle cell nevus of Reed. (**b**) Toward the center there is an untidy pattern, including suprabasal spread of cytologically banal pigmented melanocytes

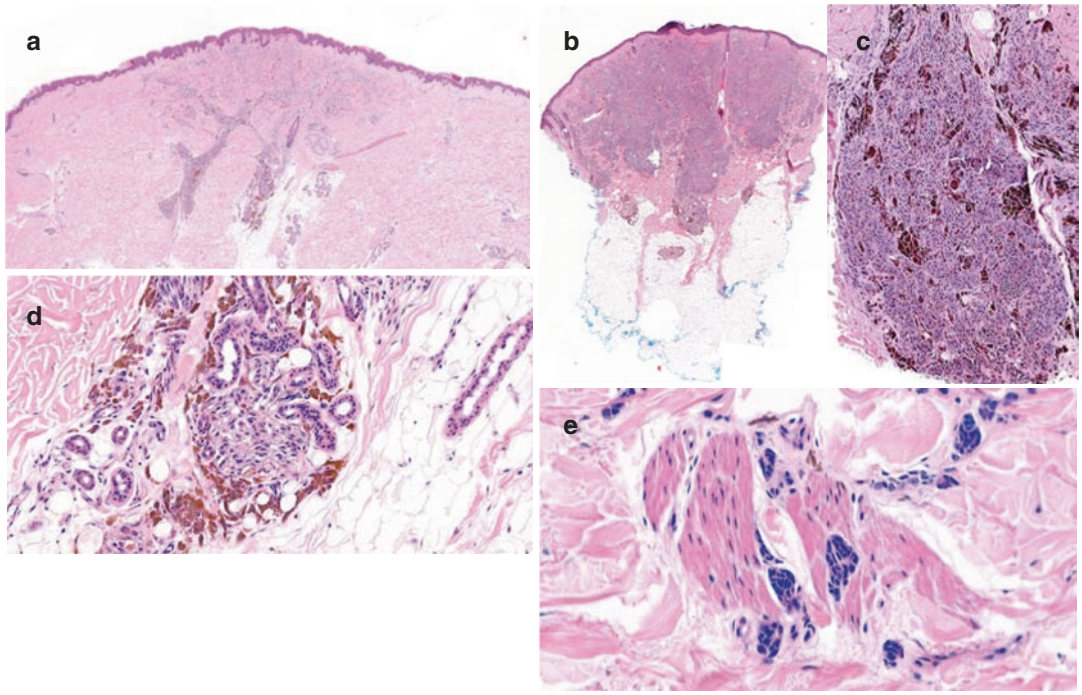


Fig. 4.19 (**a**, **b**) The characteristic architecture of deep penetrating nevus on scanning magnification. (**c**) Plump spindle cells, without maturation, and occasional mitoses often cause concern. Involvement of adnexae, arrector pili, and the neurovascular bundle is common (**d**) and (**e**)

often have mild-moderate pleomorphism but nucleoli are not usually prominent; 1–2 mitoses may be seen but are seldom more numerous. Nuclear pseudoinclusions are common. An appreciable proportion of DPN have admixed features of common acquired nevus, and/or dendritic spindle cells similar to blue nevus. There appears, therefore, to be overlap with combined melanocytic nevus [78, 80–82]. Features that can cause concern include asymmetry—particularly in those lesions with admixed other forms of nevi, cytological atypia, lack of maturation, mitotic activity, and inflammation. One or more of these is not uncommon in DPN [80, 82] but are not associated with an aggressive clinical course. These lesions are benign and local recurrence is very rare. Nevertheless, there are lesions, usually larger than usual and affecting an older age group, with more pronounced atypia and both deeper and increased mitotic activity, that lie outside the usual expected limits and are designated "atypical" or "borderline" DPN, or melanocytoma, indicating uncertain biological potential, including the potential to spread to locoregional lymph nodes; and examples of malignant DPN are reported [79, 83, 84]. The vast majority of DPN are benign and can be treated as such, but precise histological criteria for the distinction between these common, atypical/borderline, and malignant variants are not yet established [85, 86].

4.4.2 Combined Melanocytic Nevus

The existence of two or more histological types of nevus in a single lesion designates a combined melanocytic nevus. Most commonly these are common acquired and blue nevus (Fig. 4.20), or DPN with common acquired nevus or blue nevus. However, any combination is possible. In most cases these are entirely benign. Clinically and histologically they may be mistaken for melanoma due to asymmetry, irregular pigmentation, and the observation of melanocytes having vari-

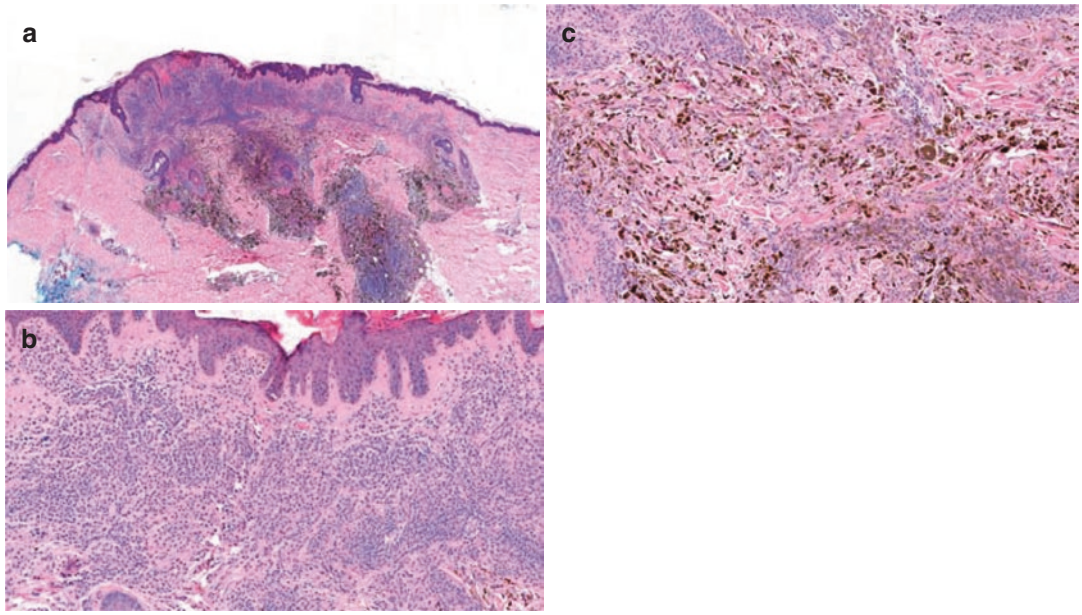


Fig. 4.20 (**a**) Combined melanocytic nevus, which is formed of (**b**) common acquired and (**c**) cellular blue elements

able cytology [87]. Recognition of the component nevi allows them to be individually evaluated according to their respective characteristic morphological features.

Wiesner, BAP-1 inactivated, nevus is a specific subtype of combined nevus, which can be germline or somatic, the former being associated with an increased risk of melanoma and non-cutaneous cancers [88]. Both sporadic and inherited forms of the nevus commonly arise on the trunk, extremities, head and neck, presenting as flesh-colored to brown dome-shaped papules. Histologically, these are mainly intradermal nevi often comprised of two distinct populations (Fig. 4.21); (Spitzoid) epithelioid cells with well-defined cytoplasmic borders, amphophilic cytoplasm, vesicular nuclei and prominent nucleoli, and smaller more regular nevocytes akin to acquired nevi. The Spitzoid cells may form an expansile nodule but mitoses are rare. Inflammation is common with "kissing" lymphocytes [89, 90]. Immunohistochemistry demonstrates lack of BAP-1 protein in the Spitzoid epithelioid cells, which also harbor BRAF mutations. Associated regular nevocytes retain BAP-1 expression. Thus, BAP-1 inactivated nevus can be considered a specific form of combined (Spitz and common acquired) nevus [91], Halo Spitz nevus or a subtype of Atypical Spitz Tumor [66, 88, 89]. The risk of progression to overt melanoma is unclear but likely low.

4.4.3 Pigmented Epithelioid Melanocytoma

This is a rare melanocytic tumor, which nosologically includes epithelioid blue nevus and animal-type melanoma [58, 87], that presents as a blue-black solitary nodular lesion on the extremities or trunk of children. Larger tumors may be ulcerated [92]. Most are sporadic [93] but it may form part of the Carney Complex. Histologically, it is a well-defined dermal tumor, sometimes with an inverted wedge-shaped scanning architecture, of interstitial heavily pigmented cuboidal epithelioid and dendritic spindled cells within short fascicles (Fig. 4.22). Intense pigmentation can obscure melanocytes [94] and be mistaken for tumoral melanosis. The spindle cells resemble those of blue nevi except have prominent nucleoli and there may be pleomorphism and multinucleation; necrosis can be found. However, mitoses are usually sparse. Some cases have a common

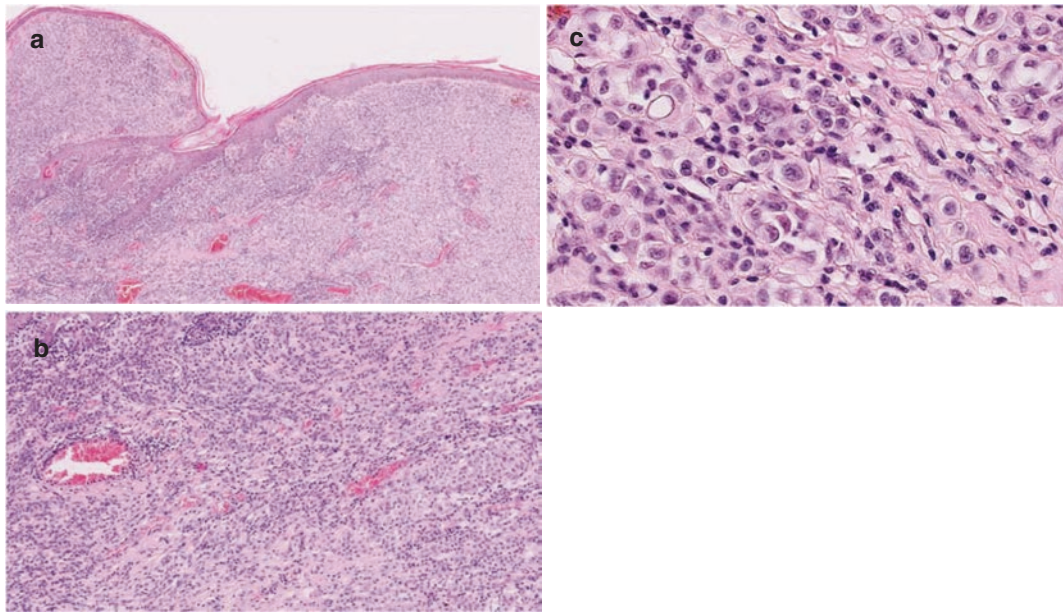


Fig. 4.21 (**a**, **b**) BAP-1 inactivated nevus, comprising two populations of nevocytes; smaller type B nevocytes visible to the left of the images, with larger epithelioid cells toward the center and right. The larger epithelioid cells have a Spitzoid cytology (**c**); note the admixed lymphocytes. These Spitzoid cells lack BAP-1 expression by immunohistochemistry. Image courtesy of Dr. Gerardo Ferrara MD, Anatomic Pathology Unit, Hospital of Macerata, Macerata, Italy

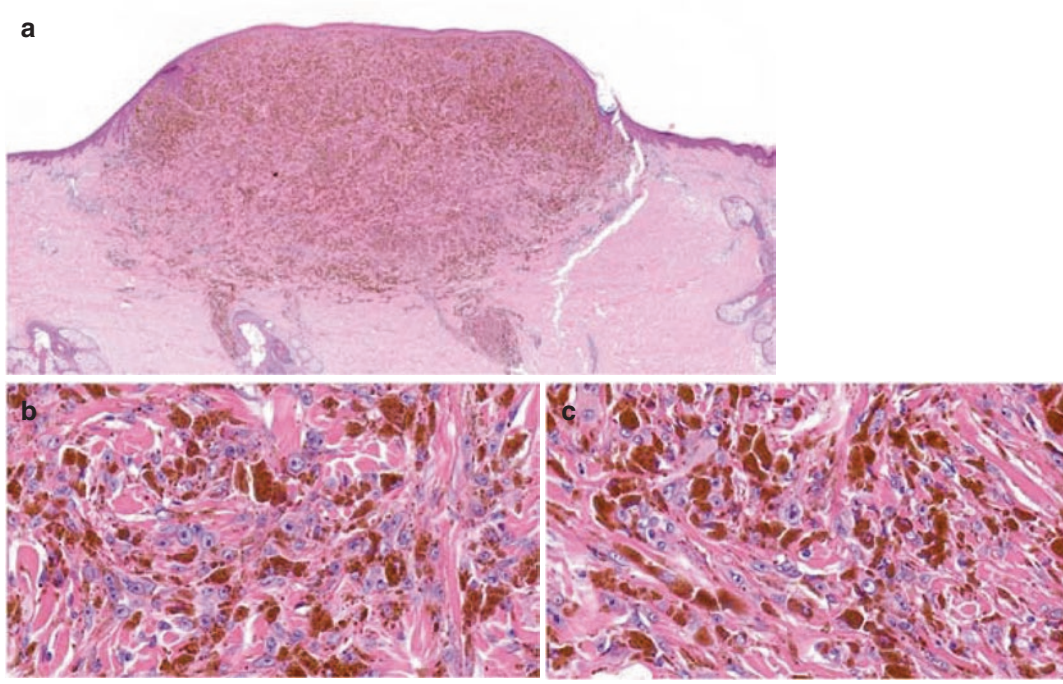


Fig. 4.22 (**a**) Scanning magnification of a pigmented epithelioid melanocytoma, comprised of a diffuse interstitial population of epithelioid melanocytes having large nuclei and prominent nucleoli. Multinucleate forms and Reed Sternberg-like cells are not uncommon (**b**, **c**)

acquired component, indicative of a relationship to combined nevus. The significance of the tumor lies in the potential for locoregional nodal metastases [58, 92, 95, 96], yet a favorable long-term outcome. An exceptional case is reported to have metastasized to viscera [95] and therefore prognostication of these very rare tumors is difficult. Thus, universally accepted guidelines for the management of PEM are not established. Complete excision should be effected, and if the tumor extends close or up to a surgical margin then a modest re-excision is prudent. Routine sentinel node sampling has little to recommend it, but lymphoscintigraphic identification of the node with subsequent monitoring by high-resolution imaging enables early recognition of growing nodal deposits that might signal a rare malignant PEM and allow removal with the possibility of adjuvant therapy.

4.5 Malignant Melanoma

The rationale for pathological examination of melanocytic lesions is to exclude malignant melanoma, and, in cases of malignancy, to provide prognostic information. Most melanomas have significant histological deviation from the characteristics of the parent nevi outlined above. Thus, any number of the following may be found: ulceration, asymmetry, poor lateral circumscription, irregularity of melanocyte distribution within the epidermis including pagetoid spread and/or confluent lentiginous growth, cytological atypia including increased numbers of (sometimes atypical) mitoses, lack of dermal maturation, vascular invasion, fibrosis, and an inflammatory cell response. Some appreciation of the difficulties that can confront pathologists is gleaned when considering that, of these, any individual observation save vascular invasion, may be identified in a benign nevus, and one or many absent from a given melanoma. It is the constellation of features that in most cases allows the ready distinction between nevus and melanoma. For this reason, any clinically atypical lesion suspected of melanoma should be removed in its entirety; partial biopsies should be avoided except in limited specific circumstances.

Architectural criteria designate the four most common morphological subtypes of melanoma, viz. superficial spreading, lentigo maligna, nodular [97], and acral lentiginous [98], with approximately 3% of melanomas having unclassifiable features [99]. The principal distinguishing histopathology is found in the intraepidermal compartment. There is increasing recognition that melanomas arise through diverse genetic routes, and classification schemes are shifting toward a molecular basis. Nevertheless, identifying malignancy remains primarily a morphological exercise. Included in this section are atypical forms of some of the nevi previously discussed; whilst these are usually associated with a benign clinical course, they are rare and present an alarming histopathology such that distinction from malignancy may not always be made with confidence.

(a) Superficial-spreading melanoma (SSM)

Particularly prevalent in people of fairer skin types, these lesions arise in adults as irregular variably pigmented tumors, often >1 cm (see Fig. 4.23). The characteristic initial intraepidermal or radial growth phase is a

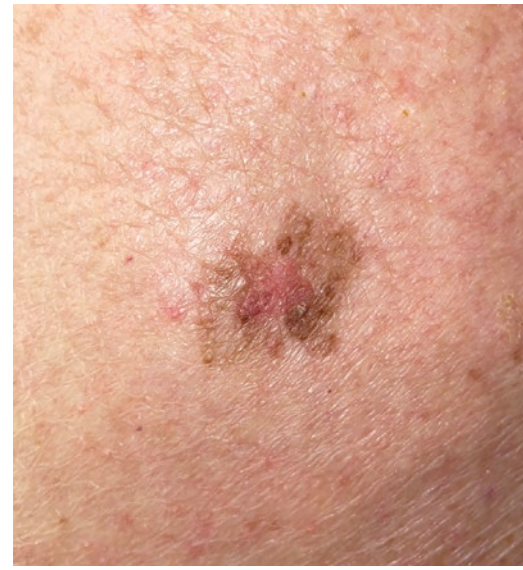


Fig. 4.23 A superficial-spreading melanoma on the back

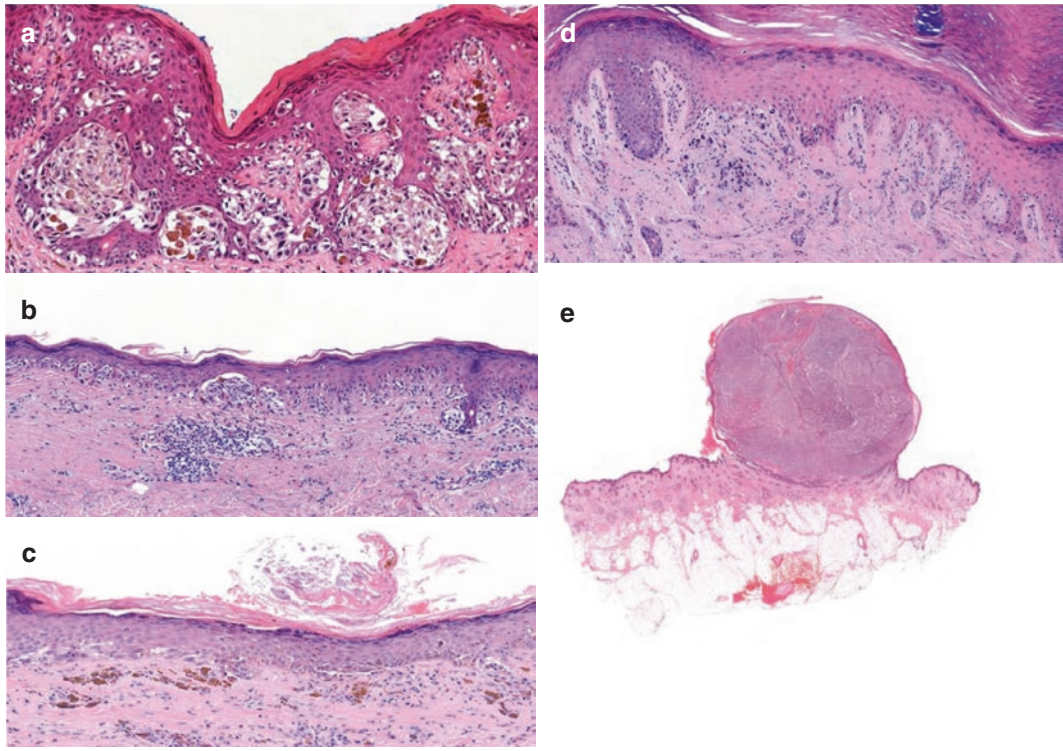


Fig. 4.24 The radial growth phases (RGP) of the three common melanoma subtypes, (**a**) and (**b**) Pagetoid and lentiginous patterns of superficial-spreading melanoma; (**c**) Lentigo maligna and (**d**) Acral lentiginous melanoma. (**e**) A nodular melanoma lacking RGP

striking intraepidermal pagetoid proliferation of uniformly cytologically malignant epithelioid cells, in nests and as individual cells, at all levels of the epidermis (Fig. 4.24a, b). Lentiginous examples have cells distributed preferentially along the basal layer of the epidermis with little suprabasal spread [100]. The epidermis is usually acanthotic, and dermal solar elastosis is mild. Confluent proliferation of malignant cells may lead to epidermal consumption and clefting around groups of tumor cells, rare in benign melanocytic tumors, eventuating in ulceration [101, 102]. The malignant cells display pleomorphism, large nuclei, coarse clumped chromatin, prominent nucleoli, and often readily identified mitoses. Kutzner *et al* reported a morphologically distinct form of SSM (Fig. 4.25) in which large junctional nests of melanocytes dominated the histopathology, such that subtle "background" pagetoid epidermal spread was easily missed without immunohistochemistry [103].

The spread of malignant cells into the dermis denotes invasive disease. The invasive cells typically possess clearly malignant cytological characteristics; pleomorphic enlarged cells and coarse hyperchromatic chromatin with prominent large nucleoli. Up to one third of SSM arise from a pre-existing nevus, and residual benign melanocytes are not infrequently identified. By convention, the epidermal growth phase should extend lateral to the dermal malignancy. Some cases of SSM have balloon change of the malignant cells, as seen in balloon nevus, but differing in having cytological atypia and mitotic figures; aside from mimicking non-melanocytic tumors there is no additional significance to "balloon cell melanoma" [7].

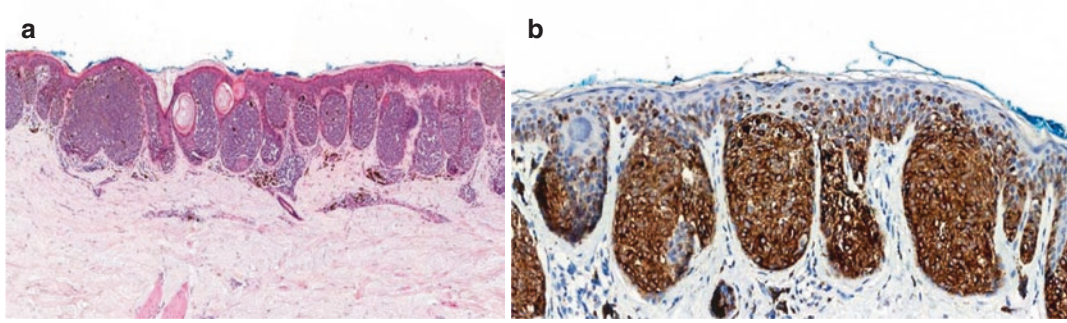


Fig. 4.25 (**a**) Nested actinic melanoma, a morphological subtype of SSM, has deceptively innocuous albeit large nests of melanocytes. Nevertheless, there is cytological atypia and immunohistochemistry (**b**. Melan A) demonstrates background pagetoid proliferation of intraepidermal melanocytes

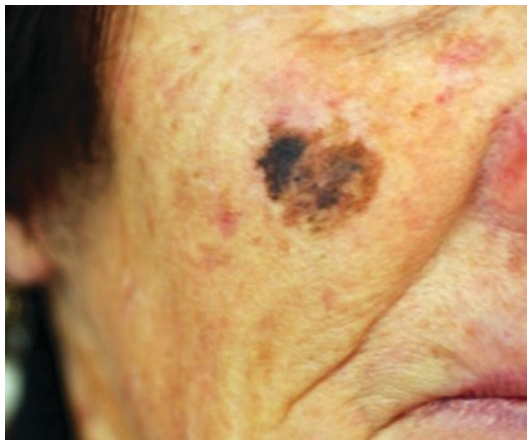


Fig. 4.26 A lentigo maligna melanoma on the right cheek. (*Courtesy of the Department of Dermatology, Instituto Português de Oncologia de Lisboa, Portugal)*

(b) Lentigo maligna melanoma

Lentigo maligna (LM) and lentigo maligna melanoma (LMM) (see Fig. 4.26) denote the intraepidermal and invasive phases, respectively, of malignant melanomas that arise on chronically sun-damaged skin, therefore presenting in older adults at anatomic sites reflecting long-standing continuous UV exposure; head and neck, including cheek, nose, forehead, scalp and ears. There is a poorly circumscribed pigmented or erythematous patch, which develops a plaque or nodule when invasive, sometimes up to 10 years after the initial lesion presented. The high cumulative solar-induced skin damage is manifest histopathologically by marked solar elastosis and epidermal atrophy (Fig. 4.33). The distinctive intraepidermal growth phase of LM is confluent lentiginous proliferation of atypical melanocytes within the basal epidermis (Fig. 4.24c). Initially there may be only mild pleomorphism, with angulated hyperchromatic nuclei, progressing in later stages to more pronouncedly malignant features; large cells and nuclei, coarse chromatin and prominent nucleoli. The later stages of the in-situ component may display some nesting of malignant melanocytes, with dyshesion [99], and pagetoid spread that can cause confusion with SSM. A less common morphological pattern mimics a dysplastic nevus, having nests of atypical melanocytes and bridging of rete; in practice, the diagnosis of dysplastic melanocytic nevus on chronically sun-damaged skin should be viewed critically.

Extension down adnexal (Fig. 4.27), particularly hair follicular, epithelium, is typical, and, if obliquely sectioned, may mimic true dermal invasion. An additional malignant dermal population, often having a spindle cell morphology, designates lentigo maligna melanoma [97], associated with desmoplasia in 10–15% [99].

(c) Nodular melanoma

Nodular melanoma (see Fig. 4.28) presents as a darkly pigmented, sometimes polypoid, nodule on the trunk or limbs of adults; ulceration is common. Histologically, an often ulcerated polypoid thick tumor is com-

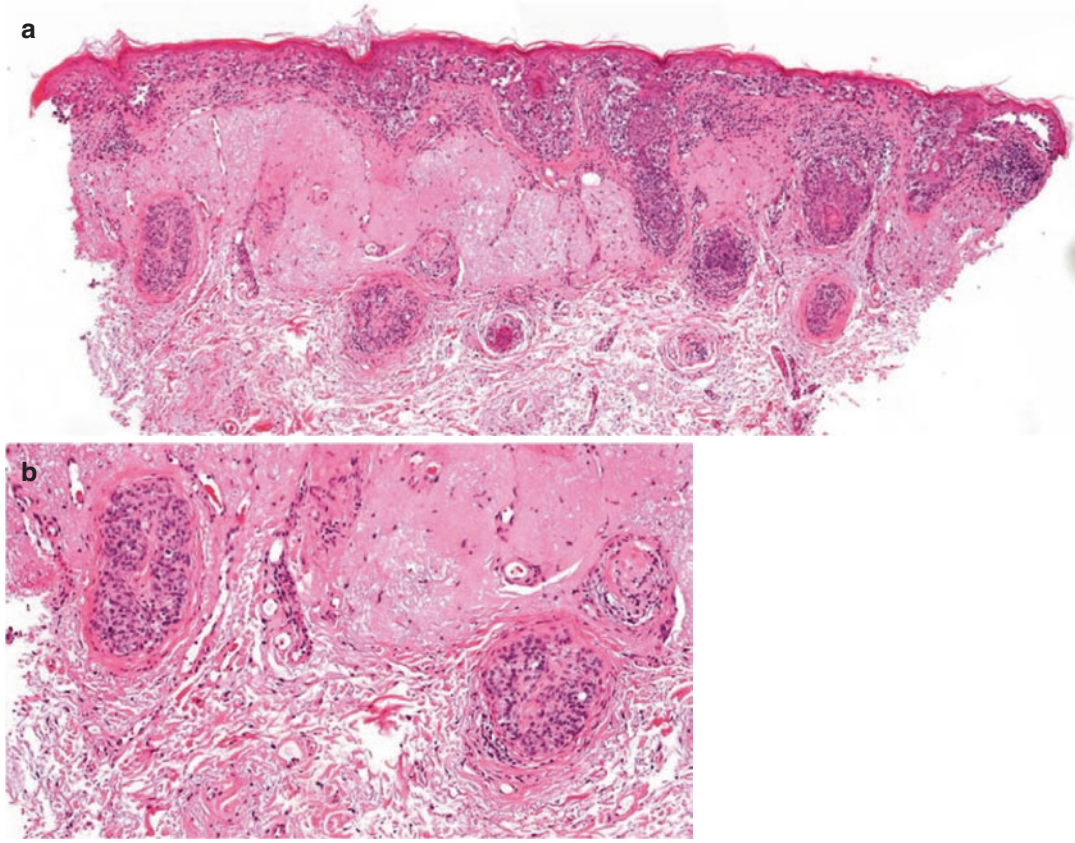


Fig. 4.27 (**a**, **b**) Extensive colonization of adnexae in LM can mimic true dermal invasion, particularly depending upon the plane of section

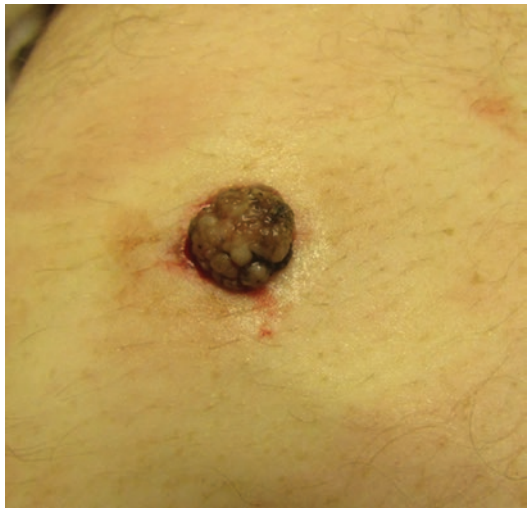


Fig. 4.28 A nodular melanoma on the right thigh

prised of large expansile sheets of clearly cytologically malignant usually epithelioid cells filling the dermis [99, 104]; spindle cells are sometimes present. Mitoses are often numerous. These tumors can be difficult to distinguish from melanoma metastases, particularly if the latter are epidermotropic. In general, a sharp circumscription of a tumor, almost entirely within the dermis, favors a metastasis. Conversely, overlying fibrosis, inflammation, and melanophages suggests regression of an initial more superficial component and therefore primary status. Necrosis is rare in primary melanoma but is often present in metastases. Nodular melanoma lacks an intraepidermal component lateral to the dermal malignancy

(Fig. 4.24e). By definition, in-situ disease cannot exist. Genetic analyses report findings that mirror those identified in SSM, LM, and acral melanoma supporting the concept of nodular melanoma as a final tumorigenic pathway of these histological subtypes [105].

(d) Acral lentiginous melanoma

Acral lentiginous melanomas (see Fig. 4.29) usually arise in adults on the soles, palms, digits—particularly the thumb or big toe, and in subungual sites, the latter accounting for around 20% of all acral melanoma. It is the most common melanoma in Hispanic, Asian, and African people. Lesions present as asymmetric and irregular black macules or tumors, sometimes ulcerated. Verrucous lesions can simulate plantar warts or pyogenic granulomas. Subungual lesions give rise to melanonychia. Nevertheless, this is a histological not anatomic designation; both superficial-spreading and nodular melanoma can arise at acral sites [106]. In practice, acral junctional proliferations in patients aged over 50 should be considered suspicious. The intraepidermal phase is formed of lentiginous melanocytes in the basal epidermal layer, which denotes acral lentiginous melanoma in-situ. Early lesions may be subtle and easily mistaken for a benign lesion [107], with irregular epidermal hyperplasia and only scattered basally located mildly atypical dendritic spindled or epithelioid melanocytes; there is increasing atypia as the lesion progresses [98, 108] (Fig. 4.24d). A study of acral lesions suggested that marked cytological atypia is the most reliable discriminant between benign and malignant lesions, and inflammation is a helpful pointer toward malignancy [19, 109]. Subungual lesions begin as a lentiginous proliferation of atypical melanocytes within the nail matrix, becoming confluent with pagetoid spread of atypical cells. Malignant cells within the dermis indicate invasive acral lentiginous malignant melanoma (ALMM), in which the cells are often very atypical, with large pleomorphic nuclei and coarse chromatin; both epithelioid and spindled cells are often present. The invasive component of acral melanoma is not infrequently desmoplastic [109]; other unusual cytological features include clear cell or giant cell change and, rarely, chondroid or osteogenic differentiation [110, 111].

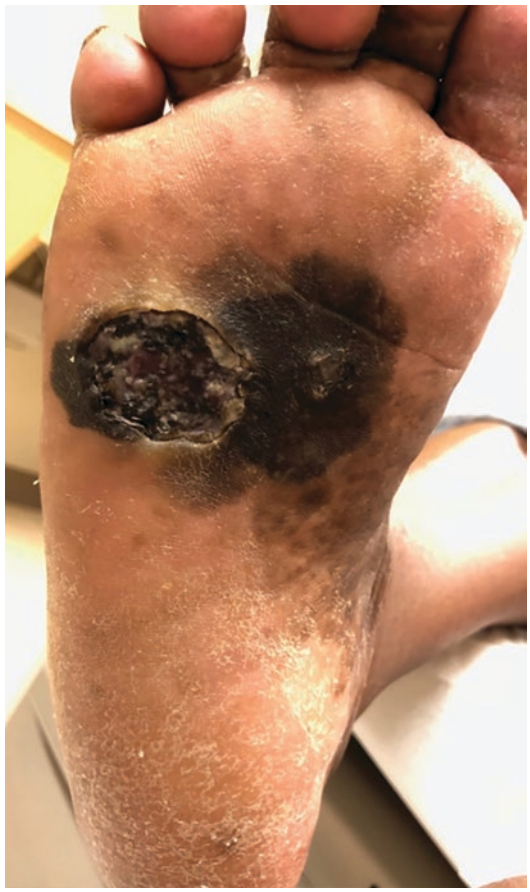


Fig. 4.29 Acral lentiginous melanoma on the right plantar foot

4.5.1 In-Situ Melanoma, Radial and Vertical Growth Phases

LMM, SSM, and ALMM each has a morphologically distinctive intra-epidermal pattern of proliferation of melanoma cells, the radial growth phase (RGP) component (Fig. 4.24a–d), which largely determines these diagnostic subtypes; if this is the only compartment the tumor occupies, the disease is considered in-situ (see Fig. 4.30)

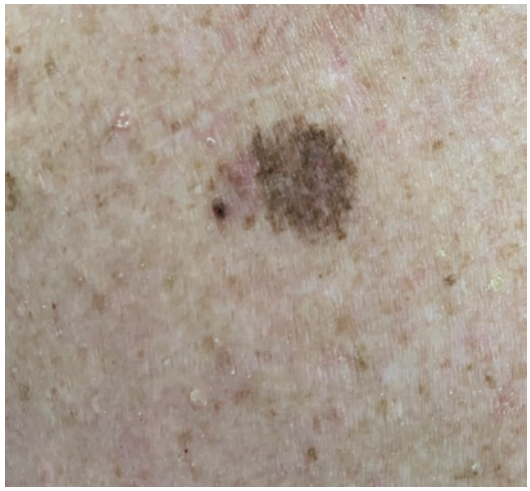


Fig. 4.30 In situ melanoma on the back

Table 4.2 Melanocytic lesions with variable intraepidermal irregularity, including pagetoid spread, potentially causing diagnostic difficulty

Recurrent nevus
Special site nevus
Reed nevus
Spitz nevus
Intraepidermal/superficial atypical melanocytic proliferation of uncertain significance
Dysplastic nevus
Radial growth phase melanoma (superficial spreading, lentigo maligna, acral lentiginous)

(LM, SSM in-situ, and ALMM in-situ, respectively) and has an almost 100% survival rate if excised. The differential diagnosis of RGP melanoma includes those nevi in which irregular or atypical, suprabasal, intraepidermal melanocytic proliferations are not uncommonly found. Thus, some irritated common acquired melanocytic nevi, recurrent nevi, special site nevi including acral nevi, high-grade dysplastic nevus, Reed's nevus, and Spitz nevus—particularly intraepidermal Spitz—can provide a diagnostic challenge [66, 71, 77, 112] (Table 4.2, Fig. 4.31). In general, poorly circumscribed asymmetrical proliferations, with florid conspicuous pagetoid spread that includes nests and individual melanocytes, uniform and marked cytological atypia, are features of RGP melanoma and are not adequately accounted for by these alternative benign settings. Nevertheless, there are many instances where there is diagnostic uncertainty. In such cases the use of descriptive terms—Intraepidermal or Superficial Atypical Melanocytic Proliferation of Uncertain Significance (IAMPUS and SAMPUS)—is recommended, with an explanatory note in the pathology report [113]. As IAMPUS, by definition, lacks a dermal component there is no risk of metastatic disease, but persistence, local recurrence, and progression are potential consequences; hence, such lesions should be adequately excised.

Extension of malignant cells into the dermis denotes invasive malignancy, which can develop the biological potential to metastasize [37]; vertical growth phase (VGP). However, Clark et al. [114] proposed the concept of invasive RGP, developing a model that sought to correlate morphological criteria with metastatic potential irrespective of tumor depth. According to Clark et al. dermal populations of malignant melanocytes have acquired the ability to metastasize (i.e., VGP) in the presence of (1) detectable mitoses, (2) dermal nests >10–15 cells across, formed of cells similar to those within the epidermis, and (3) dermal nests of malignant melanocytes larger than the largest intraepidermal nest. This VG or tumorigenic phase is expansive and distorts or compresses adjacent tissue, whilst invasive RGP, lacking metastatic potential [115, 116], usually consists of small clusters or individual malignant melanocytes. In the majority of cases, invasive RGP tumors will be no more than Clark level II and <1 mm thickness [117] (Fig. 4.32).

LM and LMM, in particular, pose practical problems in three specific settings: (1) The initial diagnosis, in which distinction between the RGP LM and the changes found on chronically sun-damaged skin can be troublesome (Fig. 4.33) [118, 119]; (2) The peripheral margins of resected tumors (Fig. 4.34); and (3) The assessment of invasive RGP. LM typically arises on skin that harbors widespread evidence of chronic sun-damage, manifest by mottled hyperpigmentation, irregular lentigos, solar lentigos, and actinic keratoses, the latter including pigmented lesions. Moreover, the histopathology of chronically sun-damaged skin, distant from any clinical lesion,

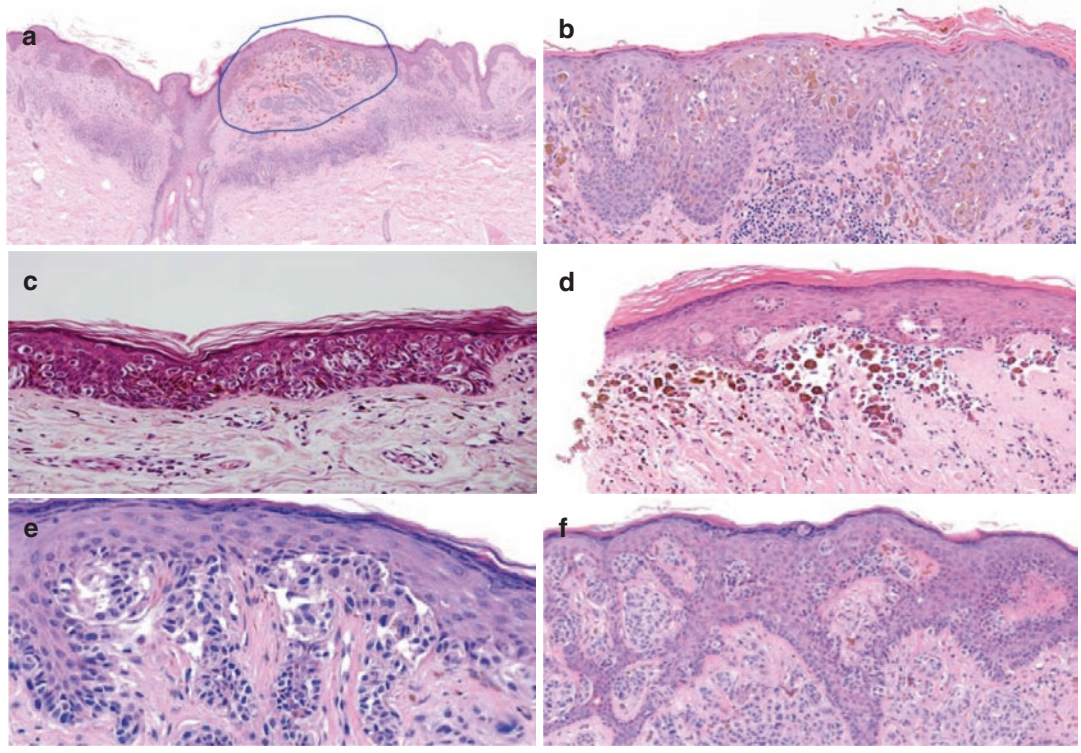


Fig. 4.31 Melanocytic nevi that have markedly irregular intraepidermal proliferations can be challenging to differentiate from melanoma in-situ. These include (**a**) Traumatized nevi, (**b**) Reed nevi, (**c**) Intraepidermal (pagetoid) Spitz nevi, (**d** and **e**) Special site (ear and vulva) nevi. (**f**) Oblique sectioning of focal activation in an otherwise banal nevus can also look alarming

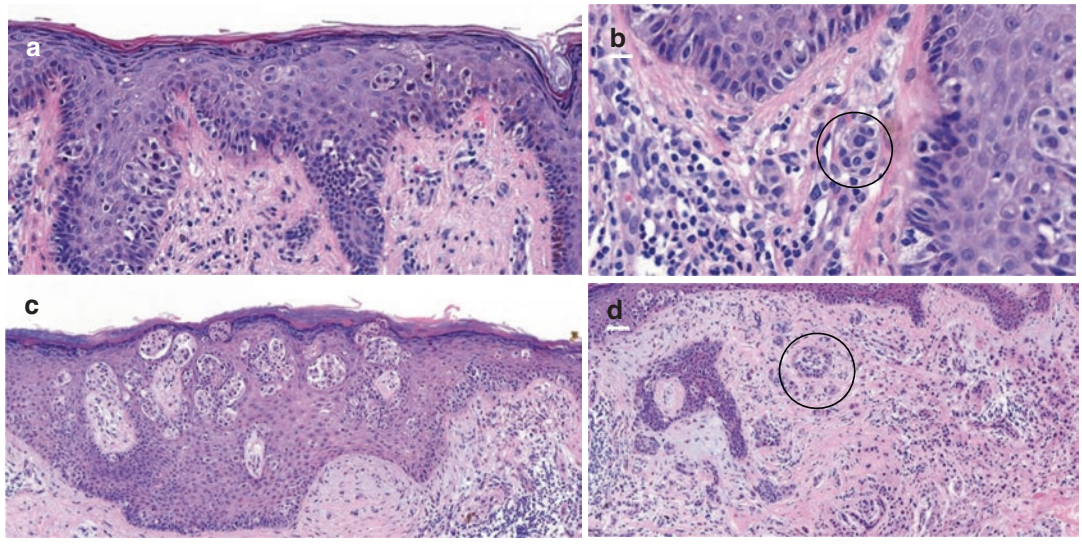


Fig. 4.32 (**a**) Invasive radial growth phase melanoma; a small cluster of non-mitotic malignant melanocytes of similar morphology to the epidermal component (**b**) in the papillary dermis. (**c**) Acquisition of the vertical growth phase is associated with larger groups in the dermis, (**d**) more frequently extends deeper and may have mitoses

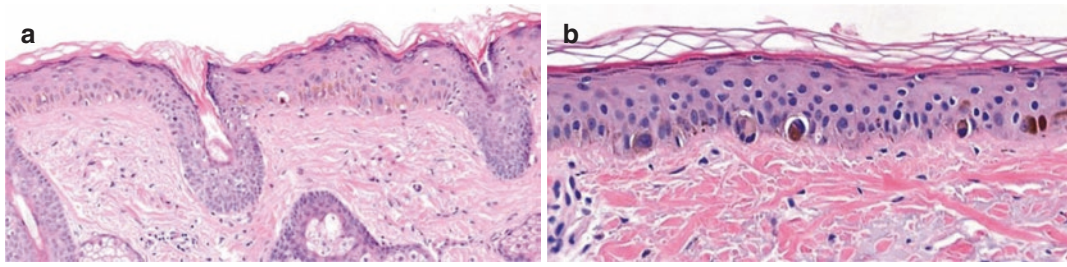


Fig. 4.33 (**a**) Chronically sun-damaged skin is usually atrophic, with marked solar elastosis, and may have increased numbers of (**b**) enlarged or atypical melanocytes, in the absence of a clinical lesion. The distinction from early, or the peripheral margins of, lentigo maligna is difficult

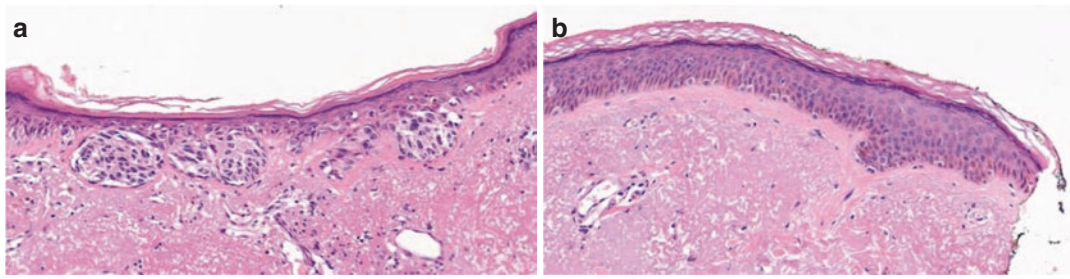


Fig. 4.34 Similar challenges face the assessment of peripheral margins of LM/LMM. (**a**) Nested lentigo maligna. (**b**) The peripheral margin, which has increased numbers of lentiginous but non-confluent and small melanocytes. Whether these represent LM or reflect the patient's "background" sun-damage may be challenging

presents epidermal atrophy, solar elastosis, and increased numbers of basal melanocytes, some of which may be enlarged and irregular. Thus, distinction from LM on an initial biopsy can be very difficult indeed. In general, the presence of *confluent* lentiginous melanocytes, marked atypia, and significant involvement of adnexae indicate LM rather than simple chronic solar damage [119]; "starburst cells" are more frequent in LM [120]. Nevertheless, these are subjective assessments. In doubtful cases, immunohistochemistry may help better demonstrate the architectural pattern of confluence [121] but care is needed in the interpretation; expression of Melan A by sun-damaged keratinocytes, which may be pigmented, can give a false impression of melanocyte proliferation [3, 122]. For these reasons, MiTF or Sox 10, nuclear immunomarkers, are more reliable [123–125]. Similar problems confront the assessment of peripheral margins of resected LM(M). Toward the peripheral portions of the tumor the confluent lentiginous pattern gives way to short clusters of melanocytes interspersed by basal keratinocytes, that eventually merges with the background, inevitably sun-damaged, skin. Precise measurements of the peripheral margins are therefore fraught with subjectivity; again, immunohistochemistry may help [126], but comparison with those skin sections that are far away from the tumor bulk can provide a useful "baseline view" of the patient's sun-damage and allow assessment as to what constitutes the outer portions of tumor and what is background field change. Finally, the use of immunohistochemistry in making these assessments often simultaneously demonstrates immunopositive cells within the superficial dermis, raising concern over invasive melanoma [127, 128]. Whilst some of these cells may represent melanocytes, others are macrophages or unidentifiable resident dermal cells. The diagnosis of invasion should not be made unless the corresponding cells can be found on the routine sections and/or appear clearly atypical.

4.5.2 Nevoid Melanoma

This is a rare form of melanoma (<1%) [129], which lacks a cogent definition, and therefore little is known regarding demographics and etiology. A unifying description is any vertical growth phase melanoma that mimics a common acquired nevus, architecturally and/or cytologically [130–133]. Thus, at first glance these tumors provide a trap to the unwary pathologist. Clinically, these lesions have a similar distribution to common acquired nevi. Histologically, there is a deceptively bland appearance at scanning magnification (Fig. 4.35a); lesions may have a papillomatous architecture, with an apparently uninvolved epidermis, and a dermal population of small melanocytes seemingly with maturation [133, 134]. Tight packing of the papillary dermis by the melanocytes, without the grenz zone of papillomatous nevi, can be a helpful clue. Nevertheless, it is often on higher magnification that the malignant nature is first appreciated (Fig. 4.35b), cytologically, with hyperchromatic atypical cells, albeit small, and easily identifiable mitoses [130, 131, 135]. There may be subtle pagetoid epidermoid spread (Fig. 4.35c). Molecular analysis can be useful in difficult cases [136]. These tumors are not infrequently missed, and a local recurrence rate of 30–75%, metastases in 14–38%, with 24% fatality has been reported [133, 135].

4.5.3 Desmoplastic Melanoma

Desmoplastic melanoma (DM) (see Fig. 4.36) usually presents on markedly sun-damaged skin of the head and neck, as a lightly pigmented macule, or indurated plaque in fair-skinned older adults. Other recognized sites include the lips, ears, and scalp, palate, gingiva, lip, vulva, anus, conjunctiva. Around half the cases are not pigmented [137] and can be mistaken for a scar. Histologically, the epidermis may have a simple lentigo or, more often, a lentiginous proliferation of melanocytes, "atypical lentiginous hyperplasia" (Fig. 4.37a), sometimes amounting to fully

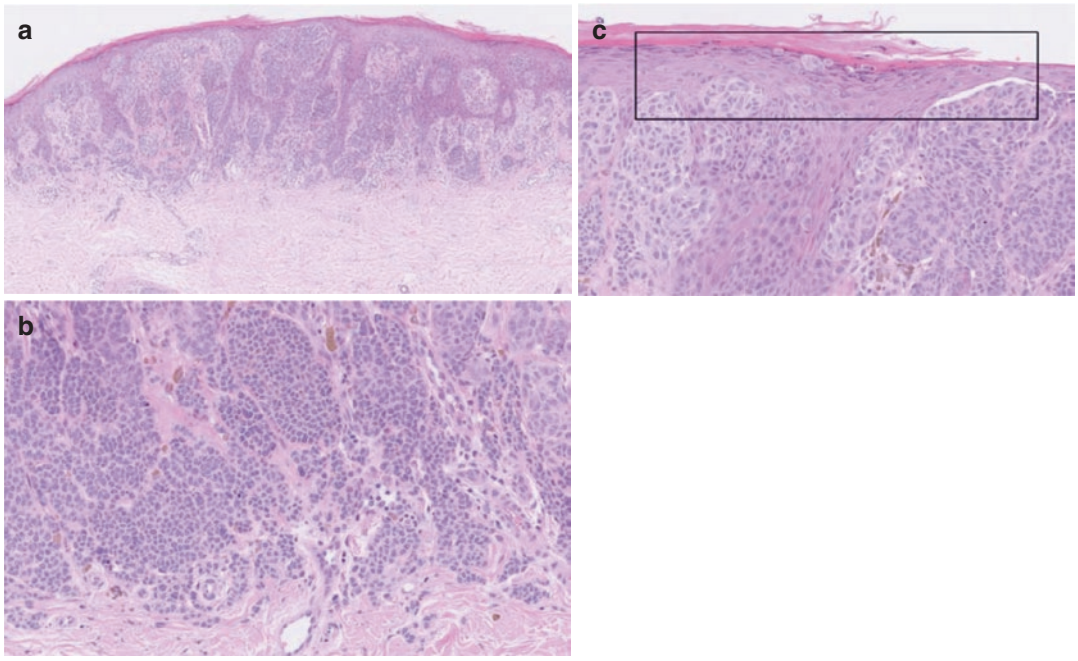


Fig. 4.35 (**a**) Nevoid melanoma, which can have a deceptively regular compound profile on scanning magnification, but the apparent maturation does not eventuate in bland atrophic type B or C nevocytes (**b**), and scrutiny may identify (**c**) subtle pagetoid spread

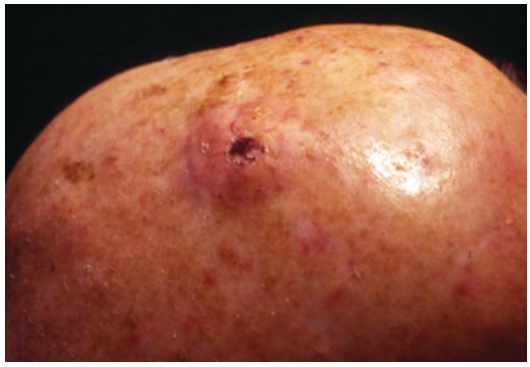


Fig. 4.36 A desmoplastic melanoma on the scalp. (*Courtesy of the Department of Dermatology, Instituto Português de Oncologia de Lisboa, Portugal*)

developed lentigo maligna [137]; indeed, there is overlap between DMM and spindle cell vertical growth phase LMM. In some cases, however, there is no junctional component. An atrophic epidermis and solar elastosis reflect the chronic sun-damage. The tumor is formed of an ill-defined spindle cell population within the dermis, varying from low cellularity to a densely fascicular proliferation; a storiform pattern may be present. Similarly, cytological atypia may vary from deceptively bland fibroblast-like cells to marked pleomorphism. Nevertheless, in lesions with little atypia careful study usually pays dividends with identification of some pleomorphic cells

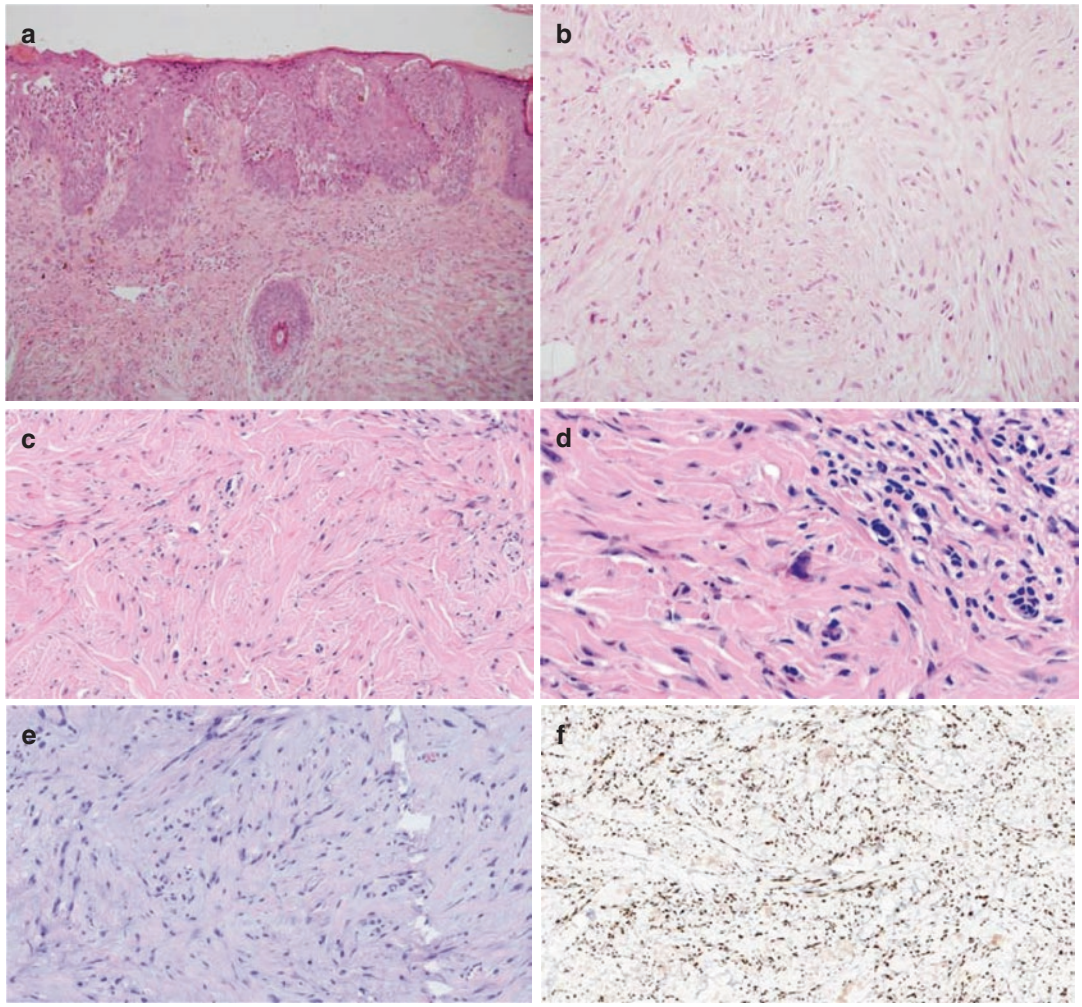


Fig. 4.37 A desmoplastic melanoma; (**a**) Note the in-situ component, but often with a deceptively bland dermis (**b**) and (**c**) such that DMM is easily missed or mistaken for a scarring process. (**d**) Careful inspection usually reveals atypical cells and lymphocytic aggregates, even in tumors of low cellularity. (**e**) DMM with a myxoid stroma resembling nerve sheath differentiation. (**f**) Sox 10 is a helpful adjunct in diagnosis and assessing tumor reach

(Fig. 4.37a–d). Mitoses vary in number and may be absent [137]. Neurotropism is common [138] and can lie distant from the tumor bulk [139]. There is often a fibrous or myxoid stroma (Fig. 4.37e), which in low cellularity tumors can further contribute to a mistaken diagnosis of a scar. DM can readily be missed on superficial biopsies, and sometimes only after several biopsies with clinically recurrent lesions is the diagnosis made successfully [1, 139–141]. Small aggregates of lymphocytes and plasma cells often lie at the advancing edge of the tumor, which, whilst not pathognomonic, are a helpful diagnostic clue that alerts the pathologist both to the presence and to the extent of the tumor in otherwise overlooked paucicellular examples [138, 140]. Immunohistochemistry can similarly highlight the breadth of the tumor [139]. S100 [142], is reliably expressed, but HMB45 and Melan A are usually negative. Reliance on S100 expression can be problematic, however, after initial surgery, in which S100(+) myofibroblasts and Schwann cells can be mistaken for residual tumor [143]; Sox 10 is more reliable (Fig. 4.37f) [144, 145].

The distinction between DM and sclerosing blue or Spitz nevus can be challenging on routine sections. Likewise, sclerosing common acquired nevi are a particular pitfall when arising on chronically sun-damaged skin and associated with foci of inflammation [146]. In addition to careful attention to the histological features most of these nevi are HMB45(+). Initial reports of immunohistochemistry for p16 being discriminatory are not universally accepted [146, 147].

In some cases there is admixed conventional melanoma. A diagnosis of DM is restricted to those tumors in which >90% of the histology is of DM type; otherwise, the tumor is considered combined desmoplastic and conventional melanoma. The mean Breslow thickness of primary DMM is greater than classical melanoma but appears to be associated with a better prognosis when stage-matched [148, 149]; hence, the presence of an admixed conventional melanoma has prognostic relevance [149]. Local recurrence is common [150] although with lower incidences reported in later series likely reflecting better recognition and management; nodal spread appears less frequent than conventional melanoma, with a predisposition for metastases to the lung [139, 150, 151].

4.5.4 Malignant Blue Nevus and Cellular Blue Nevus

These extremely rare tumors designate melanoma arising at the site of a blue or, more commonly, cellular blue nevus, most often in older adults as a rapidly growing nodule in a preexisting BN [152–155]. Dense dermal fascicles of spindled cells having marked atypia and pleomorphism, multinucleation, and plentiful mitoses are characteristic, with marked inflammation (Fig. 4.38a). Larger tumors often have foci of necrosis. The tumors reported are usually aggressive [154–156] with metastases to lung and liver [152, 157] although a comparable mortality to conventional melanoma is also claimed [158].

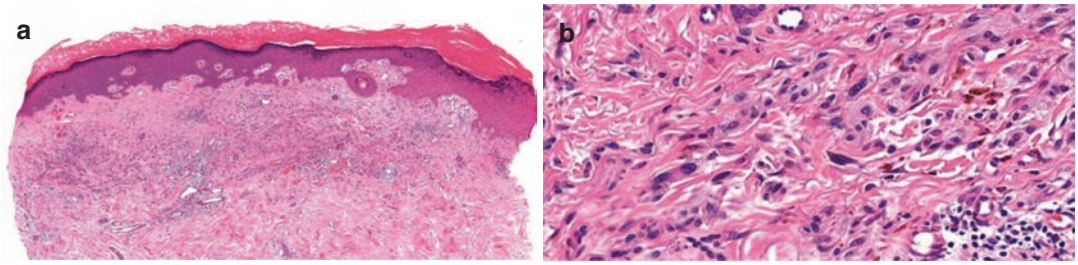


Fig. 4.38 (**a**) An asymmetric and irregular proliferation of pigmented dendritic melanocytes, with inflammation; mitotic figures were identified, and there is (**b**) mild cytological atypia. Such "atypical blue nevi" cause concern and ensuring complete excision is prudent. Retention of BAP-1 expression militates against malignancy

Several diagnostic problems may confront the pathologist; some BN may be asymmetric/infiltrative, have a few mitoses, and/or some pleomorphism and inflammation. The distinction between such "atypical" BN and malignancy may be challenging (Fig. 4.38). Loss of nuclear BAP-1 and a high (>20%) Ki67 index by immunohistochemistry supports malignancy [152, 159]; the two discrete and contrasted portions of the tumor representing the original BN (BAP-1+ and Ki67<5%) and the malignant portion may be clearly visible. Secondly, metastases from conventional melanomas can adopt a BN phenotype [160]; thus, the presence of new, or multiple conventional or atypical, BN in a patient with previous melanoma should be viewed warily. Similarly, atypical CBN has one or more worrying histological features that are commonly associated with malignancy. These include asymmetry, infiltrative architecture, hypercellularity, cytological pleomorphism and mitoses, and necrosis [161, 162] and may rarely involve regional lymph nodes [163]. Frankly malignant CBN has most of these features [152, 163], or they are more pronounced, but as this is a subjective assessment of a spectrum there is disagreement, even amongst experts [164]. In such cases FISH or CGH analyses (see later) may be helpful [165–167]. Finally, in some unequivocally malignant melanomas the BN or CBN origin might not be apparent; demonstration of GNAQ, GNA11, mutations are then informative.

4.5.5 Atypical Spitz Tumor and Spitzoid Melanoma

Classical Spitz nevus is a benign tumor. However, a morphological spectrum of Spitzoid tumors exists from benign (Fig. 4.39a) through to unequivocal Spitzoid melanoma (Fig. 4.39b), within which exists an intermediate group resembling Spitz nevus but having one or more attributes commonly associated with malignancy, designated Atypical Spitz Tumors (AST) (see Figs. 4.39c–h and 4.40). It is not clear whether the AST category denotes benign lesions that look worrisome, a biological intermediate between benign and malignant lesions, or a subset of melanoma with a better prognosis than conventional melanoma. Numerous molecular abnormalities imperfectly associate with the three categories. Kinase fusions, e.g. NTKR-1 are found across all subtypes and are a likely early oncogenic driver in Spitzoid lesions [168]. Other events portend the likely prognosis in ASTs, e.g. isolated loss of 6q23 is associated with benign clinical behavior [169], in comparison with homozygous loss of 9p21 or TERT promoter mutations, found in tumors with an aggressive clinical course [112, 170–172]. The diagnosis and classification of this group is thus a synthesis of clinical, pathological, and molecular data [173–175] (Table 4.3).

4.5.6 Other Melanoma Variants

Rarer morphological variants of malignant melanoma are documented in the medical literature, including chondroid [110, 184], myxoid [185, 186], osteogenic [111, 187], rhabdoid [188], signet ring cell [189], pseudoglandular (Fig. 4.41a), plasmacytoid (Fig. 4.41b) [190, 191], and syringotropic [192] subtypes. These tend to be more common in metastatic tumors but also arise as primary malignancies. Awareness of these is important for diagnostic accuracy, particularly as they may have an unconventional immunophenotype. Data are too limited to ascertain whether conventional staging parameters with the attendant prognostic implications are applicable to these rare subtypes.

4.6 Pathological Assessment of Prognostic Parameters in Malignant Melanoma

All pathological reports of primary cutaneous malignant melanoma should include sufficient data to enable staging according to the latest AJCC recommendations. Careful appraisal of melanoma specimens starts at the macroscopic level; appropriate sampling, orientation and marking of specimens, with detailed description

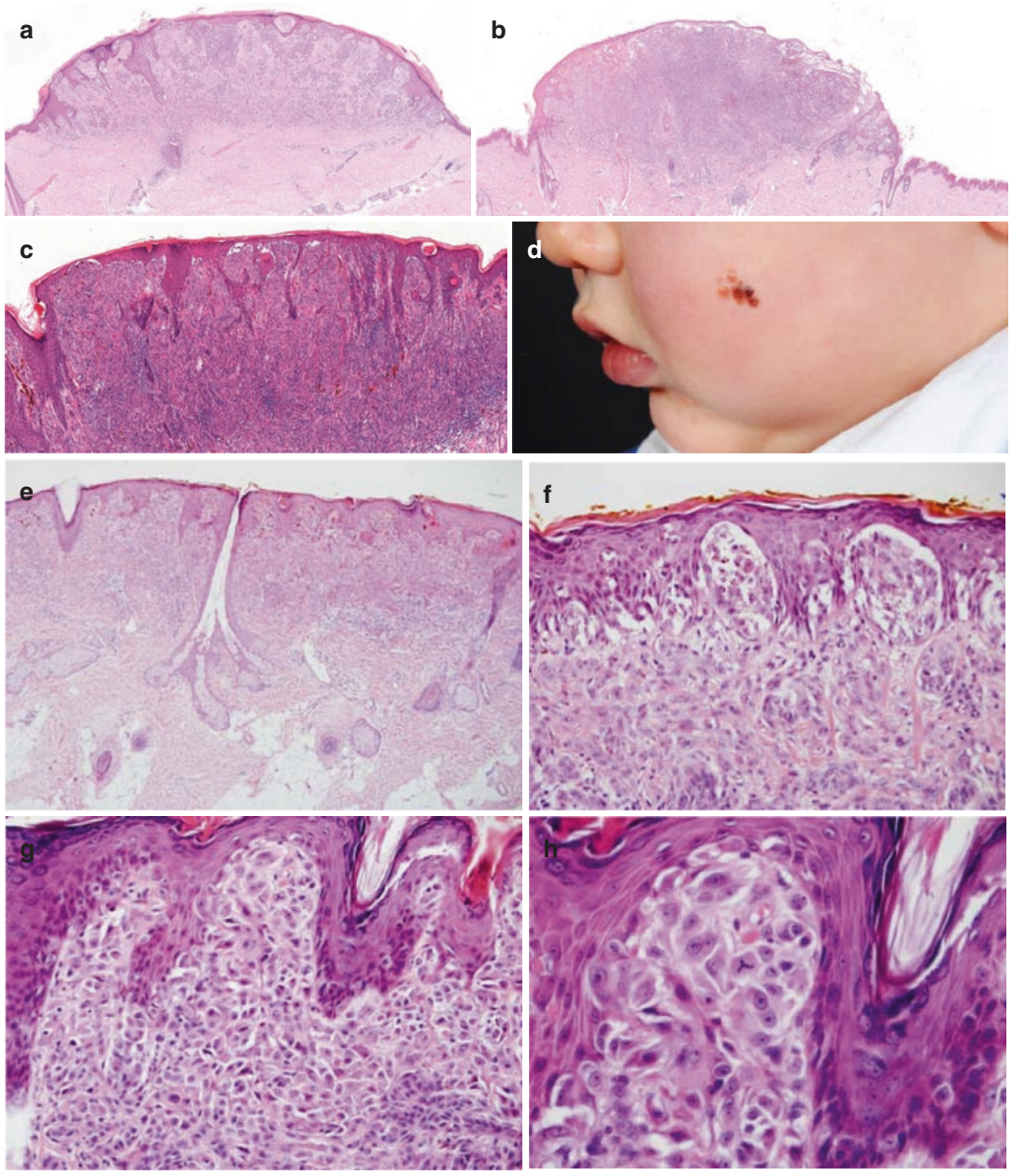


Fig. 4.39 The spectrum of Spitz tumors: (**a**) Classical compound Spitz nevus, arising in a 5-year-old child. (**b**) A Spitzoid melanoma in a 13 years old, with vascular invasion and subsequent metastases. (**c**) More problematic, a large atypical Spitz tumor in a 17 years old. Despite worrying cellularity and mitotic activity, FISH failed to demonstrate mutations, or 9p21 abnormalities, and no TERT promoter mutations were found. The patient remains well 4 years out. (**d**) and (**e**–**h**): Agminate atypical Spitz tumor in a 3 years old. There is no pagetoid spread but a packed dermis and mitoses are identified. Complete excision was followed by a subsequent uneventful course over 15 years

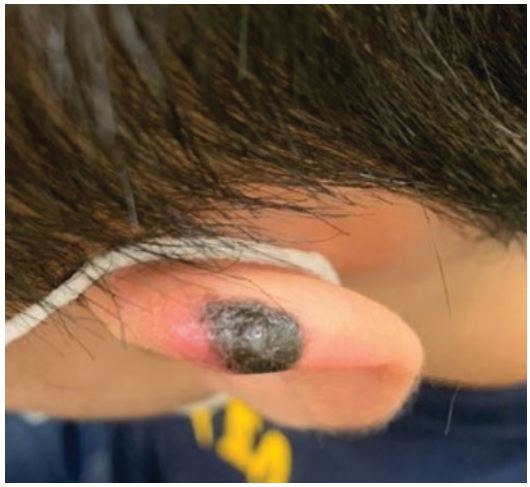


Fig. 4.40 An atypical Spitz tumor of the left ear

of any visible lesion, including measurements and presence of macrosatellites, are required. The recording of the following histological parameters has direct implications for the prognosis of individual patients, which are then used in the context of Tumor Board meetings to optimize clinical management:

- Breslow thickness
- Clark level
- Growth phase
- Ulceration
- Mitotic count
- Regression
- Tumor-infiltrating lymphocytes
- Vascular and perineural invasion
- Microsatellites
- Excision margins

Only three of these, Breslow thickness, ulceration and microsatellites, are currently used for pathological staging purposes. Nevertheless, it is broadly recognized that the remainder impact upon prognosis and are useful to document in clinical practice [193, 194]; many, e.g. tumor-infiltrating lymphocytes and regression, having application within the use of the Armed Forces Institute of Pathology survival tables [114].

4.6.1 Breslow Thickness

Measured perpendicularly to adjacent skin, from the top of the stratum granulosum of the involved epidermis to the deepest malignant melanocyte (Fig. 4.42a), expressed to the nearest 0.1 mm, the Breslow thickness remains the single most important predictor of prognosis for the common forms of primary cutaneous malignant melanoma [195]. In the context of ulcerated tumors the measurement is made from the ulcer base. Microsatellites and foci of perineural or lymphovascular invasion should be excluded from the measurement. Survival data have been predicated upon conventional melanoma subtypes and it cannot be assumed that Breslow thickness is as meaningful in other forms of melanoma, such as those arising in the dermis, e.g. malignant blue nevus, or, indeed, of the nail unit [196]. Common practical problems include distinction between melanoma and benign nevocytes, identification of cells as melanocytic rather than, e.g., macrophages, and mistaking periadnexal colonization by melanoma for true dermal invasion. Curettage or other malorientated specimens, and cases in which the deep biopsy margin truncates the tumor, preclude proper measurement. In the context of poor biopsy orientation, the tissue may be re-embedded. For curettage specimens, or in those in which the tumor has been truncated across the deep margin, a minimum Breslow thickness can be given. Periadnexal extension should not form the Breslow measurement if greater than the main tumor mass [197], unless this is the only invasion element, in which event it is measured from the middle of the pertinent adnexal structure [141]. Rashed *et al* describe the novel and enhanced prognostic value of Breslow density [198, 199], in which the horizontal extent of the tumor cells at the Breslow depth is incorporated into the measurement. This method has the attraction of distinguishing between a tumor with a small focus of malignancy at a specific depth, e.g. 0.8 mm, from a tumor of similar maximum depth but with considerable lateral dermal tumor involvement and therefore markedly

Table 4.3 Adapted from Harms et al. and Elder et al. [174, 176]. Morphological attributes of Spitz nevus, atypical Spitz tumor (AST), and Spitzoid melanoma, which have increasing probabilities of an aggressive clinical course. In contrast to Spitz nevus ASTs most often present in teenagers or young adults. Spitzoid melanoma usually arises in adults >40 years of age, as an amelanotic or pigmented irregular ulcerated nodule [177, 178]. Whilst clinical and morphological details provide a guide to classification and outcome, certain molecular analyses fine-tune the likely prognosis. Molecular events also have correlates with specific recognizable subtypes of Spitz lesions, e.g. ALK and NTKR-1 translocations give rise to tumors with plexiform fascicular spindle-shaped and filigree-pattern rete ridge hyperplastic growth patterns, respectively [179, 180]. It is important to emphasize, however, that not all genetic changes clearly map to benign or malignant categories; ALK-translocation Spitzoid lesions tend to follow a benign course, although not invariably [179, 181] and NTRK-1 fusions encompass nevi, atypical Spitz tumor, and Spitzoid melanoma [168, 180]. The repeated documentation of regional nodal metastases in AST without subsequent distant spread or patient fatality further illustrates the biological complexity of this group of neoplasms [182, 183]

	Spitz nevus	Atypical Spitz tumor	Spitzoid melanoma
Histopathology	<5–6 mm diameter Well circumscribed Epidermal hyperplasia Pagetoid spread may be present focally Dermal melanocytes show typical maturation Mitoses absent	Often >5–10 mm Well or poorly circumscribed May be asymmetrical Epidermal consumption, possible ulceration Pagetoid spread more prominent compared with Spitz nevus Dermal component can extend to deep dermis/subcutis Reduced maturation Mitoses (2–6/mm^2) Inflammatory response	Features can be identical to atypical Spitz tumor >5 mm, can be >10 mm Poorly circumscribed Asymmetrical Enlarged confluent nests and pagetoid spread; ulcerated Dermal component contains nodular sheet-like aggregates Reduced maturation Mitoses (>6/mm^2) or hotspots Prominent inflammatory response
Cytology	Enlarged epithelioid/spindle cells Little or no nuclear polymorphism	Enlarged epithelioid/spindle cells Melanocytes show increased atypia with nuclear enlargement and pleomorphism, with large prominent eosinophilic nucleoli	Enlarged epithelioid/spindle cells High grade atypia
Molecular pathology	Kinase fusions: Activating translocation events (including *ALK, NTRK1)* Loss of 9p21 is rare Mutations in HRAS common Isolated gain 11p Loss of BAP1	Kinase fusions Heterozygous or homozygous loss of 9p21 *HRAS* mutations may be present Loss of BAP-1	Kinase fusions Homozygous deletion of 9p21 *HRAS* mutations rare *TERT* promoter mutations
	Increasing probablity of an aggresive clinical course		

greater tumor volume. Whilst the initial data as reported suggest Breslow density has enhanced diagnostic value further studies are required to corroborate this; in particular, perhaps, as to whether other parameters, such as mitotic index, might not capture the same prognostic information. Clark level measures tumor thickness based on the level of skin compartment involved; this is no longer a mandatory parameter as the prognostic significance most closely correlates with absolute tumor thickness. Reproducibility is poorer compared to Breslow measurement, par-

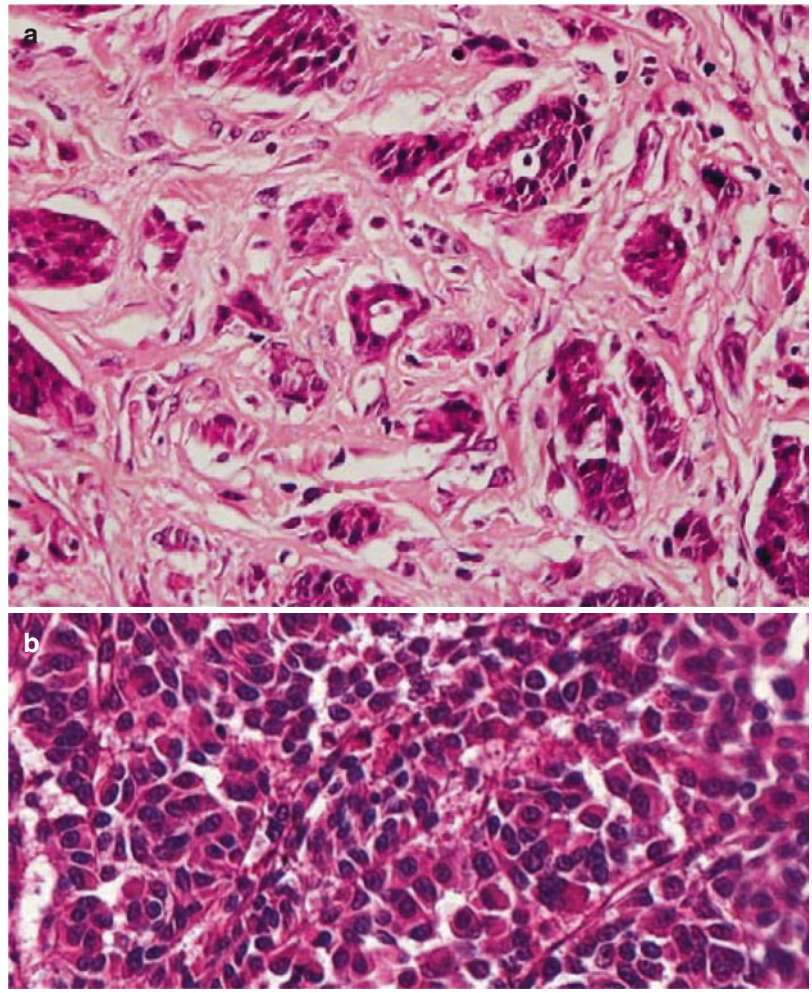


Fig. 4.41 Melanoma can adopt a wide variety of histologies, including (**a**) pseudoglandular and (**b**) plasmacytoid morphologies, particularly in metastases

ticularly for levels II–IV [193, 200]. Nevertheless, this can be useful when the Breslow cannot be measured, e.g., in a partial biopsy.

4.6.2 Growth Phase

The distinction between invasive RGP and VGP serves to identify tumors with the biological potential to metastasize. In practice, the possibility that any invasive melanoma can metastasize should never be discounted. The observation of dermal melanocytes not initially identified on the H&E sections using immunohistochemistry is important but these cells should ideally be found on the routinely stained sections and assessed for cytological features of malignancy [127, 128].

4.6.3 Ulceration

Ulceration serves to upstage the melanoma, the implication being that tumor thickness is being undervalued [141, 194]. It is not considered relevant for in-situ melanomas. Any tumoral ulceration, that is full thickness interruption of the epidermis above the tumor, with an acute inflammatory response, should be recorded. Sectioning artifacts may result in the loss of the epidermis but are not accompanied by an inflammatory

response and should not be documented as ulcerated; similarly, epidermal loss due to prior partial biopsy can be ignored. There is evidence that increasing extent of ulceration, measured either as an absolute value or percentage of the tumor breadth [201, 202], also correlates negatively with prognosis.

4.6.4 Mitotic Count

The mitotic index of malignant melanoma is considered by some to be the most powerful prognostic indicator after tumor thickness [193, 200]. Mitotic counts should begin in the identifiably most mitotically active area of the tumor and continued in the adjacent non-overlapping fields for a field size of 1 mm^2 (Fig. 4.42b). Studies suggest that there is good interobserver variation using this "hotspot" method [200]. In the absence of a hotspot, the count begins over a field including a mitosis, proceeding in similar fashion. Some tumors will have <1 mm^2 of invasive component, but the resulting count should nevertheless be expressed per this area. In cases where there is an initial biopsy and excision specimens the highest mitotic count should be used. Common practical problems include recognition of a genuine mitosis, whether a mitosis is junctional or dermal, and determining if a cell in mitosis is a melanocyte. Immunohistochemical dual-staining may assist in the latter [203].

4.6.5 Regression

Regression of malignant melanoma, apparent clinically as gray or white foci, has, confusingly, been reported as both a poor and good prognostic factor [194, 204–206]. It is recognized histologically as a zone of loss or interruption in the melanoma (Fig. 4.42c), and the replacement of tumor by fibrosis (Fig. 4.43), inflammation including lymphocytes and melanophages, prominent blood vessels, and melanin pigment. This needs distinction from changes attributable to previous surgery, as seen in recurrent nevi (pseudomelanoma); indeed, re-excisions of malignant melanoma can also misleadingly suggest regression. Effacement of rete ridges is a useful pointer to prior trauma or surgery, but in doubtful cases the original biopsy material should always be reviewed. The presence of regression should be recorded as it implies that the melanoma may

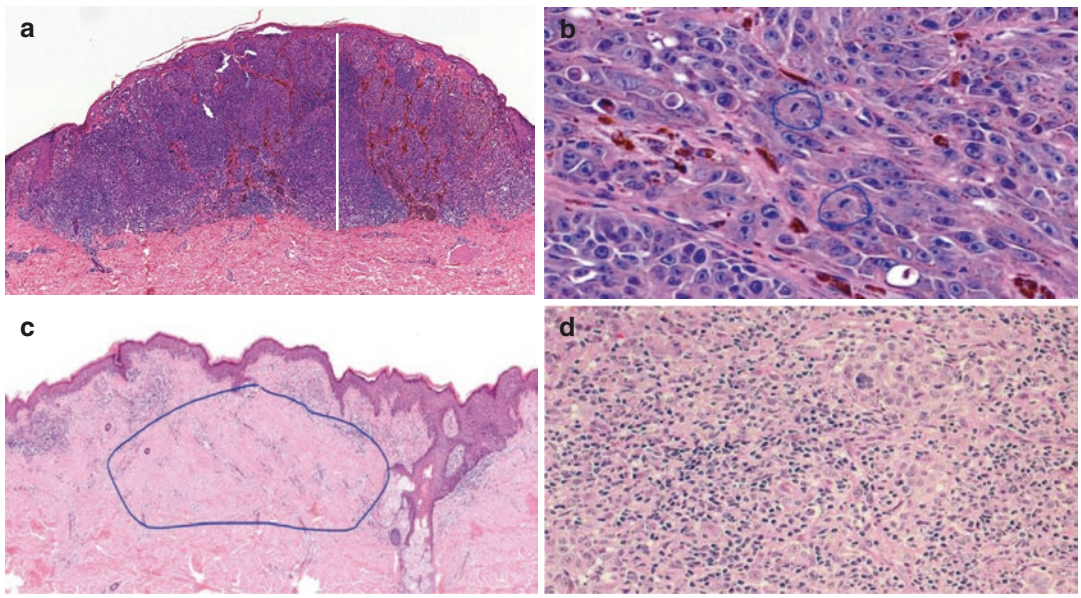


Fig. 4.42 Prognostic indicators that should be included on the pathology report include (**a**) Breslow thickness (**b**) Mitotic count (**c**) Regression (**d**) Tumor-infiltrating lymphocytes, "brisk" in this image

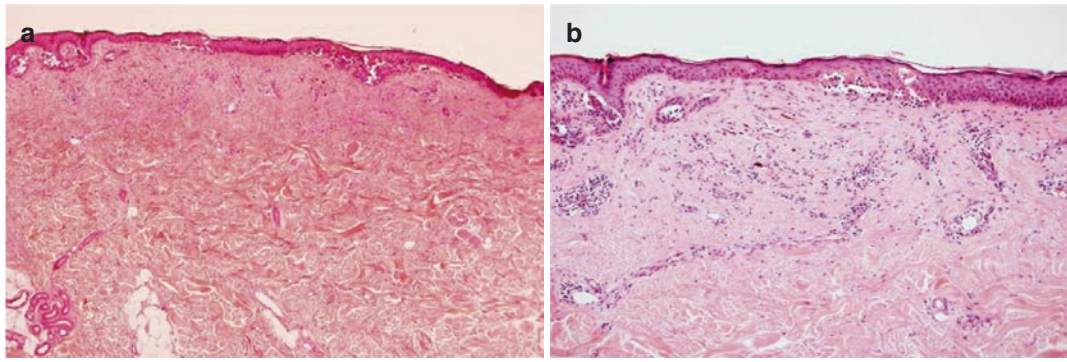


Fig. 4.43 (**a**) A zone of superficial dermal fibrosis (**b**) associated with this in-situ melanoma was recorded as likely regression. The patient presented 2 years later with regional metastases

have been thicker than the Breslow thickness; accordingly, it is potentially under-staged: this is particularly pertinent when affecting in-situ melanoma or even severely dysplastic melanocytic nevus, profoundly changing the clinical significance of the lesion. The depth of regression should not be added to the Breslow thickness although a comment should be made if it is clearly affecting a greater depth than the extant tumor. Halo nevus represents a form of "regression" but is dominated by a florid lymphocytic response without the associated fibrosis and vascularity.

4.6.6 Tumor-Infiltrating Lymphocytes (TILs)

Three categories of assessment of the inflammatory response found in primary malignant melanoma correspond to lymphocytic infiltrates that permeate the invasive tumor throughout its body or advancing edge ("brisk") (Fig. 4.42d), only focally ("non-brisk") or not at all ("absent"). "Absent" is also used in cases with marked inflammatory cell responses that do not extend into the tumor. Studies indicate TILs are associated with a favorable prognosis in VGP melanoma [114, 207–209]. It is possible that some authors have labelled such features as "regression," which might account for reporting regression as a favorable prognostic feature. A novel method of evaluation, with estimations of tumor volume affected by TILs has been proposed [210] that correlates with overall survival and claims better interobserver agreement, although awaits wider validation.

4.6.7 Vascular and Perineural Invasion

Intravascular or lymphatic tumor portends a poorer prognosis in numerous studies (Fig. 4.44) [211–213]. This should be distinguished from melanocytes within blood vessel walls, which does not constitute true invasion and may be found in some, particularly congenital, nevi. Pseudo-vascularization is common in intradermal nevi but is rarely confused with vascular invasion, which requires the identification of an endothelial-lined space. In cases where there is doubt, immunohistochemical staining for CD31, CD34, or ERG for endothelium, or D2–40 for lymphatics, may facilitate recognition of genuine invasion. Indeed, studies indicate that lymphovascular invasion is under-recognized when solely relying upon routine sections [214, 215]. Perineural invasion (PNI), associated with an increased risk of local recurrence, is often present in desmoplastic melanoma, but may also be found in nevi. Thus, congenital, blue and Spitz nevi can have extension around dermal nerves that has no sinister connotation. PNI is best identified at the advancing tumor margin rather than within the

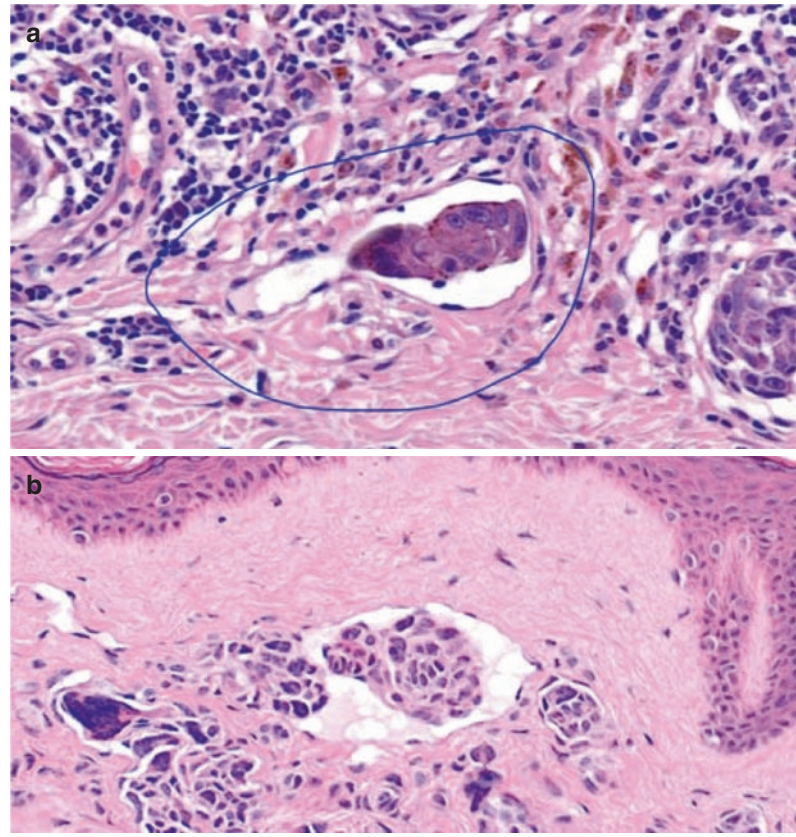


Fig. 4.44 (**a**) Lymphovascular invasion in melanoma and (**b**) pseudoinvasion in a nevus

tumor bulk where a tumor mass may simply surround small dermal nerves. Care should be particularly taken in re-excision specimens in which there may be perineural thickening, or even benign epithelial cells sleeving the nerve, as a response to previous surgery.

4.6.8 Microsatellites

The presence of a portion of melanoma, of any size, separated from the parent primary tumor by normal stroma, in the same histological section, defines a microsatellite. Such deposits imply intra-lymphatic/vascular spread and are associated with a poorer prognosis [216, 217]. This simple definition engenders a practical problem; there is often inhomogeneity in the dermal tumor, most of which will not be genuine microsatellite spread; thus, some regulatory bodies have retained both a minimum size of malignant cluster (>0.05 mm) and minimum distance (0.3 mm) as recommended in earlier versions of AJCC publications [218]. Levels may be needed to determine an apparent separate portion of tumor that lies in continuity with the main tumor. The definition of microsatellites excludes examples in which the intervening stroma has fibrosis, inflammation, and other features that suggest tumor regression.

4.6.9 Excision Margins

Local recurrence with attendant morbidity is influenced by the adequacy of excision of primary melanoma [219–221]. Thus, measurement of the nearest peripheral and deep margins, and whether involved by in-situ or invasive tumor is important. Some forms of in-situ melanoma may also require a deep margin, for example LM, in which deep dermal colonization of adnexae can

extend toward the base of the specimen despite lacking dermal invasion proper. The distance of microsatellites, PNI, and foci of regression to the excision margins should be the given margin if any is less than the tumor proper.

4.7 Molecular Analysis in Melanocytic Tumors

The genetic analysis of melanocytic lesions has found applications in melanoma classification and in providing the rationale for targeted therapy in advanced stage disease. An important further development lies in assisting in the diagnostic evaluation of elliptical tumors (Fig. 4.47). The distinction between nevus and melanoma is usually undemanding [200] but can also provide one of the most challenging areas of dermatopathology. The assignation of benign or malignant depends upon the assessment of a number of independent parameters of the tumor; ambiguous tumors are problematic precisely because several features are characteristic of a nevus, whilst there simultaneously exist one or more that are classically associated with malignancy [222]. Such ambiguous tumors are commonly dubbed MelTUMPs or STUMPs (Melanocytic Tumor of Uncertain Malignant Potential and Spitz Tumor of Uncertain Malignant Potential, respectively). The presence or absence of clonal chromosomal rearrangements provides the basis for comparative genomic hybridization/SNP (CGH) and fluorescent in-situ hybridization (FISH) analyses, techniques which can be of diagnostic use in resolving these challenging tumors as likely benign or malignant. CGH analyzes the entire genomic DNA in cells for copy number changes and findings have since been used to stratify prognosis [165, 223–225]. FISH analysis builds upon the observations from CGH testing. Fluorescently labelled DNA probes target specific loci that have discriminant value between benign and malignant lesions. The algorithm has since been refined with the addition of other loci, some with prognostic information, giving rise to commercially available probes [112, 226, 227]. Typical applications include tumors in which the histological differential diagnosis lies between acquired melanocytic nevus and melanoma, proliferating nodules and melanoma within congenital nevi [34] and, in Spitzoid neoplasms, between Spitz nevus, atypical Spitz tumor, and Spitzoid melanoma. Such challenging lesions often have poor diagnostic reproducibility, even between experts [228]. Applications of these techniques enhance diagnostic accuracy [227, 229]. Nevertheless, histopathology remains the gold standard; for example, there are unequivocally malignant cases that have been FISH "negative" [230, 231].

4.8 Immunohistochemistry in Melanocytic Tumors

Immunohistochemistry (IHC) allows target proteins to be identified in tissue sections through antibody binding, subsequently visualized using a brown or red chromogen reporter reaction. The usual application for IHC is assigning lineage and, given that the distinction between benign and malignant melanocytic lesions is largely predicated upon morphological features, IHC currently plays only a modest role. The commonly used immunomarkers for melanocyte identification (Table 4.4) will not discriminate between nevus and melanoma.

Nevertheless, IHC is an important adjunct in several specific instances. Demonstration of melanocytic lineage, using a combination of sensitive and specific markers, may be necessary in the context of a dermal or ulcerated tumor lacking junctional melanocytes or pigment, and non-pigmented metastases. Melan A and MiTF are adjuncts in the diagnosis of rare S100(−) melanomas, or if the differential diagnosis includes S100(+) non-melanocytic neoplasms. In challenging primary melanocytic lesions, the architecture and distribution of melanocytes is better appreciated using IHC (Fig. 4.45) which can be helpful in the distinction between nevi (particularly recurrent, special site, dysplastic, halo) and in-situ melanoma, clearly highlighting the distribution of intraepidermal melanocytes. Similarly, when evaluating

Table 4.4 Common immunohistochemical markers

Markers of melanocytic differentiation		
Marker	Sensitivity/specificity	Comment
S100	Sensitivity ~93–100% [232–236] Specificity ~75–87% [237–239]	Highly useful marker due its high sensitivity. S100 is a calcium binding protein and was the first IHC marker that was discovered to be useful in melanoma by Gaynor in 1980 [240]. 'S100' derives from solubility in 100% saturated ammonium sulfate solution [241]. Commonly expressed in all subtypes of melanoma, including desmoplastic melanoma. Its limitations are its low specificity. Positive in a variety of other cells including nerve sheath cells, myoepithelial cells, adipocytes, chondrocytes and Langerhans cells and the tumors derived from them. For this reason, S100 should be used in conjunction with other markers. The staining pattern is nuclear and cytoplasmic, and generally strong and diffuse.
HMB-45	Sensitivity ~70–90% [242, 243]	Highly specific for melanocytic lesions, but much lower sensitivity than S100. HMB-45 is a marker of the pre-melanosomal glycoprotein gp100. It shows cytoplasmic staining in a granular pattern. HMB45 is very useful for detecting the pattern of maturation of melanocytic nevi; superficial, type A melanocytes are positive, deeper type C melanocytes appear negative. Blue and Spitz nevi are exceptions, in which the whole lesion is labelled. In melanoma, the staining pattern is irregular. Epidermal staining can be helpful in illustrating pagetoid spread. Negative in spindle cell melanomas, including desmoplastic lesions [244].
Melan A (MART1)	Sensitivity 85–97% [245, 246] Specificity 95–100% [247]	Targets melanoma antigen recognized by T-cells (MART-1). Most melanocytic lesions, benign and malignant, express it. Sensitivity is decreased in metastatic lesions but generally shows more diffuse and intense staining that HMB-45. Also expressed in PEComas and clear cell sarcomas. Staining pattern is cytoplasmic.
MiTF	Sensitivity ~81–100%, Specificity ~88–100%, lower in spindle cell lesions [232, 236, 248–250]	Targets microphthalmia transcription factor, a protein necessary for the development of melanocytes and melanin synthesis. Of low specificity being present in various malignancies including mesenchymal and lymphoid tumors, breast and renal carcinomas. A nuclear stain which is helpful when evaluating epidermal melanocytic proliferations on sun-damaged skin.
Tyrosinase	Sensitivity ~84–94%, Specificity ~97–100% [232, 238, 242, 251]	High sensitivity/specificity that targets tyrosinase, an enzyme needed to melanin synthesis. Staining pattern is cytoplasmic and similar to HMB-45. Sensitivity decreases with advanced clinical stage and in metastatic lesions. Most clear cell sarcomas and pigmented neurofibromas, and some (20%) angiomyolipomas express this marker.
Sox10	Sensitivity ~78–100% Specificity ~84–93% [144, 233, 252–254]	Highly sensitive nuclear marker, particularly useful in desmoplastic melanoma and sclerosing nevi, differentiating them from mimics, e.g. scars [144, 145], and in metastases [253]. Also stains other neural crest derivatives, e.g. malignant peripheral nerve sheath tumors [144, 233, 255] and some breast carcinomas [256]. Useful in evaluating melanocytes on sun-damaged skin.

compound common acquired and Spitz nevi, both morphological maturation and a low proliferation rate are features in support of a benign tumor; conversely, loss of maturation and a higher than usual proliferation fraction favor a malignant interpretation. These may be more objectively assessed in atypical lesions using HMB45 and Ki67. Ki-67 is a nuclear antigen present in all active phases of cell proliferation and the most widely used marker of proliferation. Benign tumors largely confine HMB45 expression to the more superficial aspects of the tumor and have a low Ki67 index; intradermal Spitz and sclerosing blue nevi, which diffusely express HMB45, are exceptions. Malignant melanomas lose this HMB45 gradient whilst sporting a high proliferation index. Decisions regarding dermal invasion (growth phase), Breslow thickness, and excision margins—particularly in lentiginous proliferations, may be informed by immunohistochemically highlighted cells.

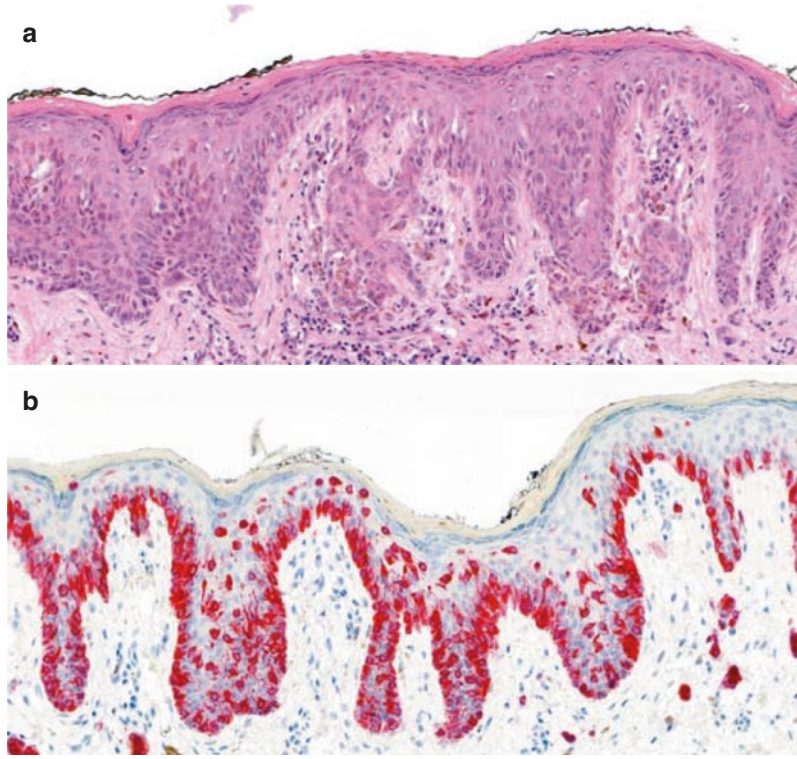


Fig. 4.45 Immunohistochemistry for Melan A (**b**) highlighting the focal pagetoid spread of melanocytes, not obvious on the routine H&E section (**a**)

Non-melanocytic specific markers act as adjuncts in specific situations. PHH3 is associated with chromatin condensation at the G2 and M phases of the cell cycle and a sensitive and specific marker of mitosis. Expression has been shown to correlate with increased risk of metastases and decreased overall survival [257, 258]. PHH3 is not recommended in lieu of identification of mitoses on H&E sections but can be useful to assess whether equivocal cytopathic morphology represents a genuine mitosis and, using double labelling, whether a mitosis is within a melanocyte [203, 259]. Preferentially expressed Antigen in Melanoma (PRAME) is a promising member of the Cancer Testis Antigens group. Lezcano *et al* reported expression in >83% of 255 primary and metastatic melanomas but found 86% of nevi—including recurrent/traumatized and dysplastic lesions—were completely or mainly negative. In addition, it is a potential adjunct in margin assessment, again particularly in lentiginous proliferations [126].

Immunohistochemistry can act as a cipher for underlying molecular events. Loss of BAP-1-expression facilitates the diagnosis of Wiesner nevus and malignant blue nevi, as discussed above. Linkage of familial melanoma to 9p21 gene locus—the site of the CDKNA2 gene—commonly lost in melanoma, produced intense interest in IHC p16 protein expression. Numerous reports describe the IHC retention and loss of p16 expression in benign and malignant lesions, respectively; these include diagnostic challenges such as Spitz nevus versus malignant Spitz [260–265], desmoplastic Spitz and other sclerosing nevi versus desmoplastic melanoma [266]. However, others report caution in reliance on p16 alone [267], and a meta-analysis concluded that there is little evidence for the uncritical use of p16 IHC [268]. The addition of p16 to the cock-

tail of HMB45 and Ki67 described above, using a combinatorial scoring system [269, 270] is reported to help distinguish between benign and malignant lesions. Finally, with the recent emergence of targeted therapies IHC may be used as a rapid screening tool for detecting BRAF-V600E mutations (Fig. 4.46) and for assessing PDL-1 expression [271].

4.9 Conclusions

Melanocytic tumors are a common specimen in dermatopathology. Whilst most are routine, in some cases a histological distinction between benign and malignant is not possible. Emerging molecular analyses are beginning to assist in diagnosis (Fig. 4.47) but are also eroding the tra-

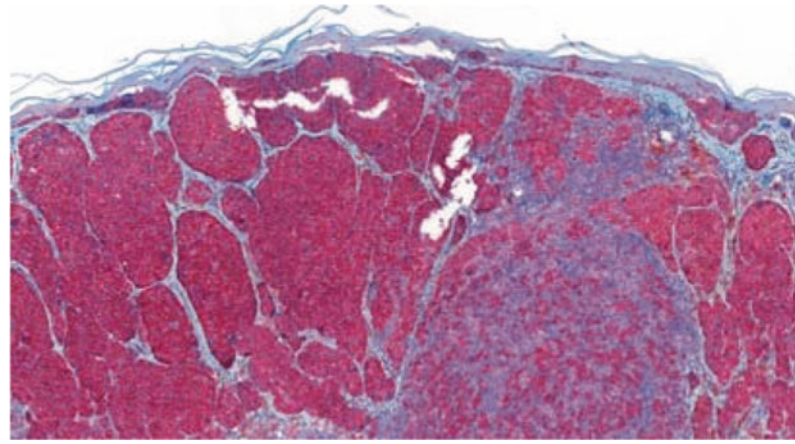


Fig. 4.46 Expression of BRAF V600e in an advanced melanoma; immunohistochemistry is useful as a screening tool for this driver mutation and identification of a likely candidate for targeted therapy. However, a negative stain requires molecular analysis for definitive exclusion

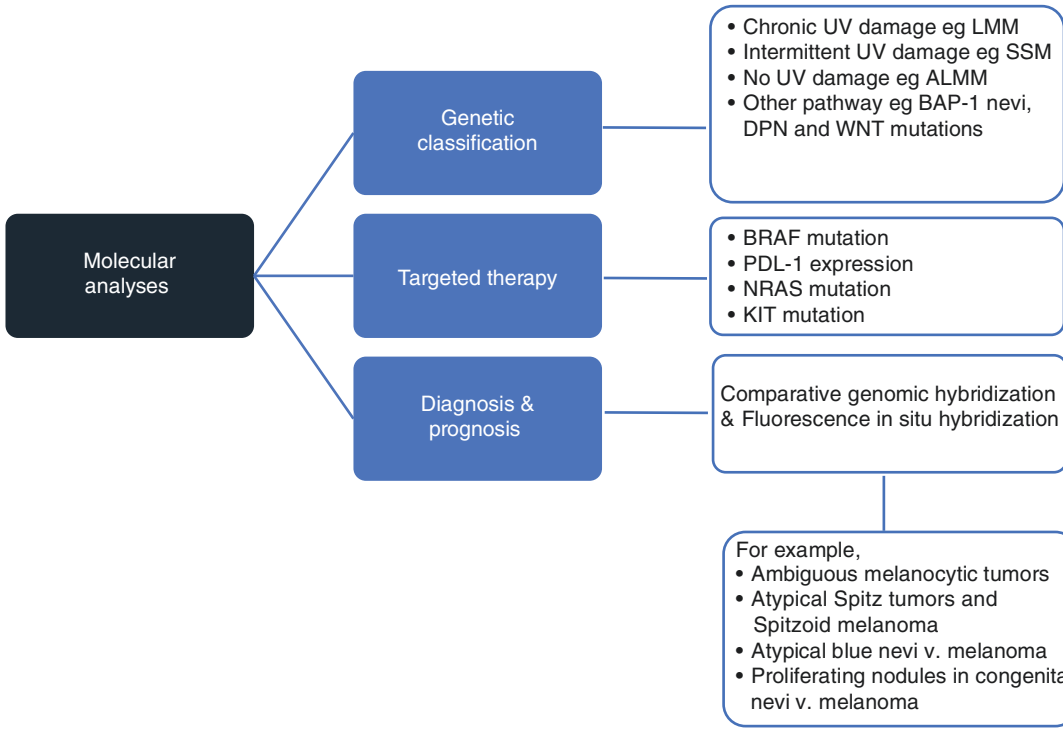


Fig. 4.47 Molecular analyses find multiple applications in melanocytic biology, informing targeted treatment options, and assisting in diagnosis

ditional edifice of morphology, and it is certain that the classification of melanocytic lesions is very much in flux. Nevertheless, histopathology remains the gold standard for diagnosis and the prism through which novel genetic data are largely interpreted. Familiarity with the morphological varieties of melanocytic nevus, intermediate lesions, and melanoma is therefore still required both for diagnostic accuracy and to inform appropriate patient management.

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Part II

Evaluation and Staging of Disease

Aids to Detecting Melanoma

5

Jette V. C. Hooper and Jane M. Grant-Kels

5.1 Introduction

Melanoma is still increasing in incidence in almost all ethnic groups worldwide. Although initially, mortality rates were simultaneously increasing, a leveling-off phase was observed in the 1990s. This development is hypothesized to be attributable to early melanoma detection [1] and, since 2011, new innovative and targeted therapies. Prognosis is closely correlated with the depth of cutaneous invasion, making early recognition of paramount importance [2]. A thorough full-body skin exam utilizing visual inspection is still regarded as the first step and standard of care in the detection of melanoma; however, there are a number of new noninvasive detection tools which may serve as adjuncts to the total body skin exam and prove beneficial in patient management. The goal of incorporating these tools into practice is to increase the detection rate of early melanomas while concurrently decreasing unnecessary biopsies. We will focus here on available noninvasive adjunctive technologies that should be considered for incorporation into clinical practice. Most of these technologies have been developed to enhance our ability to detect in situ or very early superficially invasive melanomas, while others seek to improve prognostic accuracy.

5.2 Total Body Photography

Total body photography (TBP) is a noninvasive melanoma detection technique that employs standardized digital photography to help identify new skin lesions, as well as to track, compare, and monitor existing lesions. Baseline total skin surface photographs can now be coupled with select dermoscopic images so that lesions can be followed clinically and dermoscopically (Fig. 5.1). TBP facilitates early detection of new or changing skin lesions and is particularly useful in those patients with innumerable skin lesions. TBP affords the ability to detect new lesions or changing lesions while simultaneously avoiding unnecessary biopsies of stable atypical nevi. Employing TBP in clinical practice has been associated with an increased rate of detection of early and in situ melanomas, demonstrating the role of TBP in earlier detection of melanoma [3]. Furthermore, it has been suggested that the depth of invasion at

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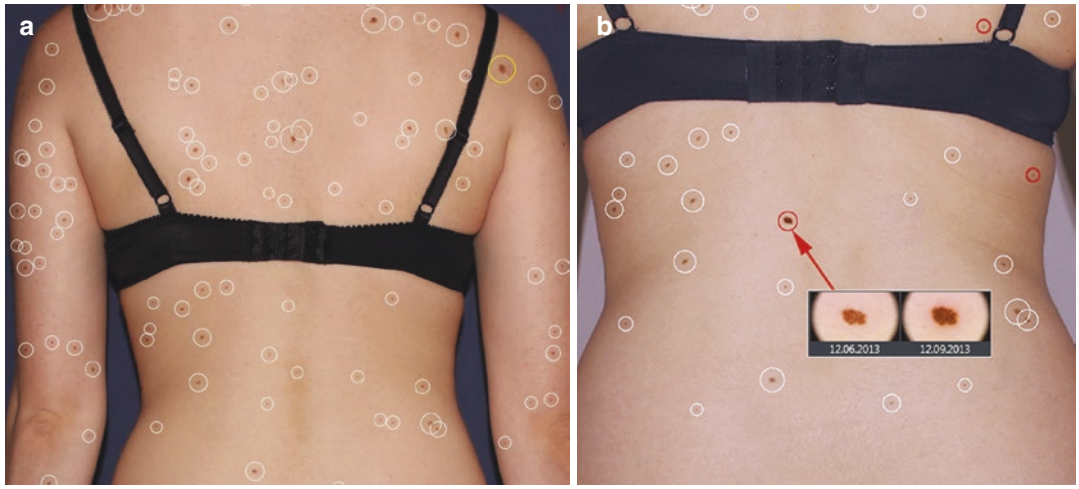

Fig. 5.1 Fotofinder system images: (**a**) Back overview (**b**) Associated dermoscopic images for a selected lesion (images supplied by FotoFinder Systems)

diagnosis of melanomas correlates with the length of the interval between baseline and follow-up TBP using a computer-assisted automation for serial comparisons of TBP images, suggesting that more frequent clinical assessments with the aid of TBP images allow for detection of earlier stage disease [4]. Additionally, in patients with a personal history of melanoma, TBP was shown to decrease their anxiety regarding future recurrence and metastasis of their melanomas [5]. TBP can be utilized at teledermatology sites as TBP can be performed remotely via telehealth, potentially providing melanoma screening to a larger demographic [6].

TBP typically incorporates the "two-step method of digital follow-up" [7], combining TBP with sequential dermoscopic follow-up, further enhancing early diagnostic accuracy by incorporating both technologies. A 2019 international DELPHI consensus among melanoma experts recommended TBP, especially for patients who meet specific criteria (Table 5.1) [8].

Table 5.1 Criteria for performing total body photography

The 2019 consensus guidelines for total body photography
TBP recommended for patients over the age of 50 who meet any of the following criteria: • Familial atypical multiple mole melanoma syndrome • Greater than 50 nevi and multiple prior cutaneous melanomas • Greater than 50 nevi and a history of amelanotic melanoma or multiple pink nevi • Greater than 50 nevi and a genetic syndrome that predisposes them to the development of cutaneous melanoma

Adapted from Waldman R, Grant-Kels JM, Curiel CM, et al., Consensus Recommendations for the Use of Noninvasive Melanoma Detection Techniques Based on Results of an International DELPHI Process. J Am Acad Dermatol 2019 Sep 26. pii: S0190-9622(19)32794-X. doi: 10.1016/j.jaad.2019.09.046. [Epub ahead of print] [8]

5.2.1 Available Devices

There are many commercially available TBP imaging devices, most of which harness the ability to superimpose images, compare side by side images obtained at different times and utilize a zoom-in capability as well as the ability to include dermoscopic images of specific lesions. Commercially available units vary in capabilities, price, and size. Most systems include automatic camera settings and focusing, resulting in high-quality images without variation and dependence on a trained medical photographer. Some of the products have unique capabilities. For example, FotoFinder, has a computer setting that will automatically compare follow-up images to prior TBP photos and digitally circle new or changed lesions to prompt the dermatologist to examine specific lesions (Fig. 5.2). Many of the

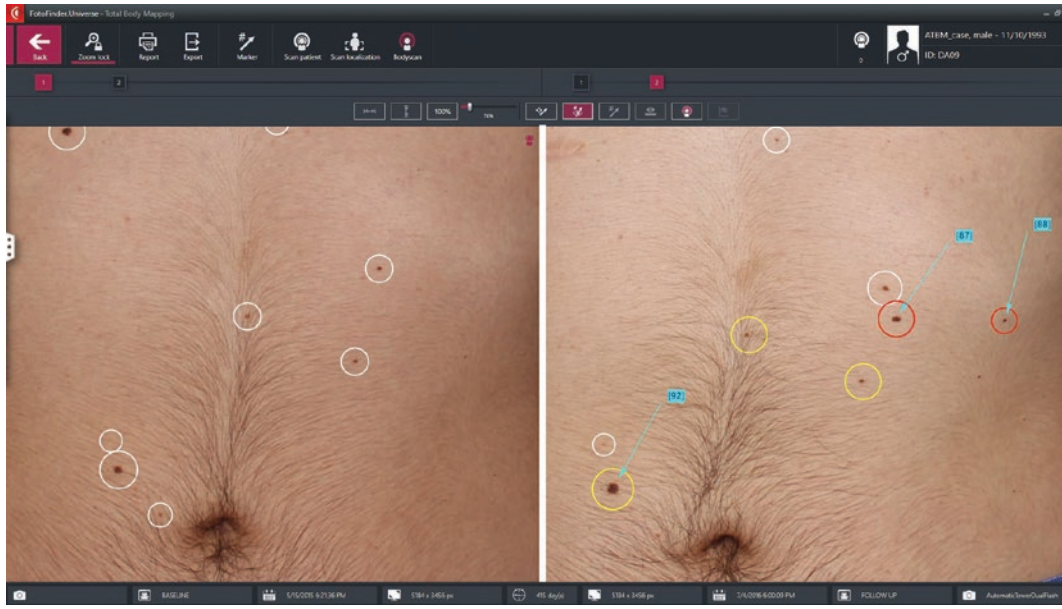

Fig. 5.2 FotoFinder system automatically circling new and changing nevi (images supplied by FotoFinder Systems)

newer TBP imaging devices also include the capability of "mole analysis." These may incorporate the ability to calculate clinical and/or dermoscopic diameter, borders, symmetry, and structures within the pigmented lesion as well as determine if there has been change over time. Finally, some also include artificial intelligence applications that have been incorporated after extensive training of the computer via "deep learning" or learned algorithms. Although most imaging technologies are two dimensional, there is now a product that produces a digital three-dimensional avatar of the patient. Table 5.2 provides an overview of features specific to some of the currently available systems.

Because of the sensitive nature of the images, the technology requires sophisticated IT, patient security and HIPAA capabilities. Unfortunately, most insurance companies still do not reimburse for this type of photography, offsetting the costs to patients.

As with all technology, there are limitations associated with TBPs: (1) Hypopigmented lesions are less reliably detected [15]; (2) Lesions in poorly lit regions on the skin surface, such as the axilla or beneath the chin [16], may be less well imaged; (3) Some areas of the body are not usually imaged including oral mucosa, behind the ears, scalp, and genital skin (particularly of women); (4) Imaging specifications such as lighting, magnification, and resolution have not been defined leading to variable image quality and limited comparison between imaging techniques [17] although recent publications have attempted to make recommendations to provide this information [18, 19].

5.3 Sequential Digital Dermoscopy

When evaluating a clinical lesion with our naked eye, we are only able to visualize structures on the superficial skin surface because most of the light does not penetrate the stratum corneum. Therefore, only structures on the superficial skin surface are visualized and those structures deeper in the skin are not seen. A dermatoscope is a handheld instrument that affords us the ability to inspect skin lesions unobstructed by skin surface reflection. The dermatoscope is composed of a magnifier, a transparent plate, and a light source (polarized or non-polarized). There are three varieties of dermatoscope (many of which now come as hybrids with all three capabilities): (1) contact (requiring a liquid medium between the

Table 5.2 Total body photography systems

Total body photography commercially available devices			
TBP system	Features	Dermoscopy (Y/N)	Websites
FotoFinder	• AI detection of new or changing lesions • Measures structures • Mole risk assessment • Second opinion services • Mole analyzer	Y	https://www.fotofinder-systems.com/
DermaGraphix by Canfield	• A password protected and encrypted USB drive for each patient with their images for at home monitoring • Wireless capture and tagging of dermoscopic images • Full screen close up imaging review	Y	https://www.canfieldsci.com/imaging-systems/dermagraphix/
VECTRA WB360 by Canfield	• 360 and 180 degree imaging • Ability to add clinical history note to each tracked lesion • Searchable lesional attributes	Y	https://www.canfieldsci.com/imaging-systems/vectra-wb360-imaging-system/
MoleMap	• Patient access to personal mole mapping photos • Only available in New Zealand	Unknown	https://www.molemap.net.au/
DermEngine	• Cell phone compatible dermatoscope • Integration with multiple medical records • AI visual searchability for similar lesions	Y	https://www.dermengine.com/
MoleSafe	• Available for primary care office implementation since lesion evaluation is performed remotely by experts • Full diagnostic report provided to primary physician and patient • Online patient portal with all images for at home monitoring	Y	https://www.molesafe.com/

TBP Total body photography, *AI* Artificial intelligence [9–14]

instrument and the skin, which is usually 70% alcohol) non-polarizing, (2) contact polarizing, and (3) non contact polarizing. The enhanced ability to visualize subsurface structures aids in the early detection of melanoma and other types of skin cancer. Non-polarization is best to visualize more superficial structures in the skin. The two filters used in polarizing dermatoscopes cancel out light reflected off the stratum corneum, allowing better visualization of deeper skin structures, like vascular structures and the presence of dermal fibrosis.

Sequential digital dermoscopy (SDD) utilizes digital dermoscopic images taken chronologically and compared for the possibility of change, increasing the ability to recognize clinically imperceptible alterations within a lesion. Unlike TBP, in which gross changes can be observed, SDD allows for the detection of subtle dermoscopic variations, which on occasion can be overlooked on gross clinical imaging. Employing SDD in a practice has been demonstrated to increase the frequency of detecting in situ melanomas, representing up to 53.3% of all melanomas diagnosed [7]. Additionally, the mean Breslow thickness of invasive melanoma diagnosed when utilizing SDD (0.41 mm thickness) versus only standard detection techniques (0.62 mm thickness) was significantly thinner [20], confirming earlier detection and improved prognosis. To enhance diagnostic accuracy, SDD can easily be combined with TBP programs to integrate both technologies.

SDD is associated with some known limitations. Melanocytic nevi, especially in younger patients, can change over time, and this will be highlighted by SDD. It has also been demonstrated that when follow-up is shorter

than 3–4.5 months, changes between nevi and melanoma may not be distinguishable [21, 22]. Conversely, when follow-up is greater than 4.5 months, dermoscopic changes within melanoma demonstrated greater changes in color and symmetry [22].

5.4 Reflectance Confocal Microscopy

Reflectance Confocal Microscopy (RCM) is a noninvasive "virtual biopsy" that allows visualization of lesional tissue to the depth of the papillary dermis (about 250 μm) on a cellular level simulating what would be seen with histology. RCM uses a diode, near-infrared monochromatic and coherent (830 nm) laser that passes through a beam splitter and optical lens to penetrate a focal target in the tissue. The light is then reflected off the lesional tissue [23] and passes through an objective lens that focuses the light through a pinhole aperture which filters out surrounding scattered light. This allows for visualization of epidermal and superficial dermal structures horizontally, resembling sections seen in Mohs histopathology. The images are based upon the varied refractive indices of different components within the skin.

5.4.1 Available Devices

There are currently two commercially available RCM devices in the USA: VivaScope 1500 (Fig. 5.3a) and VivaScope 3000 (Fig. 5.3b), both available from Caliber Imaging and Diagnostics, Rochester, NY [24]. The VivaScope 1500 can acquire a dermoscopic image as well as RCM mosaics that utilize a fixed wide probe scope involving a distal 2 cm metal ring that requires direct contact with the skin for imaging. RCM can capture a lesion up to 8 by 8 mm in diameter and acquires horizontal mosaics or planes sequentially at various levels of the epidermis into the papillary dermis. It also has the ability to acquire a <1 mm in diameter stack from the stratum corneum down to approximately 250 μm,

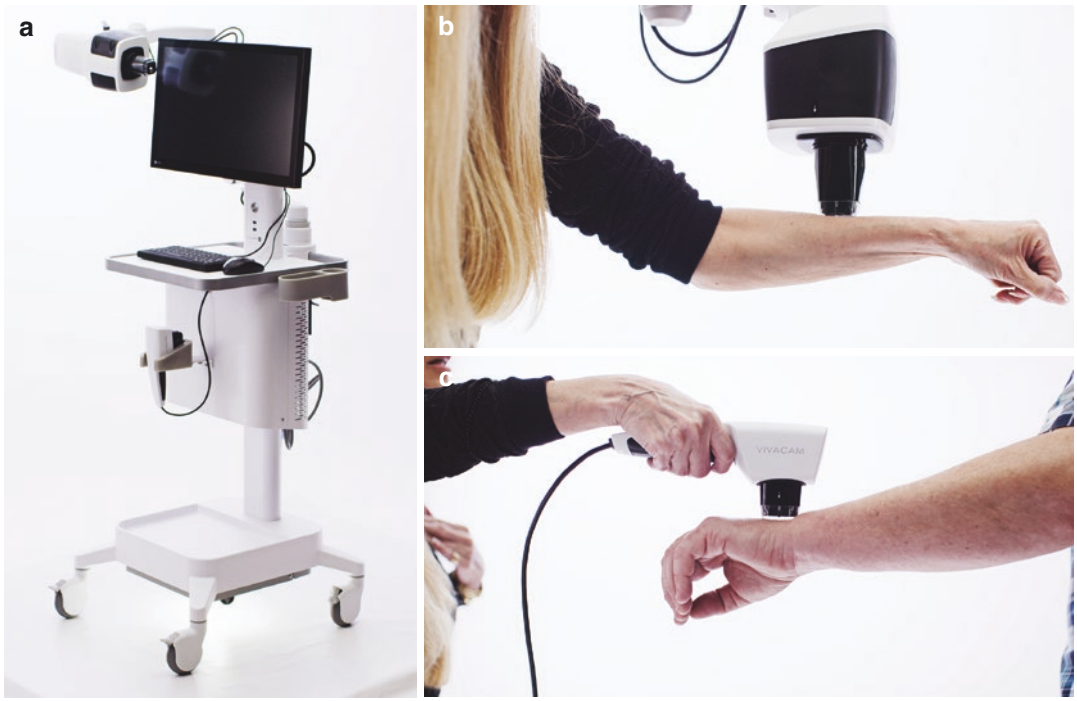

Fig. 5.3 (**a**, **b**) VivaScope 1500 (**c**) VivaScope 3000 (images supplied by Caliber Imaging and Diagnostics)

Table 5.3 Comparison of reflectance confocal microscopy devices that are commercially available [25, 26]

Reflectance confocal microscopy commercially available devices			
Device	Style	Advantages	Disadvantages
VivaScope 1500	Attached wide-probe	• FDA approved with reimbursable CPT codes • 8 × 8 mm maximum image • Captures dermoscopy and RCM images (both mosaics and stacks) • Real-time imaging	• Limited utility on curved or narrow surfaces • Time consuming to capture images
VivaScope 3000	Handheld	• Flexible and mobile • Real-time video capture • Less time to acquire stack • Easier to assess multiple lesions or areas	• 0.75 mm^2 image size (<1 mm in diameter) • Not reimbursable • No dermoscopic correlation • No mosaic captured; only stacks

RCM reflectance confocal microscopy, *FDA* federal drug administration, *CPT* current procedural terminology

allowing further examination of clinical or dermoscopic areas of clinical concern. The 2 cm metal ring limits specific locations on the body (curves or narrow regions) due to the inability to create appropriate contact. The VivaScope 3000 is a handheld probe, which is more readily moved around the body and uses a smaller probe that is more versatile in difficult to reach or curved body regions but only allows one to capture a stack that has a total final frame size of 0.75 mm^2 (<1 mm in diameter). Table 5.3 highlights the differences between the two devices.

The VivaScope 1500 was granted valued current procedural terminology (CPT) codes (96931–96936) [27] in 2016; however, the VivaScope 3000 has yet to be assigned CPT codes.

5.4.2 Virtual Biopsy Process: Wide Probe vs. Handheld

After identification of a suspicious lesion, RCM imaging can be performed by a trained nonphysician health care professional. Prior to starting the procedure, patient demographics and lesional history are entered into the software. An adhesive metal ring with an optically clear window is attached to the skin after the application of mineral oil. Then a dermoscopy image can be acquired. Next, the vivascope wide probe is magnetically attached, and ultrasound gel is placed on the window. Images are obtained in horizontal cross-section and stitched together into a mosaic up to 8 × 8 mm at a specific anatomic level. This is repeated at deeper or more superficial levels [28] as needed. In contrast, the handheld probe is able to acquire stacks only and does not require an adhesive window; it can simply be moved from one location to another without the need for reattachment of the initial window. The images are usually stored securely with cloud computing software. Imaging can then be read by a trained dermatologist at the bedside or similar to a biopsy specimen, referred to a dermatopathology laboratory able to interpret these images [23].

5.4.3 Terminology for RCM

In 2007 a consensus of six RCM investigators, who had previously contributed descriptive terminology to the literature, developed standardized RCM nomenclature relating to pigmented lesions with the intent of unifying the vocabulary used to describe RCM findings [29]. In 2019 an international DELPHI consensus further agreed upon 15 melanoma-specific RCM terms (Table 5.4). Recently two key features for the RCM diagnosis of melanoma were identified: “atypical cells” and “dermoepidermal junction (DEJ) disarray” [30]. Atypical cells, as defined by Pellacani et al. denote “large (>20-

Table 5.4 Basic terminology for RCM for melanoma

Melanoma reflectance confocal microscopy consensus features in melanoma		
Terminology	Visual appearance	Clinical meaning
Dermal papillae: Edged	Normal papillae with dark holes (dermal papillae) surrounded by a circumscribed rim of refractile cells at the periphery. The presence of many edged papillae is called the *Ring Pattern*	Normal DEJ. Can be seen in normal skin, simple and solar lentigines, seborrheic keratoses, and some melanocytic nevi
Dermal papillae: Nonedged	Absence of this rim of refractile cells around the dermal papillae	Loss of DEJ architecture due to a cellular proliferation (of melanocytes) at the DEJ; seen in atypical nevi or melanoma.
DEJ disarray	Nonedged papillae and disorganized or irregular asymmetrically distributed ring, meshwork, or clod pattern	Disruption of the DEJ suggestive of an atypical melanocytic lesion
Nests	Collections of melanocytes forming small uniform clusters (nests)	Large, irregular, unevenly spaced, and asymmetrical nests can be seen in melanoma
Cellular characteristics: • Cell size and shape • Monomorphic versus pleomorphic • Atypical	Cell size in comparison to the size of surrounding keratinocytes. Cells that are similar or vary in size and shape	Features that may be helpful to establish the diagnosis of a melanoma
Pagetoid spread: Present or absent Pagetoid cells: • Size • Shape • Density • Distribution (focal, diffuse, periadnexal) • Extension to stratum corneum • Pleomorphism	Presence of enlarged cells twice the size of keratinocytes with bright cytoplasm and dark nuclei in epidermis	Presence of round and/or dendritic refractile cells in the upper layers of the epidermis. Usually seen in atypical melanocytic processes. Must distinguish dendritic melanocytes from dendritic refractile Langerhans cells due to Birbeck granules

DEJ dermoepidermal junction [30]

μm), roundish and/or dendritic cells in the suprabasal epidermis and/or DEJ and/or dermis, either presenting as single isolated cells or forming clusters." DEJ disarray includes "nonedged papillae" as well as "disorganized/chaotic pattern" or "poorly defined areas" at the DEJ that "encompass more than 10% of the lesion area" [30].

5.4.4 Technology Requirements, Training, and Cost

This technology has the following issues:

1. The initial cost of the device is relatively high. A cost estimate published in 2014 approximated the initial price of the machinery around 90,000 pounds (117,140 dollars) [31]. However, the presence of valued CPT codes allows for this technology to be reimbursable, affording the physician a way to add this technology to their practice.
2. Training requires months of guided instruction with the evaluation of many cases before a physician becomes competent in interpreting the mosaics and making a diagnosis. This limitation can be offset by the Vivanet telemedicine server that can send RCM images for remote evaluation to an expert [32]; therefore, a practice could physically implement this service without training or hiring a dermatologist/dermatopathologist competent in interpreting RCM mosaics by employing teleconfocal microscopy. Additionally, there is a free website (Confocal101.com) created

by Dr. Harold Rabinovitz and colleagues that contains a lecture series and even unknown practice cases with answers [33].

5.5 Optical Coherence Tomography

Optical coherence tomography (OCT), is a non-invasive laser optical imaging technique that uses infrared light to visualize a lesion. OCT creates backscatter through the reflection of photons by internal structures, which are used to create two-dimensional and three-dimensional images. It shares some similarities to ultrasound imaging, but instead of using sound waves to create an image, it relies on near-infrared relatively long wavelength light waves. OCT does not require contact with the skin or a conductive medium (ultrasound gel) to pass through skin appropriately. Although OCT shares similarities with RCM, RCM provides mosaics with cellular detail down to approximately 250 um while OCT provides cross-sectional images with the structural-level resolution, but not cellular detail, into deeper skin layers down to a depth of approximately 1.5 mm.

There are three main types of OCT: conventional optical coherence tomography (conventional OCT), high-definition optical coherence tomography (HD-OCT), and speckle variance optical coherence tomography (SV-OCT). Conventional OCT can provide architectural structure down to 1 mm below the skin surface but does not allow for clear cellular visualization [34]. This can allow for assessment of invasion in predetermined cutaneous melanomas but makes the initial diagnosis of melanoma challenging. However, HD-OCT can provide both architectural structure and some cellular resolution to a similar penetration depth [34]. The clear visualization of cellular components of a lesion allows for improved diagnostic function. SV-OCT relies on shifting particles within blood vessels to differentiate microvasculature from static tissue and forms four-dimensional images [35], which incorporate flow or movement into the imagery. This type of OCT can be thought of as being similar to angiography.

5.5.1 Structural Features

Although no consensus guidelines on terminology or characteristics currently exist, a descriptive review of current literature as it pertains to melanoma diagnosis has been published [36]. Similar to many other diagnostic techniques, there are specific melanoma-related features more readily viewed with the different types of OCT (Table 5.5) [36]. Further clarification on terminology will be required for OCT prior to widespread implementation.

5.5.2 Disadvantages

As with the previously mentioned technologies, OCT has substantial start-up requirements, including the purchase of an OCT device. The current commercially available devices are directed towards ophthalmology and are not suitable for skin lesions. Currently, there are no commercially available systems for use in

Table 5.5 Structural features of melanoma seen using OCT [36]

Structural features of melanoma seen using optical coherence tomography		
Type of OCT	Visual appearance	Histopathology correlation
Conventional OCT	Absence or ill-defined lower border of the lesion	Invasion of melanoma into the dermis
HD-OCT	Icicle shaped structures in the epidermis	Pagetoid spreading melanocytes
	Broadening and blurring of the rete ridges	Irregular or discohesive junctional or superficial dermal nests
SV-OCT	Multiple densely organized dots	Irregular and increased vasculature

dermatology. With regard to lesion recognition, OCT is largely limited in distinguishing between basal cell carcinoma and amelanotic melanoma since the cellular resolution is not adequate [37], and the diagnosis with OCT relies heavily on architectural alterations. Finally, there are no CPT codes for this technology at the time of preparing this text, further limiting the feasibility of incorporating this technology into clinical practice.

5.6 Electrical Impedance Spectroscopy

Electrical impedance is a measure of the ability of a circuit to resist the flow of an electrical current. Electrical impedance spectroscopy (EIS) utilizes a handheld device that painlessly measures electrical impedance or resistance between cells in tissues at various frequencies. This technology allows measurement of opposition to an electrical current when a circuit is created by the contact of an EIS device with the skin. The electrical impedance in banal nevi and melanoma differ, allowing for determination between benign and malignant lesions [38]. These handheld devices (Fig. 5.4a) include a disposable electrode that can be applied directly to the skin while the impedance is visualized on an attached screen with a device that calculates an EIS algorithm. The electrode (Fig. 5.4b) is covered with microinvasive pins, which painlessly penetrate the stratum corneum, applies a voltage, and measures the electrical impedance within seconds of application [39]. Subsequently, the display screen reports a number between one and ten, with lesions four and above regarded as "positive" and those below that range as "negative." A negative test has a 98% negative predictive value and therefore, according to this device's algorithm, does not warrant a biopsy [40]. Higher positivity (range 4–10) is directly correlated with a higher degree of histologic atypia [39]. Although the EIS unit is not as compact as a dermatoscope it can be easily moved between exam rooms.

Although EIS is highly sensitive with reported numbers up to 96.6%, specificity is limited (around 34.4% for melanoma) when using a positivity score of four or greater on the Nevisense device [38]. Due to the low specificity, this device is best utilized by a dermatologist for differentiating lesions already suspected as malignant. For example, when the device was used clinically on lesions that were already deemed suspicious, based on clinical morphology, the specificity increased to 58.6% while simultaneously increasing the number of malignant neoplasms biopsied and decreasing the rate of benign melanocytic nevi biopsied [41]. The device is not intended for thick lesions (greater than 2 mm), ulcerated lesions, scarred lesions, fibrotic lesions, acral sites, or hair-bearing areas [42]. If EIS is combined with other technologies, including dermoscopy, TBPs, and sequential digital dermoscopy, it has been postulated to further increase the specificity in identifying suspected melanomas [43]. Although the technology is FDA approved, there are no CPT codes for billing insurers. Figure 5.5 further elucidates the recommended stepwise approach to EIS utilization in clinical practice.

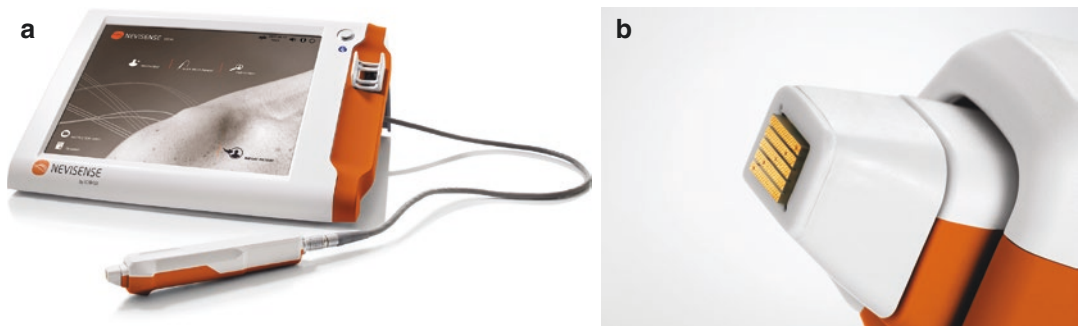

Fig. 5.4 (**a**) Nevisense device and display screen. (**b**) Disposable electrode (images supplied by Scibase)

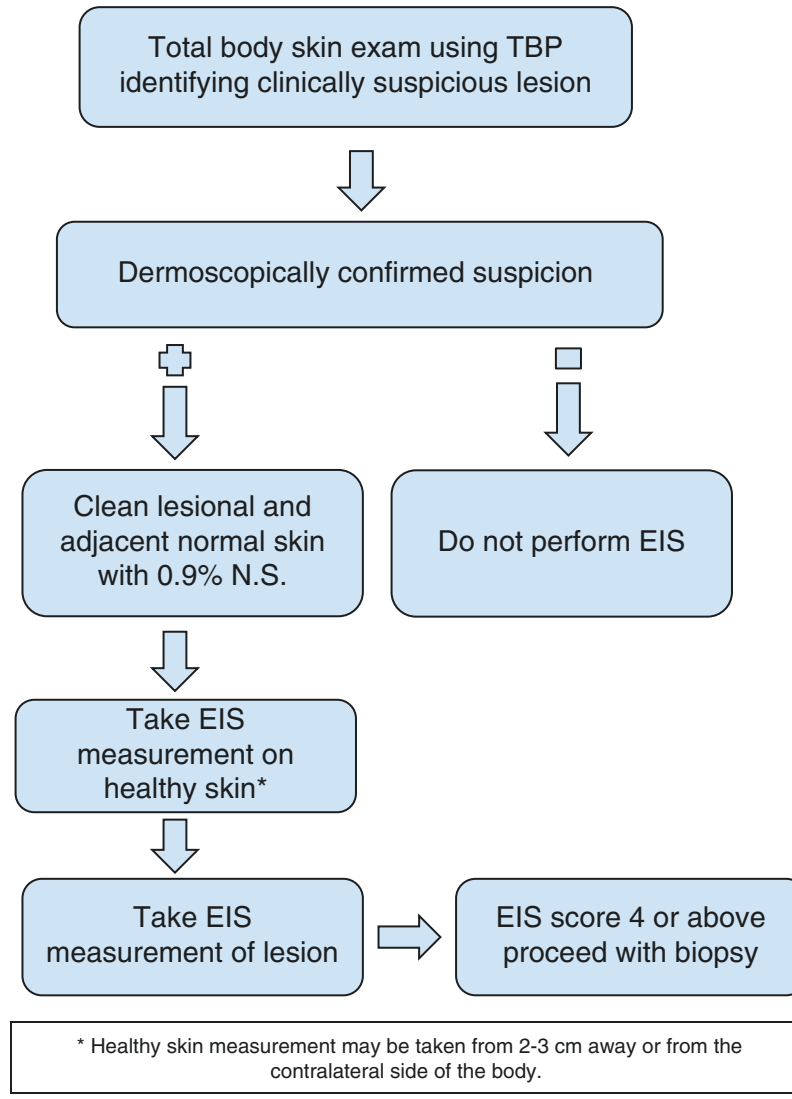

Fig. 5.5 Proposed stepwise approach to electrical impedance usage. *TBP* total body photography, *EIS* Electrical impedance spectroscopy, *NS* normal saline

5.7 Genetic Applications for Diagnosis and Prognosis

5.7.1 Adhesive Patch Biopsy

The technique of adhesive patch biopsy (also referred to as tape stripping) requires the application of an adhesive tape to a skin lesion with subsequent removal and harvesting of cells. Adhesive patch biopsy kits that are commercially available (through DermTech, Inc) require four tape application and removal cycles to a suspicious lesion (Fig. 5.6). Each application and removal cycle collects a thin layer of stratum corneum in addition to genetic debris from keratinocytes, melanocytes, basal cells, T lymphocytic cells, and dendritic cells [44]. Studies have shown that lesional ribonucleic acid (RNA) from patch biopsy samples can then be successfully amplified and used for gene expression profiling [45].

Unfortunately, due to technical requirements, this option is not appropriate for mucous membranes due to the inability of the adhesive to appropriately attach, palms and soles due to the thickened stratum corneum, bleeding lesions, and ulcerated lesions. Areas with terminal hairs or

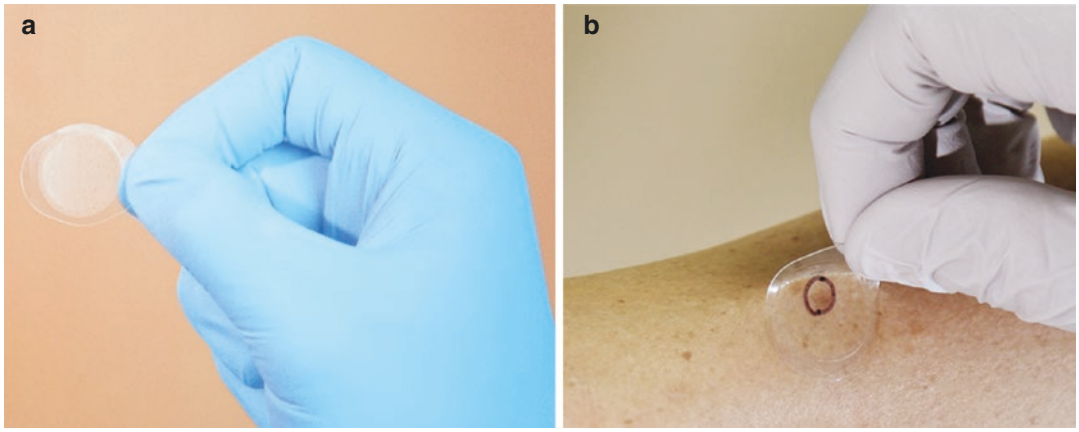

Fig. 5.6 (**a**) Adhesive patch biopsy strip. (**b**) Removal of adhesive patch during biopsy (images supplied by DermTech, Inc)

high-density vellus hair-bearing regions can only be sampled if the hair is cut down with scissors. Shaving is not recommended as it can remove essential genetic material and contaminate the sample with blood, which interferes with processing.

5.7.2 Pigmented Lesion Assay

The company DermTech, Inc. has developed a two-gene molecular assay called the Pigmented Lesion Assay (PLA) which is able to differentiate benign and malignant pigmented lesions by utilizing skin cells obtained through adhesive patch biopsy. The two-gene assay includes the long intergenic non-coding RNA 518 gene (LINC00518) and the preferentially expressed antigen in the melanoma gene (PRAME) [46]. An initial validation study and subsequent confirmation study found that the process of adhesive patch biopsy with subsequent genomic analysis via PLA was capable of detecting cutaneous melanoma with a sensitivity of 91% and a specificity of 69% [46, 47]. When assessing for clinical utility, Ferris et al. found that 93% of cases that were positive for both genes (PRAME and LINC00518) were histologically confirmed as melanoma, while 50% of PRAME only and 7% of LINC00518 only were consistent with melanoma [48]. When incorporating PLA results into the decision to perform a biopsy of pigmented lesions, dermatologists increased their specificity from 32.1% to 56.9%, decreasing the number of unnecessary biopsies [49].

Unfortunately, PLA must be performed at a specialized laboratory, and the patch biopsy samples must be mailed to DermTech, Inc., which would necessitate a delay in biopsy for any lesions that are suspicious for melanoma (based on PRAME and LINC00518) positivity. The patient would then be required to return for an additional appointment for the biopsy. Lastly, even when sampling an appropriate area, there is a 14% chance of obtaining an inadequate sample [46], which may necessitate the patient returning for additional evaluation. To date, there are no CPT codes associated with this non-FDA-approved tool.

5.7.3 Gene Expression for Prognosis

Melanoma prognosis is highly variable, with a multitude of factors influencing patient outcomes, many of which are still being elucidated. Many tumor characteristics have been well documented to influence prognosis (location, depth of invasion, ulceration, number of mitoses, etc.), yet these factors do not perfectly characterize the heterogeneity of melanomas and, therefore, the prognostic outcomes. Many research laboratories

have sought to identify critical biomarkers which may accurately predict patient outcomes for melanoma. A product from Castle Biosciences was developed that evaluates the gene expression profiles (GEP) of 31 melanoma-specific genes [50]. This classification allows biopsy-proven melanomas to be differentiated into low or high-risk categories for recurrence or metastasis, class 1 or class 2, respectively [50]. In a cohort of 523 patients with cutaneous melanoma, 5 year recurrence-free survival was calculated as 88% for class 1 and 52% for class 2 [51]. In a prospective analysis of 322 stage I to III cutaneous melanomas, a recurrence rate of 27% and 2% in class II and class I, respectively, have been reported [52]. Initial research suggests the GEP is able to assist in successfully stratifying cutaneous melanomas into high and low-risk groups with the intention of altering clinical decision-making (frequency of screening exams, imaging, and sentinel lymph node biopsy) based on GEP classification. Based on the American Academy of Dermatology level of evidence criteria, this test was recently awarded an evidence level of IIA as only short-term follow-up is available [53].

This test has not been validated in patients with melanoma in situ, distant metastases at the time of presentation, mucosal melanomas, or pediatric patients, thereby limiting the utility in many patients. Furthermore, the assay can only be performed at the Castle Biosciences laboratories; tissue from the primary biopsy or subsequent excision must be mailed directly to their facility for processing, which may prove cumbersome for pathology laboratories. Finally, CPT codes have not been assigned to this FDA-approved technology.

5.8 Artificial Intelligence

Artificial intelligence (AI) relies on a computer to perform tasks that are normally performed under the guidance of human thought. The process of developing AI to perform complex tasks requires the development of a deep neural network algorithm. The concept of neural networks, aka deep learning, is modeled around neurons. There are multiple variables that are input into the system (analogous to dendritic inputs into a cell body), which in turn generates only one output (or action potential along an axon) (Fig. 5.7). AI programs are taught to not only interpret but also weigh the importance of various morphological structures of a pigmented lesion and then make an output determination of benign or malignant. This learning involves showing the computer more than 100,000 images of confirmed malignant and benign skin cancers and melanocytic nevi and then revealing the diagnosis for each image.

An algorithm is only as advanced as the material it is initially taught; therefore, the quality of recognition depends on the training received, similar to the training a dermatologist receives throughout their career. When an extremely large data set of images is used to train a computer for a specific algorithm, the diagnostic accuracy becomes comparable or slightly superior to that of a board-certified dermatologist [54–56].

How this technology will be incorporated into primary care offices in areas with limited access to dermatologists or into dermatologists' offices remains unknown. The goal of AI would be to improve the quality of consults referred to dermatologists and improve accuracy for dermatologists who implement this technology into their practice. When AI was combined with clinical decision-making by a trained dermatologist, an initial study showed an increase in sensitivity of diagnosing melanoma from 86% to 89% [57]; another recent study showed similar improvement [56].

This data suggests that the combination of technology and clinical acumen may be superior to that of technology or expert dermatologic care alone. The dermatologist plays a vital role as AI does not currently integrate clinical context or history of lesions into its processing which can clearly have an impact on clinical decision-making [58]. Furthermore, AI focuses on the science of medicine while ignoring the equally important concept of the art of medicine, human connection, compassion, and empathy.

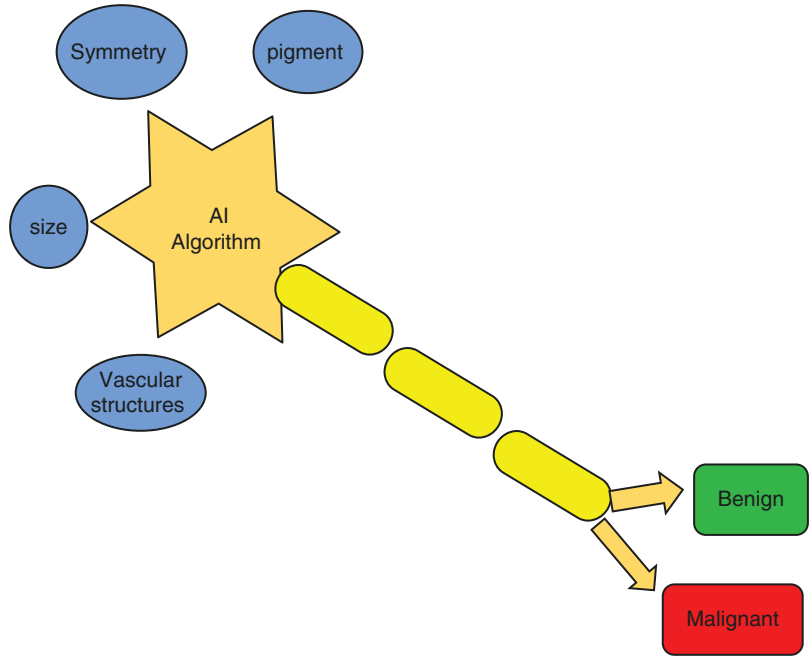

Fig. 5.7 Visual representation of AI algorithm interpreting data in the determination of malignancy status of a lesion

5.9 Conclusion

There are currently a myriad of new and evolving melanoma detection tools with varying utility and feasibility for clinical practice, and we have highlighted currently available resources to improve detection and diagnostic accuracy further. The utilization of these newer technologies will be up to the discretion of each individual physician. It is likely that many of the aforementioned technological advances will become the standard of care in the years to come as their feasibility, accessibility, accuracy, and utility are continually improved.

Conflicts of Interest None.

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Evolution of Melanoma Staging

6

Candice E. Brem and Lynne J. Goldberg

6.1 Introduction

The frontiers of melanoma staging are constantly in flux. In this chapter, we seek to explore the historical and current literature which has allowed for various changes and modifications of the staging classification for melanoma over time. Specific emphasis will be placed on those changes which have not only served to form the foundation of our current understanding of melanoma biology and behavior, but those which may also impact future directions and changes to come in subsequent editions. The current melanoma staging is outlined in the eighth edition of the American Joint Committee on Cancer (AJCC) Staging Manual. However, for the most up-to-date information for the melanoma staging system, we direct the readers to the AJCC website: www.cancerstaging.org.

6.2 History of Melanoma Staging

6.2.1 Background

Melanoma, an invasive cancer composed of atypical melanocytes, is arguably one of the most aggressive and deadly malignancies. In the United States, although melanoma accounts for only for 1% of all skin cancers, it is responsible for the vast majority of skin cancer-related deaths [1]. In the last decade advances have been made in melanoma treatments, including molecular targeted therapies against the v-raf murine sarcoma viral oncogene homolog B (BRAF) proto-oncogene and mitogen-activated protein kinase kinase (MEK), along with immunotherapies for various checkpoint inhibitors targeting cytotoxic T cell lymphoma-associated antigen 4 (CTLA-4), and both programmed death-1 (PD-1) and its ligand (PD-L1) [2]. These changes to our treatment armamentarium have allowed for significant improvement in patient outcomes and overall survival, especially in those patients with advanced stage and/or metastatic melanoma [3]. In some patient cohorts, median survival rates have increased from 7 to 9 months to >4–5 years [4]. Now, perhaps more than ever before, it is of utmost importance to have a method by which to stage these patients in order to offer appropriate treatment modalities.

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The overall purpose of such a unified classification system, like that provided by the AJCC Cancer Staging Manual, is to create a universally applicable system that can assist in patient risk-stratification, prognosis, and treatment recommendations. The most important of those is an accurate assessment of prognosis, a quality that even in the infancy of cancer staging was deemed a priority. It is understandable that over time our protean melanoma staging system has changed, given the features thought to be the most relevant for a particular time period [5]. In fact, to understand our current staging system, it is helpful to historically review where the staging system started, and how it has morphed into its current form as seen in the eighth edition of the AJCC Cancer Staging Manual.

6.2.2 Before the AJCC Staging Manual (Prior to 1977)

The history of melanoma is vast, extending well into antiquity, with the first credible literary description or mention documented by Hippocrates in the fifth century BCE. The first physical evidence of cutaneous and metastatic melanoma comes from multiple Peruvian, pre-Colombian Incan mummies estimated (by radiocarbon 14) to be 2400 years old. Additionally, melanoma has also gone by many names over the years, including the descriptive "fatal black tumors with metastases and black fluid in the body" of the 1600s, Laennec's 1806 "la mélanose," and finally Robert Carswell's 1938 recommendation for the usage of the term melanoma to describe malignant pigmented tumors [6]. However, it is not until 1953 that Allen and Spitz specifically mention certain clinical features with prognostic and diagnostic significance, including the importance of depth in melanocarcinoma (malignant melanoma), specifically the designation of a tumor as superficial or deeply invasive [7].

In 1954, Ackerman and Del Regato were among the first to subdivide patients into groups based on extent of disease, lymph node status, and distant metastasis, with rough estimates of survival advantage in certain groups [5]. The first official melanoma staging system based on histology came in 1962, when Petersen et al. enumerated the following three-stage classification system: Stage 1, no invasion of the dermis (melanoma in situ); Stage 2, invasion of the superficial dermis without tumor formation; and Stage 3, tumor formation [8]. This initial staging system, along with Mehnert et al.'s study in 1965 which further refined the stages of invasion as Stage 0, in situ; Stage 1, superficial; Stage 2, intradermal; and Stage 3, subcutaneous [9], would lay the foundation for the anatomic or so-called Clark levels of invasion.

Clark et al.'s 1969 study, based on the analysis of 269 malignant melanomas collected at Massachusetts General Hospital (MGH) prior to 1958 until May of 1968, subdivided depth of invasion into five levels based on prognosis, although it is unclear if Clark's levels of invasion predated or were based upon statistics of disease-free survival and death. Stage 0 became Level I and remained as melanoma in situ and Stage 3 became Level V, defined as tumor entering the subcutaneous tissue, the deepest level, with a disease-free survival (DFS) of 12% at 3 years and a melanoma-related death rate of 52%. Stage 2 was further divided into Levels II, III, and IV. Level II, with a DFS of 72% at >5 years and a melanoma-related death rate of 8%, encompassed superficial invasion of the thin and fine collagen of the papillary dermis, including the areas directly adjacent to the adnexal or appendageal structures, without extension into the thicker collagen fibers of the reticular dermis. Level III, with a DFS of 47% at >5 years and a melanoma-related death rate of 35%, filled the papillary dermis impinging upon the reticular dermis. Level IV, with a DFS of 32% at >5 years and a melanoma-related death rate of 46%, demonstrated invasion between the deeper collagen bundles of the reticular dermis [10]. In 1970, McGovern would use a similar five-tiered histologic staging method, with the exception that Level III was defined as extension to the level of the subpapillary vascular plexus, which confirmed survival differences in stages two through five [11].

Even with improvements in staging, there remained issues with the reliability of prognostic estimates. Occasional cases of "small" or superficial melanomas would somehow unexpectedly recur, become metastatic, and result in death [12]. In 1970, Breslow suggested that perhaps calculating maximal tumor depth with an ocular micrometer and maximum cross-sectional area, which would be roughly proportional to tumor volume, could yield improved prognostic estimates. Breslow studied 98 patients and subdivided them into the following groups: <0.76 mm, 0.76 mm–1.50 mm, 1.51 mm–2.25 mm, 2.26 mm–3 mm, and >3.00 mm [13]. While these divisions demonstrated "reasonably good agreement" with Clark's previous five-level system, there was a key difference. Breslow noted that within his grouping system, some Clark level II and III lesions with a measured depth of <0.76 mm had an excellent prognosis and did not recur or metastasize. He would use this piece of information to argue against prophylactic lymph node dissection in this population [13]. In the following years, additional staging methodologies would be put forth, including a clinically based four-stage system by McNeer and Das Gupta at MD Anderson Hospital in 1976, which did not address tumor thickness or Clark level [5].

6.3 AJCC Cancer Staging Manuals, 1977 to Present

Based heavily on the work of the aforementioned dermatopathology giants (i.e., Breslow, Clark, and McGovern), the first edition of the AJCC Cancer Staging Manual was published in 1977. This staging system would combine some of the earliest ideas, identified by Ackerman et al. in 1954 [5], with a histopathologic assessment of the primary tumor to form the Tumor, Node, Metastasis (TNM) staging system that remains the basis for current staging modalities.

A total of 8 subsequent editions have since been published. Below, the various editions have been split into first through fifth editions and sixth through eight editions, based on changes in thought and research focus. The initial editions of the AJCC Cancer Staging Manual synthesize previous research to establish a framework and general staging criteria with subsequent modifications focusing predominantly on deeper lesions. In contrast, the newer editions take a special interest in thin melanomas and further modify the node and metastasis stages, occasionally with clinical and serologic patient information.

6.3.1 Tumor Stage, First through Fifth Editions (1977–2002)

The four pathologic Tumor (pT) stages appear to be based on Breslow's 1970 article [13], with the exception that his five divisions were simplified into four T stages (groups three and four were combined into the pT3 group, measuring 1.51–3.00 mm) (Table 6.1**,** second row). Subcategory designations were reserved for lesions with (a) regional satellites and (b) in-transit metastases. Additionally, it had been decided that both Clark level of invasion and Breslow depth (thickness) of the primary lesion should be recorded, given that there was not enough data to predict which would provide the most accurate assessment of prognosis [14].

In 1978, just a year after the first edition was published, Breslow was part of the group that evaluated the correlation between survival and both Breslow depth and Clark level of invasion. Correlation was statistically significant for tumor thickness with a p value of 0.0002, while the level of invasion had a p value of 0.04 [22]. In that same year, Balch et al. would similarly confirm these findings indicating that Clark level, while it correlated with survival, was less predictive of 5-year survival rates when compared to Breslow depth ($p = 0.032$) [23]. However, given that Clark level still had merit, it was kept as a component of the T stage, even serving to further subdivide thin pT1 melanomas in the sixth edition (Table 6.1, seventh row) [19] until it was omitted, although still recorded, in the seventh edition [20].

The second edition would only see minor changes in reporting guidelines, though the changes themselves would involve the most

Table 6.1 Summary of the AJCC cancer staging pathologic Tumor (T) stage, first through eight editions

AJCC edition	pT0	pTis	pT1	pT2	pT3	pT4
First edition [14]	N/A	N/A	<0.75 mm and/or L II	0.75 mm–1.50 mm and/or L III	1.51 mm–3.0 mm and/or L IV	>3.0 mm and/or L V
			pT1a: regional satellites	pT2a: regional satellites	pT3a: regional satellites	PT4a: regional satellites
			pT1b: in-transit metastasis	pT2b: in-transit metastasis	pT3b: in-transit metastasis	pT4b: in-transit metastasis
Second edition [15]	AMH	N/A	≤0.75 mm or L II	0.76 mm–1.5 mm or L III	1.51 mm–4.0 mm or L IV	>4.1 mm or L V
Third edition [16]	No known 1^0 tumor	In situ	≤0.75 mm and L II	0.75 mm–1.5 mm and/or L III	>1.5 mm–4 mm and/or L IV	>4 mm and/or L V
					pT3a: <3 mm	pT4a: invades subcutis
					pT3b: 3 mm–4 mm	PT4b: satellites within 2 cm of 1^0
Fourth edition [17]	No/minimal change from AJCC third edition					
Fifth edition [18]	No/minimal change from AJCC third edition					
Sixth edition [19]	No known 1^0 tumor	In situ	≤1.0 mm	1.01 mm–2.0 mm	2.01 mm–4.0 mm	>4.0 mm
			pT1a: L II, III, ulceration absent	pT2a: ulceration absent	pT3a: ulceration absent	pT4a: ulceration absent
			pT1b: L IV, V or with ulceration	pT2b: ulceration present	pT3b: ulceration present	pT4b: ulceration present
Seventh edition [20]	No known 1^0 tumor	In situ	≤1.0 mm	1.01 mm–2.0 mm	2.01 mm–4.0 mm	>4.0 mm
			pT1a: ulceration absent, and mitoses <1/mm^2	pT2a: ulceration absent	pT3a: ulceration absent	pT4a: ulceration absent
			pT1b: ulceration or mitosis ≥1/mm^2	pT2b: ulceration present	pT3b: ulceration present	pT4b: ulceration present
Eighth edition [21]	No known 1^0 tumor	In situ	≤1.0 mm	>1.0–2.0	>2.0–4.0 mm	>4.0 mm
			pT1a: <0.8 mm, ulceration absent	pT2a: ulceration absent	pT3a: ulceration absent	pT4a: ulceration absent
			pT1b: <0.8 mm with ulceration or 0.8–1.0 mm	pT2b: ulceration present	pT3b: ulceration present	pT4b: ulceration present

AJCC American Joint Committee on Cancer, *N/A* not applicable, *AMH* atypical melanocytic hyperplasia, *LN* lymph node, *1^0* primary, *L* Clark level

significant prognostic factor to date: tumor depth. Specifically, the pT3 category would expand from 1.51–3.0 mm to 1.51–4.0 mm, and the pT4 category would change from >3.0 mm to >4.1 mm [15] (Table 6.1, rows 2 and 3). These changes were based upon various studies, including Van Der Esch et al. in 1981 who observed significant changes in mortality when patients were divided into the following groups (1) <2 mm, (2) 2.01–4.00 mm, and finally, with the worst prognosis, (3) >4.01 mm. It was noted that when the patients with thicker lesions were compared, the 5-year survival rate fell from around 65–66% in group 2 to below 50% in group 3 [24]. Additional studies would also indicate that the incidence of nodal metastases also increased to

approximately 50% in lesions >4.0 mm in thickness [25], further supporting the change in T stage cutoffs.

The third edition, apart from the creation of a Tis category for melanoma in situ, would likewise see a similar focus on the pT3 and pT4 categories (Table 6.1, row 4). To give more information regarding tumor thickness, pT3 was further subdivided into pT3a lesions measuring >1.5–3 mm and pT3b lesions measuring >3–4 mm, while pT4 was further divided into lesions that (a) invaded the subcutaneous fibroadipose tissue and (b) demonstrated satellites within 2 cm from the primary tumor site [16]. These changes would persist and remain relatively unchanged in the subsequent fourth [17] and fifth [18] editions of the AJCC staging manual (Table 6.1, rows 5 and 6). Note that in the sixth edition and onward these satellites would be grouped with microsatellites and in-transit metastasis (Table 6.2, rows 7 and 9) as manifestations of lymphatic spread, rather than in the T staging

Table 6.2 Summary of the AJCC cancer staging pathologic Node (N) stage, first through eight editions

AJCC edition	NX	N0	N1	N2	N3
First edition [14]	N/A	NP	Regional lymph nodes, first station only	Other lymph nodes	N/A
Second edition [15]	CBA	NP	(1) 1 (+) regional LN <5 cm or (2) 0 (+) LN and <5 in-transit metastases >2 cm from primary site	(1) >1 (+) regional LN, or (2) LN > 5 cm or fixed, or (3) ≥5 in-transit metastases (4) any in-transit metastases >2 cm from 1^0 site and (+) regional LN	N/A
Third edition [16]	CBA	NP	Regional LN involvement, ≤3 cm in dimension	N2a: >3 cm in diameter	N/A
				N2b: in-transit metastasis	
				N2c: N2a and N2b	
Fourth edition [17]	No/minimal change from AJCC third edition				
Fifth edition [18]	No/minimal change from AJCC third edition				
Sixth edition [19]	CBA	NP	1 (+) LN	2–3 (+) regional LN or intra-lymphatic regional metastasis with (−) LN	(1) ≥4 regional LN, or (2) matted LN, or (3) in-transit metastasis/ satellites with (+) regional LN
			N1a: microscopic (clinically occult)	N2a: microscopic (clinically occult)	
			N1b: macroscopic (clinically apparent)	N2b: macroscopic (clinically apparent)	
				N2c: satellite or in-transit metastases with (−) LN	
Seventh edition [20]	No/ minimal change from AJCC sixth edition				
Eighth edition [21]	CBA	NP	N1a: 1 (+) LN, clinically occult	N2a: 2–3 (+) LN, clinically occult	N3a: ≥4 LN, clinically occult
			N1b: 1 (+) LN, clinically detected	N2b: 2–3 (+) LN, clinically detected	N3b: ≥4 LN, clinically detected, or matted LNs
			N1c: 0 (+) LN, (+) in-transit, satellite or microsatellite	N2c: 1 (+) LN and (+) in-transit, satellite or microsatellite	N3c: 2 (+) LN or matted LNs, and (+) in-transit, satellite or microsatellite

AJCC American Joint Committee on Cancer, *N/A* not applicable, *CBA* cannot be assessed, *NP* not present, *LN* lymph node, (+), positive; (−), negative, 1^0 primary

system. This was due in part to the observation that patients with thick melanomas (>4 mm) with satellite lesions behaved differently than lesions without satellites, and instead demonstrated a similar prognosis to those with in-transit and even nodal metastases [26].

6.3.2 T Stage, Sixth though Eight Editions (2002 to Present)

In the twenty-first century, we as a scientific community have been able to marvel in this new era of both immunotherapy and check point inhibitor therapy, which has drastically changed our overall survival statistics in ways that will only be fully realized in the coming years. Now more than ever, the general public is also armed with information so that they, too, may play a role in surveillance of their own melanocytic lesions. In 1985, Friedman et al. stressed the importance of teaching patients how to perform skin self-examinations and introduced the key clinical characteristics of early malignant melanoma. These features would go by the acronym "ABCD": **a**symmetry, **b**order irregularity, **c**olor variegation, and **d**iameter (>6 mm) [27]. In 2004, this acronym would be revised to "ABCDE" which would take into account an evolving or changing lesion [28]. This increased public awareness, along with improved screening of patients by dermatologists, has led to earlier and earlier detection of thin melanomas. Though some have considered this a great screening success, others have suggested that some of these thin melanomas biopsied are the equivalent of an "inconsequential cancer" that may not have produced any issues in that patient's lifetime [29]. Nonetheless, it is worth noting that patients with thin melanomas (pT1) make up the vast majority of all melanoma patients, and thus also account for the largest number of melanoma-related deaths [30].

The sixth, seventh, and eighth editions of the AJCC Cancer Staging Manual have made risk sub-stratification in the group of thin melanomas an area of particular importance. Specifically, there is a focus on determining histologic variables responsible for affecting prognosis of individuals with thin melanomas. The overall goal would be to divide these lesions into clinically meaningful groups, separating the relatively indolent lesions from aggressive lesions warranting increased surveillance and/or sentinel lymph node dissection. For this reason, based on various studies, three variables have been tried as differentiators of the subcategories pT1a and pT1b in these last three versions: lesional depth, ulceration, and mitoses.

6.3.2.1 Breslow Depth

Before we proceed and discuss changes in pT1a and pT1b subcategories, it is important to address changes in how Breslow depth measurements are recorded, a feature that influences all T stage groups. The original Breslow depth groups, described by Breslow et al. in 1970, were measured via ocular micrometer and recorded to include up to the second decimal point (i.e., hundredths place) [13]. Though pathologists have continued to measure Breslow depth from the top of the granular cell layer to the point of deepest invasion, the standardization of the measurement has been called into question in recent years. In general, the Breslow depth measurement can be impractical, cumbersome, and non-reproducible. Various confounding factors from the patient's underlying anatomy to specimen processing can all influence the Breslow depth, making precise, and confident measurement to even one decimal place a challenge. Some of these characteristics include, but are not limited to, the following: tissue sampling, tangential sectioning, variation of tumor thickness between sections, very large or deep lesions, complex architecture rendering assessment of an in situ component versus an invasive component difficult, or even an incidental underlying nevus. Ge et al. identified similar factors leading to inconsistencies in the Breslow depth, the most interesting of which was "pseudo-precision." Pseudo-precision is basically a term used to describe a false feeling of having given a more accurate Breslow depth by recording an increased number of decimal places (i.e., two decimal points) [31]. As such, a consensus of consistent measuring definitions was needed.

The first through seventh editions of the AJCC staging manual follow Breslow's example with their cutoff numbers for the various T stages documented to the second decimal place. Although not specifically stated, these numbers implied the need to report melanoma depth to the one-hundredth of a mm. These measurement guidelines were not universally accepted. The British Association of Dermatologists recommended the use of one decimal point (to the nearest tenth of a mm) [32] while, though indicating exactly how to measure the depth with an ocular micrometer, the College of American Pathologists did not address the one or two decimal place question [33]. This lack of detailed and specific guidelines for measurement became problematic. For example, prior to the eighth edition, two patients with melanomas measuring 0.96 mm and 1.04 mm would fall into two different categories, pT1 and pT2, respectively. If these numbers were rounded and only one decimal point reported, both would measure 1.0 mm; thus, making both patients a pT1. While the difference on paper appears meager, in the past a pT2 stage, and not a pT1, generally warranted a sentinel lymph node biopsy [34], a procedure not without risk [35]. Thus, to clarify any ambiguity, the eighth edition clearly states that though one may measure thinner melanomas to two decimal points, all final measurements should be rounded (using the generally accepted rules for rounding) to one decimal place [21].

Starting in sixth edition, the overall Breslow depth cutoff points were again revisited (Table 6.1, row 7). These changes mirrored a 1995 article by Büttener et al., which performed a univariable and multivariable analysis demonstrating that optimized cutoff points of 1 mm, 2 mm, and 4 mm were prognostically more powerful than previous T stage cutoff points (Table 6.1, row 4). While the previous TNM stage 10 year survival rates were 95.2% (pT1), 92.7% (pT2), 70.3% (pT3), and 47.7% (pT4), the survival rates of the newly proposed divisions were 94.5% (≤1.0 mm), 83.3% (1–2 mm), 59.9% (2–4 mm), and 46.6% (>4 mm) [36]. These new divisions would allow for relative simplicity in staging, using whole numbers, and would better divide groups 2 and 3, removing more favorable outcomes from group 3. These investigators also demonstrated that Clark level of invasion was only statistically significant in lesions measuring <1.0 mm. For example, Clark level III or deeper lesions had a 3.5 times greater relative risk of death than level II lesions [36]. Vilmer et al. would add further credence to this finding by describing nine cases of thin melanomas (<0.76 mm) with short disease-free intervals, all of which demonstrated level III or IV invasion [37]. Moving forward, the sixth edition would adopt both Büttener et al.'s newly proposed divisions and would likewise use Clark level along with ulceration (to be discussed under the heading "ulceration") to sub-stratify pT1a and pT1b lesions (Table 6.1, row 7).

Subsequent editions have maintained these various cutoffs for pT1, pT2, pT3, and pT4 lesions. However, the same cannot be said regarding the pT1a and pT1b subcategories. The seventh edition, while still noting the importance of ulceration in the pT1b subcategory, shifted its focus from Clark level to mitotic rate with a pT1a having <1 mitosis/mm^2 and a pT1b having ≥1mitosis/mm^2 (Table 6.1, row 8) [20]. In turn, the eighth edition has somewhat radically transformed the pT1 subcategories by using melanoma depth and ulceration (Table 6.1, row 9), while excluding Clark level and mitotic rate (to be discussed under the heading "mitoses"), to determine pT1a and pT1b lesions [21].

In 2017, Lo et al. performed univariable and multivariable analyses of long-term survival in 6263 patients with thin (pT1) melanomas. In this study, the multivariable analysis revealed that patients with thin melanomas between 0.9 mm and 1.0 mm had a significantly worse prognosis (hazard ratio (HR) of 2.22) in comparison to those with melanomas measuring ≤0.8 mm. Overall melanoma-specific survival rates at 10 and 20 years were 93.4% and 85.7% in the ≤0.8 mm group, and 81.1% and 71.4% in the 0.9 mm to 1.0 mm group [30]. Given these survival differences, this breakpoint of 0.8 mm was evaluated in 7568 patients with T1 N0 melanomas in the International Melanoma Database and Discovery Platform (IMDDP), a database containing over 46,000 patients with clinical Stage I

through III melanomas from over 10 different institutions. Multivariable analysis demonstrated a HR of 1.7 ($p = 0.057$) in lesions ≥0.8 mm versus lesions <0.8 mm [38].

Additionally, 0.8 mm has also been indicated as a possible cutoff point for sentinel lymph node (SNL) biopsy. Previous studies have demonstrated positive SLNs in 4.9–12.8% of lesions ≥0.76 mm, and only 0–2.3% positive SLNs in lesions <0.76 mm. These findings were confirmed by Han et al. in their 2012 study, which demonstrated a 5% (pT1a) to 13% (pT1b) positive SLN rate in lesions ≥0.76 and no SLN metastases in pT1a lesions <0.76 mm [39]. Thus, based on this 0.8 mm breakpoint, with both survival and clinical implications, the eighth edition now divides the pT1 category as follows: pT1a <0.8 mm, and pT1b 0.8–1.0 mm or < 0.8 mm with ulceration.

6.3.2.2 Ulceration

Ulceration, though initially mentioned and recognized as a poor prognostic indicator in the second edition [15], finally came to the forefront in the sixth edition and continues to this day to be the sole differentiation of (a) and (b) subcategories for pT2, pT3, and pT4 lesions (Table 6.1, row 7). Ulceration, subcategory (b) as defined in the eighth edition, is the complete/full-thickness absence of intact epidermis with underlying host reaction [21]. Generally, an ulcerated primary lesion is considered to behave like a non-ulcerated primary lesion from the T stage one level above. This is demonstrated by the 5-year survival rates of pT2b and pT3a patients lacking lymph node metastases, which are 93% and 94%, respectively [38]. In the pT1a and pT1b subcategories, ulceration serves as an additional prognostic marker. The above IMDDP database investigation not only elucidated the 0.8 mm cutoff for Breslow depth, but also demonstrated a HR of 2.6 when comparing ulcerated and non-ulcerated T1N0 lesions [38]. Thus, together ulceration and Breslow depth currently form the two most powerful predictors of thin melanoma behavior.

Additionally, over the years some have sought to improve prognostic predictions by attempting to quantify the amount of ulceration by measuring ulceration as a percent of the invasive melanoma tumor width. In 't Hout et al. demonstrated a HR of 1.53 in patients with minimally to moderately ulcerated tumors (≤70% of total melanoma tumor width), and a HR of 2.22 for extensively ulcerated tumors (>70%) [40]. Other authors confirm the importance of excessive ulceration (HR of 1.83) and mention the importance of the ulceration type. The two types of ulceration identified were infiltrative, with consumption of the epidermis, and attenuative, with thinning or stretching of the epidermis as noted over nodular melanomas. Attenuative ulceration, with a HR of 3.02, was found to be an independent prognostic factor [41]. Further characterization of ulceration, either amount or type, is not currently included in the staging classification system, yet may prove useful with additional investigation in future editions.

6.3.2.3 Mitotic Rate

Mitotic rate, while featuring prominently in the pT1a and pT1b subcategories of the seventh edition (Table 6.1, row 8), has been removed from the official pT stages, although it will still be recorded in the eighth edition. The reason behind this change is that on analysis of the IMDDP database, mitoses were not statically significant in the pT1 category [38]. That being said, having ≥1 mitoses/mm^2 has been correlated with nodal disease ($p < 0.05$) [39], and a 2018 study of 17,273 patients with thin melanomas and mitotic rate data demonstrated positive SLNs in 7.9% of patients with 1 mitosis/mm^2 and in 44.5% of patients with >11 mitoses/mm^2 [42]. Even the eighth edition agrees that mitotic rate will likely be an integral part of future prognostic models [21] and maybe back in future editions.

6.3.3 Node (N) Stage

As early as Pack et al.'s 1952 retrospective analysis of 744 patients from 1917 to 1950, there was a clear difference in five-year survival rates in patients with (14%) and without (40.5%) lymph node metastases [43]. Lymph node status was also a major component of Ackerman and Del

Regato's 1954 division of patients into survival groups [5]. Thus, it should come as no surprise that the first edition of the AJCC would include lymph node assessment as its own category, namely: N0 indicating no nodal metastasis, N1 representing first stage (regional) lymph nodes only, and N2 representing distant positive nodes (Table 6.2, row 2) [14]. The second and third editions would see modifications of the N1 and N2 staging groups based on the size of the largest involved lymph node, with cutoff points at 5 cm and 3 cm, respectively (Table 6.2, rows 3 and 4). The reason for the inclusion of these cutoff points is not well explained [44] and supporting reported data is absent [26]. Subsequent studies, including Buzaid et al., would demonstrate on univariable analysis that nodal size (by physical examination) was not significant for DFS, and that the AJCC 3 cm cutoff demonstrated no significant difference in DFS or overall survival (OS) [26].

In 2002, White et al.'s long-term outcome study of patients with regional lymph node metastases would help radically modify the N staging system. In this study, the authors demonstrated a drastic decrease in five-year survival with increasing nodal positivity, from 53% with one positive lymph node to 25% with >4 positive lymph nodes. Overall, these results suggested that the number of positive lymph nodes was the most powerful predictor of OS in these patients [45]. Afterward, the sixth and seventh editions would remove nodal size and subdivide N1, N2, and N3 by the number of positive lymph nodes (Table 6.2, row 7 and 8).

While the structure of the AJCC eighth edition has remained relatively unchanged, a few modifications are noticeable (Table 6.2, row 9). The first is a change in wording: "clinically occult" replaces microscopic and "clinically apparent" replaces macroscopic. The second is the addition and homogenization of the N1c, N2c, and N3c subcategories, which now reflect the presence of various types of metastases, including in-transit metastases, satellite lesions, and microsatellites [21]. These three entities, likely manifestations of intralymphatic spread, have all been implicated in poor prognosis. In the eighth edition they have been grouped together, given that no significant survival differences were encountered on univariable analysis [38].

The third and last change, however, is not grossly evident. In the seventh edition, microsatellites were strictly defined as discontiguous nests measuring at least 0.05 mm and separated from the primary melanoma by at least 0.3 mm [20]. The eighth edition has eliminated both size and distance criteria, now defining microsatellites as any focus of metastatic tumor cells separated by uninvolved dermis or subcutis from the primary lesion [21]. Never has it been easier for pathologists to indicate the presence of microsatellites. This definitional change, when paired with the new N stage subcategories, could see a rise in future N1c, N2c, and N3c patients.

6.3.4 Metastasis (M) Stage

6.3.4.1 Background

Metastasis of any cancer generally portends poor prognosis, and melanoma, in particular, has a long history of widespread dissemination [6]. In modern times, and as early as Einhorn et al.'s 1974 article, metastatic melanoma was considered relatively chemoresistant with an abysmal prognosis of just under 5 months [46]. Perhaps, for this reason, the first edition of the AJCC Cancer Staging Manual merely sought to identify the absence (M0) or presence of distant metastatic disease (M1) (Table 6.3, row 2) [14]. However, Einhorn et al. also noted that some locations of metastatic disease correlated with longer patient survival. Those with either metastatic disease confined to the skin and subcutaneous disease, or pulmonary metastases only, had the longest median survival of 11 months and 10 months, respectively. In contrast, individuals with central nervous system (CNS) metastases fared the worst, with a median survival <3 months [46]. While the second and third editions would make an effort to further separate cutaneous metastases from visceral metastases (Table 6.3, row 3 and 4), it would not be until the eighth edition that CNS metastases received their own M1 subclassification [21].

Table 6.3 Summary of the AJCC cancer staging pathologic Metastasis (M) stage, first through eight editions

AJCC edition	M*x*	M0	M1	M2
AJCC first edition [14]	CBA	No metastasis	Distant metastasis	N/A
AJCC second edition [15]	CBA	No metastasis	Skin or subcutis beyond primary LN drainage	Visceral metastasis
AJCC third edition [16]	CBA	No metastasis	Distant metastasis	N/A
			M1a: subcutis or non-regional LNs	
			M1b: visceral metastasis	
AJCC fourth edition [17]	No change from AJCC third edition			
AJCC fifth edition [18]	No change from AJCC third edition			
AJCC sixth edition [19]	N/A	No metastasis	M1a: metastasis to skin, subcutis, or distant LNs	N/A
			M1b: lung involvement	
			M1c: all other visceral sites or any site with increased LDH	
AJCC seventh edition [20]	No/minimal change from AJCC sixth edition			
AJCC eighth edition [21]	N/A	No metastasis	M1a: skin, soft tissue (muscle) and/or non-regional LN M1a (0): LDH normal M1a (1): LDH elevated	N/A
			M1b: lung involvement M1b (0): LDH normal M1b (1): LDH elevated	
			M1c: other visceral sites, excluding CNS M1c (0): LDH normal M1c (1): LDH elevated	
			M1d: CNS involvement M1d (0): LDH normal M1d (1): LDH elevated	

AJCC American Joint Committee on Cancer, *CBA* cannot be assessed, *N/A* not applicable, *LN* lymph node, *LDH* lactate dehydrogenase

6.3.4.2 New Divisions in the M1 Category

In the eighth edition, subcategories have been refined and an additional subcategory designation given (to be discussed under the heading "serum lactate dehydrogenase"). These subcategories are now as follows: M1a, M1b, M1c, and M1d. In comparison to the seventh edition, the M1c subcategory has been split into two groups c and d, with the new M1c subcategory containing metastasis in all distant organ sites except pulmonary and CNS, and the new subcategory of M1d reserved for CNS involvement (Table 6.3, row 9).

Each M1 subcategory is based on prognosis: M1a, best prognosis; M1b (lung involvement), intermediate prognosis; M1c (anatomic sites other than CNS or lung), worse prognosis; and M1d (CNS involvement), worst prognosis [21]. A recent meta-analysis and systematic review of the effect of various targeted and immunotherapies in patients with brain metastases (M1d) demonstrated increases in long-term progression-free survival and OS in patients treated with combination immunotherapy [47]. Given these therapeutic advances, the M1d subcategory is particularly important in the determination of eligibility for clinical trials [38].

6.3.4.3 Serum Lactate Dehydrogenase

Recently, Wilpe et al. noted that in patients with high tumor burdens, increased glycolysis due to hypoxia-induced tumor necrosis results in elevated lactate dehydrogenase (LDH) levels [48]; however, the importance and implications of

elevated LDH in melanoma patients is not a new concept. Finck et al.'s 1983 article, was one of the first studies in the English literature regarding elevated LDH levels in melanoma, specifically in those patients with clinical Stage II and III disease (taking into account that the AJCC used a three-tiered system at that time). These patients had a mean survival of 5.9 months following serum LDH elevation [49]. In 1989, Heimdal et al. performed regression analyses in patients with metastatic melanoma which indicated that LDH levels >450 U/l were among a set of significant prognostic factors associated with survival <3 months [50]. A subsequent article in 1996 confirmed decreased survival, and also indicated that elevated LDH levels may be associated with poor response to immunotherapy (interferon-alpha and high dose interleukin-2) [51].

Since that time, various investigators have continued to associate elevated LDH levels with poor prognosis and poor response to therapy. Additional investigation of treatments with the BRAF inhibitor dabrafenib, both alone and in combination with the MEK inhibitor trametinib, again supported elevated LDH to be a poor prognostic indicator. Posttreatment deaths in the elevated LDH group were reported as 31% (combination therapy) and 51% (dabrafenib alone) in comparison to the normal LDH group deaths of 12% (combination) and 14% (dabrafenib alone). Of interest, in the elevated LDH group there was a 52% reduction of death when these patients were treated with combination therapy instead of monotherapy [52]. Additionally, while studying LDH and immunotherapy with ipilimumab, Kelderman et al. noted that therapy with ipilimumab was unlikely to benefit patients whose LDH levels were twice the upper limit of normal. This group further speculated that these high serum LDH levels may decrease the potency of the immune response at the tumor site, and suggested that lactate, produced from LDH, makes the overall tumor environment more acidic, which may negatively impact the function of lymphocytes in the area [53].

Thus, though unusual for a clinical marker to be present in a staging classification system [21], LDH has proven itself as both a strong prognostic indicator and a possible guide for treatment planning. LDH was first included in the melanoma M staging system in the sixth edition as a marker of M1c disease (Table 6.3**,** row 7), placing all individuals with metastasis of any anatomic location with an elevated LDH into one category. Given the above studies on LDH and therapeutic outcome, in the eighth edition, an effort was made to associate elevated LDH levels with anatomic site of metastatic disease. As such, the previously mentioned M1 subcategory divisions now have additional subcategory designations, specifically (0) for normal serum LDH and (1) for elevated serum LDH (Table 6.3, row 9). In time, perhaps these subcategory designations will further clarify which groups respond better, or at all, to various treatment modalities.

6.4 The Future of Melanoma Staging

TNM stages, when placed together, form pathologic and clinical staging groups. The four clinical stages (I through IV) incorporate the pathologic stage and help clinicians assess risk, generate a treatment plan, and counsel their patients. While improvements and adjustments in the eighth edition of the AJCC Cancer Staging Manual for melanoma will allow clinicians to better sub-stratify their patients in the coming years, the TNM stage-based system excludes some variables which appear to also have prognostic significance. These include, but are not limited to, age, gender, the location of primary neoplasm, and full extent of the microscopic tumor burden [54].

In response, especially in this new era of personalized medicine, various authors have suggested alternate staging and prognostic risk assessment systems focusing on the individual patient. Cochran et al., for example, sought to create a formula to predict an individual's probability of survival based on the following criteria: gender, location of primary neoplasm, age, Breslow thickness, and ulceration (both presence and extent) [55]. An additional study sug-

gested the diagnostic utility of a validated, perhaps AJCC sanctioned and distributed, computer-generated prognostic estimate based on this previous formula, where patients are then assigned to different staging groups [5]. In 2010, Soong et al. designed the first localized melanoma predictive statistical model based on the large AJCC melanoma database, with a subsequent web-based electronic prediction tool/website (AJCC predictor) [56]. They were able to calculate an individual's one, two, five, and ten-year survival with a 95% confidence interval, allowing for surveillance and treatment planning and even possible selection of patients for certain clinical trials [54].

Since that time, additional web-based prognostic models for a wide variety of cancers have been made universally available not only to clinicians, but to their patients. In 2013, when Rabin et al. conducted a systematic review of various prognostic tools, they identified 107 different calculators used for the assessment of 89 different cancers [57]. In 2016, Mahar et al. specifically identified 17 clinical prognostic tools for primary cutaneous melanoma [58], including five that were available as web-based calculators. While these online tools provide an opportunity for patients to gain a better understanding of their prognosis and further participate in their care, there has been variability between different web-based resources. Zabor et al.'s 2018 review of three such web-based applications (AJCC predictor, Sunbelt Melanoma Trial predictor, and MGH predictor) revealed that although these tools may provide a better estimate of individual survival compared to traditional staging methods, differences in methodologies, each with their respective limitations, and variations in patient characteristics included between calculators resulted in somewhat variable survival estimates [59]. Overall, additional studies and continued development of these web-based models are needed.

The creation of a high-quality risk calculator is a complex task. In the past, the AJCC has created the Precision Medicine Core (PMC), a committee with the goal of providing/creating web-based outcome probability models for major cancer sites, and discussed the minimum endorsement quality criteria for such a calculator, which included a checklist of 16 items necessary for AJCC approval [60]. However, it appears that up to the present day, four risk assessment models for melanoma have been reviewed by the PMC and have not met the agreed-upon criteria [61]. For the most up-to-date information on the progress of the PMC's assessment of risk assessment models, we suggest the following website: https://cancerstaging.org/references-tools/deskreferences/Pages/Supplementary-Material.aspx.

Perhaps, in the coming years, the eventual goal of a unified web-based prognostic modeling program to pair with the current AJCC Cancer Staging Manual will be able to synthesize individual patient variations and deliver survival estimates worthy of a personalized, modern, and twenty-first century medical staging system.

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Part III

Melanoma Management: Treatment of the Primary Lesion

Lentigo Maligna Melanoma

7

Sara Snyder Phillips and Michelle Nguyen

Lentigo maligna is a subtype of melanoma that typically manifests on sun-exposed areas, most commonly the head and neck of elderly patients [1]. Lentigo maligna (LM) is considered melanoma in situ (MIS), whereas lentigo maligna melanoma (LMM) implies an invasive component of the melanoma. The incidence of LM is increasing and currently represents 15% of all cases of malignant melanoma [2].

7.1 Challenges in Treating LM

LM is associated with indistinct clinical margins, which can make treatment challenging [1]. Furthermore, LM can also demonstrate indistinct histological margins, which increases the risk of misinterpreting the excision specimen as completely excised when this is not the case [2]. This challenge in correctly defining the margin of the lesion likely underlies the high rate of recurrence, which is between 6 and 20% following standard excision with 5 mm margins [2].

Some advocate for the use of reflectance confocal microscopy (RCM) to provide an in vivo proxy for histologic analysis. This enables the surgeon to better define the border of the tumor prior to surgery, including subclinical extension [1]. In the setting of a tumor like LM which tends to have indistinct clinical margins, RCM is promising; however, the utility is ultimately operator dependent and the technology is not so readily accessible in the clinic (see previous chapter on Aids to Melanoma Detection). More experienced technicians and data are needed prior to developing a consensus on its use.

Wood's lamp is another tool that may help to better define the clinical margins of LM, although no studies rigorously examine its use. However, the efficacy of a Wood's lamp is again dependent on the experience of the user. Furthermore, LM typically occurs in the setting of sun-damaged skin, where background photo-aging and lentigines may complicate the interpretation of Wood's lamp visualization [2].

Likewise, dermoscopy is another tool that may help estimate the margins of LM non-invasively. Thus far, only descriptive terminology has been published to help distinguish LM from non-LM skin under dermoscopy [3]. While studying these descriptors and examples in the literature would likely benefit the general dermatologist (especially in the context of high dermos-

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copy use in everyday general dermatology), further validation regarding its use in defining the border of the lesion prior to surgical treatment is needed before establishing a consensus statement on its use.

7.2 Surgical Management of Lentigo Maligna

Although surgical treatment is the gold standard for LM and LMM, the type of surgical treatment remains a debated topic. Surgical treatment options include wide local excision (WLE), Mohs micrographic surgery (MMS), and staged excision with permanent sections (SEP). The various surgical treatment options primarily differ in regard to the type of embedding and sectioning, as well as speed of results (see Table 7.1). Mohs utilizes frozen, en face sectioning, complete deep and peripheral margin examination, and yields same day results. In contrast, WLE involves paraffin-embedded (permanent) sections, vertical (bread-loaf) sectioning, results may take several days, and closure occurs before pathology comes back. The vertical sectioning performed following WLE leads to examination of about 5% of the surgical margin [3]. SEP utilizes paraffin-embedded sections, but the angle at which tissue is excised and the type of sectioning varies. Some studies of SEP use 45 degree excision (as performed in classic MMS) followed by either en face or radial sectioning, and others perform a perpendicular 90 degree excision followed by bread-loaf sectioning [3, 4]. When SEP is performed with 45 degree excision followed by en face sectioning, this is also called "slow" Mohs [3]. SEP yields results within 24 h, and requires a delayed closure. Various studies draw different conclusions when comparing recurrence rates and surgical outcomes of WLE, MMS, and SEP in treating LM and LMM. Furthermore, many of the studies assessing the efficacy of surgical interventions for LM are single institution or perhaps only single-operator, thus decreasing the broader applicability [5].

Many experts agree that MMS or SEP offer better outcomes for treating LM or LMM patients over WLE. Both Mohs and SEP allow for assessment of margins and subsequent decisions to either continue or conclude the surgery prior to closure. Additionally, Mohs and the subtype of SEP which uses en face sectioning ("slow" Mohs) allow for complete peripheral histologic margin assessment compared to WLE. A review assessment of these techniques concluded that MMS and SEP with either en face or radial sectioning provide the lowest recurrence risk of all these surgical interventions [3]. Although other experts suggest that MMS or slow Mohs in the setting of LM or MIS increases the chance of false negatives given the potential for skip lesions in LM, this has not been supported by recurrence data.

There is ongoing debate about whether MMS or SEP is better for the treatment of LM and LMM. One retrospective chart review of 57 patients found that staged excision with permanent sections had a significantly lower recurrence rate (7.3%) compared to MMS (33%). Furthermore, there was no significant difference in surgical defect size [4]. The mean duration of follow-up was 95 months in the staged excision group and 117.5 months in the MMS group. In this study, SEP was performed variably depending on the size of the specimen: specimens >3 mm wide were sectioned via bread-loafing, whereas specimens <3 mm wide were sectioned en face [4]. As this chart review was small and data was drawn from a single non-academic practice, further data perhaps in the setting of a randomized controlled trial are needed to more clearly address this question.

When examining the efficacy of treating LM with WLE, a central detail to be evaluated is the

Table 7.1 Comparison of different surgical treatments for LM

	Embedding	Section direction	Margin exam	Speed of results
MMS	Frozen	En face	Complete deep + peripheral	Same day
SEP	Permanent	Variable	Variable	Within 24 h
WLE	Permanent	Vertical	~5% of margin examined	Several days

size of the margin used in the study. Multiple studies suggest that treating LM using standard WLE with 5 mm margins is not adequate [1]. Hilari et al. found that a surgical margin of 5 mm was not adequate in 69.2% of recurrent LM and 26.5% of primary LM [6]. It is likely that the lack of both comprehensive and real-time histologic margin assessment may contribute to the high recurrence rate of LM following WLE with 5 mm margins. A retrospective review of 882 cases of MIS of the trunk and extremities treated with MMS found that 9 mm margins were needed to fully excise 97% of MIS whereas 6 mm margins only fully excised 83% of MIS. These authors suggest that margins of at least 9 mm should be used when treating MIS of the trunk and extremities with surgical options lacking total margin evaluation, including WLE [7]. A concern for the conclusions of this type of study is that tumor characteristics that lead to MMS referral in the first place may not be present in lesions referred for WLE, thus skewing the data. Additionally, a retrospective cohort study of 423 LM lesions comparing risk of recurrence following Mohs versus WLE with 5 mm margin showed no statistically significant difference in outcomes. Out of the 415 lesions that had follow-up data, 16 recurrences were discovered at a mean of 3.2 years following biopsy, and the remaining 399 lesions that did not recur were followed for a mean of 7.9 years. Recurrence rates were low in both surgical approaches, thus leading the authors to suggest that both were reasonable treatment approaches [2]. Some investigators suggest that WLE with margins >5 mm might be comparable to outcomes achieved with MMS or SEP. An expert consensus from Australia in 2019 advocated for "surgical removal" (type not specified) with 5–10 mm margins as the first-line treatment for LM. While they commented on the various pros and cons of each surgical method, no definitive conclusion was reached on which method was best [1].

While some practitioners postulate that Mohs is more beneficial on the head and neck and WLE may be a better choice elsewhere on the body, there is no data to support this. Mohs tends to be used more commonly to treat LM on the head and neck than WLE, so it is difficult to compare whether it is truly better than WLE for lesions in this distribution given the lack of randomized controlled trials [2]. However, there is data to suggest that larger margins are required in both LM and melanoma in situ of the head and neck (12 mm) compared to the trunk and extremities (9 mm) in order to achieve a 97% clearance rate in patients treated with MMS [8].

There are also drawbacks to treating patients with MMS. The main drawback in performing MMS to treat LM and LMM is the difficulty in examining frozen sections for melanocytic atypia [2]. Furthermore, the success of MMS in treating these tumors is likely operator dependent and correlated with operator experience, although this has not been proven. Currently, Melan A/Mart 1 is the most commonly used immunostain in MMS to identify abnormal melanocytes [3]. Mart 1 is also used with excellent success in the setting of MMS to treat atypical intraepidermal melanocytic proliferations, many of which are subsequently upstaged to melanoma in situ or invasive melanoma [9]. New promising stains are under ongoing investigation, including Mel-5 [10]; however, various experts continue to express concern that stains on frozen sections of LM permit too many false positives and false negatives in light of the confounding histologic features associated with sun-damaged skin and the histologically indistinct margins, respectively [2, 3].

Another concern with using MMS to treat LM is that invasive LMM could be transected accidentally with a tangential debulking section [3]. This in turn has raised fears that performing MMS for lentigo maligna may impact management of tumors that are upstaged. Recent data from a retrospective chart review of 117 patients suggests that there is an approximately 8.5% risk of upstaging when performing Mohs surgery for lentigo maligna or in situ melanomas and a 1.7% risk of subsequently requiring wide local excision and sentinel lymph node biopsy. This study concludes that the risk of requiring further surgical intervention following MMS for MMIS or LM is low [11].

7.3 Non-Surgical Management of LM

The prevailing standard of care for treating both LM and LMM is surgical management. However, non-surgical options do exist and are of particular importance in the setting of individuals for whom surgical treatment is not feasible. Non-surgical treatment options include radiation therapy, topical imiquimod, cryotherapy, and laser treatment [1]. Given that LM and LMM often occur in elderly adults with comorbidities, non-surgical approaches are an appealing option for both the patient and the clinician. While no randomized controlled trials (RCTs) exist comparing surgical to non-surgical treatment options, expert consensus is that surgical treatment is preferred, followed by radiotherapy, followed by topical imiquimod. Cryotherapy and laser treatment are not generally recommended [1]. One review article from 2011 concluded that Mohs micrographic surgery and staged excision with permanent sections demonstrated lower recurrence rates compared to non-surgical treatments including cryosurgery, imiquimod, lasers, radiation therapy, and electrosurgery and curettage [12].

While surgical treatment remains the standard of care, data supports the use of topical imiquimod particularly in the setting of patients unwilling to pursue or ineligible for surgery or radiation therapy [1, 13]. One retrospective chart review of 33 patients demonstrated a 72% clearance rate of LM following topical imiquimod with a mean follow-up period of 4.1 years. The patients in this study applied imiquimod once daily 5 days/week for 6 weeks to the lesion. The dose was increased after this to twice daily 7 days/week for another 6 weeks if no inflammatory response was achieved. Another round of twice daily application for 10 weeks was applied if still no inflammatory response. These authors argue that inflammatory response is essential for clearing LM [14]. A recent systematic review concluded that treatment with imiquimod of varying regimens resulted in an overall clinical clearance in 78.3% of patients, and histological clearance in 77% of patients. The mean length of follow-up for all patients in this study was 21.9 months, and in only 2.2% of patients was a recurrence found at a mean follow-up of 18.6 months [13]. This same study also demonstrated that the best treatment schedule was applying imiquimod at least 6–7 times per week and for a total of at least 60 applications within 12 weeks. Notably 1.8% of patients were diagnosed with LMM after treatment [13].

Some experts are resistant to using topical imiquimod to treat LM in any patient. They highlight that the studies examining this are small and have short follow-up periods. Furthermore, the most rigorous studies demonstrate sub-optimal cure rates. They postulate that topical treatment may be unsatisfactory for MIS because biopsies may not account for a possible focus of invasion which may then be discovered on excision [5]. This is an ongoing area of research.

While imiquimod is currently being used as a third-line treatment for LM, this topical medication is also being studied as a neo-adjuvant treatment prior to surgical intervention. In 2012, Hyde and colleagues published the first randomized controlled trial to treat LM with neo-adjuvant imiquimod prior to conservative staged excision. Unfortunately, this study only compared neo-adjuvant imiquimod to the combination of neo-adjuvant imiquimod and tazarotene rather than vehicle alone. The group that was treated with single agent therapy had a 36% rate of residual LM on staged excision versus 22% in the combination group. As the study failed to include an arm with a neo-adjuvant placebo, and study results were not statistically significant, it is impossible to ascertain the value of neo-adjuvant imiquimod versus no neo-adjuvant therapy based on this RCT [15]. Another retrospective chart review found that neo-adjuvant 5% imiquimod cream applied five nights a week for 2–3 months before conservatively staged excisions allowed for a median final margin of 2 mm; furthermore, this approach yielded similar recurrence rates compared with surgical management with either Mohs or staged excisions with en face permanent sections [16]. This data suggests that neo-

adjuvant topical imiquimod is likely beneficial in terms of tissue-sparing surgical removal and suggests similar recurrence rates compared to standard surgical treatment.

7.4 Conclusion

The treatment of LM is an area requiring ongoing research. To date, there is a dearth of RCTs, leading to reliance on many single-center retrospective studies with small sample sizes. Expert consensus recommends surgical management as first-line treatment, followed by radiation, followed by topical imiquimod, while the precise method of surgical management is an area of ongoing debate. Most studies agree that either MMS or SEP are superior to WLE with 5 mm margins. However, there is no conclusive evidence when comparing MMS, SEP, and WLE with margins >5 mm. Topical imiquimod remains a reasonable option for patients requiring non-invasive at-home treatment. Although cure rates are sub-optimal, many patients may prefer this to surgical interventions, particularly in the setting of the predominantly elderly LM population. We expect additional well-designed research studies will further clarify the best treatment modalities for LM and provide definitive guidance using an evidence-based approach.

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8 Surgical Treatment of Primary Melanoma

Brendin Beaulieu-Jones and Michael R. Cassidy

8.1 Introduction

The surgical management of primary cutaneous melanoma is based upon knowledge generated from landmark prospective randomized trials [1–6]. While the guidelines dictating surgical management have evolved with the establishment of new evidence, definitive treatment via wide local excision remains a mainstay of treatment. An immense body of clinical research has informed current treatment guidelines, with particular efforts to define the optimal lateral margins for surgical excision. Still, further prospective clinical trials are ongoing in an effort to optimize surgical management and the primary treatment of melanoma [7].

8.2 Diagnosis Via Excisional Biopsy

For patients with suspected cutaneous melanoma, tissue diagnosis should be established via a full-thickness excisional biopsy with lateral clinical gross margins of 1–2 mm and deep margins into the subcutaneous tissue, excluding the epithelial attachments [8, 9]. A full-thickness excisional biopsy is indicated for nearly all patients in order to accurately assess maximum tumor thickness, the presence or absence of ulceration, and depth of tumor invasion. Excisional biopsies should be oriented in order to facilitate future wide local excision, as needed. This last point is important for dermatologists to note, given they are most often the specialty who perform the diagnostic biopsy for melanomas.

For large lesions (>1.5 cm) and for lesions located on the face and other difficult anatomic sites, an excisional biopsy may not be easily performed. In such instances, a full thickness incisional biopsy with a 6-mm punch instrument or scalpel may be an appropriate alternative [10]. The deep margin should still incorporate the subcutaneous tissue; however, determination of tumor thickness and clinical stage cannot be made until the entire lesion has been excised. The biopsy should be performed at the most clinically suspicious part of the lesion. Repeat punch biopsies may be needed if there is a discordance between clinical impression and histologic diagnosis.

For all lesions, shave or curette biopsies are contraindicated, as Breslow thickness cannot be reliably measured, and prior shave biopsies can prohibit accurate depth assessment thereafter.

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8.3 Definitive Surgical Management with Wide Local Excision

For biopsy-proven melanoma (or melanoma-in-situ), treatment includes two components:

- Excision of the primary tumor via wide local excision
- Management of the regional nodal basin (if indicated)

In this section, we will discuss the research and principles underlying definitive surgical excision.

Surgical excision with wide margins is the cornerstone of treatment of primary melanoma [8, 9]. By removing all melanoma cells at the primary site, wide margins are used to achieve local disease control and to reduce the rate of local recurrence. Available evidence indicates that local recurrence is likely mediated by microscopic satellites of metastasis, or discontinuous nests of intralymphatic metastatic cells, which are at least 0.05 mm in diameter and separated by normal dermis from the invasive portion of melanoma by a distance of at least 0.3 mm [11]. Wide excision to normal tissue is intended to eliminate such microscopic satellites, and thereby minimize local recurrence, which is associated with markedly poor overall disease survival [12].

8.4 Evidence for Wide Local Excision: Defining the Optimal Margin

Historically, the acceptable lateral margin for surgical excision of melanoma was 4–5 cm of normal skin, regardless of tumor thickness [13]. However, between 1991 and 2011, a series of six randomized controlled trials [12, 14–18] were conducted to compare rates of local recurrence, as well as melanoma-specific survival between narrow excision margins (1–2 cm) and more traditional wide excision margins (3–5 cm). With 4233 total participants, the six trials provided definitive evidence that smaller 1 or 2 cm margins (dependent upon tumor thickness) were safe compared to traditional resection margins. These landmark trials represent a cornerstone of melanoma research and continue to inform current guidelines.

8.4.1 World Health Organization (WHO) Melanoma Program Trial #10 [1980] [14, 19]

The WHO Melanoma Program published the first prospective, randomized clinical trial comparing narrow excision (defined as <1 cm in the study) and wide excision (≥3 cm) among 612 patients with primary melanoma with tumor thickness <2 mm. Disease-free and overall survival rates were similar between the two groups. At 12-year follow-up, survival was 87.2% and 85.1% for patients randomized to narrow and wide excision, respectively. Subgroup analysis stratifying the cohort by tumor thickness (0.1–1.0 mm and 1.1–2.0 mm) was completed and no difference in survival was identified based on excision margin in either thickness group. This trial provided preliminary evidence that a lateral excision margin of 1 cm was safe for primary melanoma with tumor thickness <2 mm.

In addition, the WHO trial found that local recurrence, as the first sign of recurrent melanoma, was uncommon, occurring in a total of 11 patients (1.8% of the 612 patients). Local recurrence was more common following 1 cm versus 3 cm excision (2.6% and 1.0%, respectively); however, the difference was not statistically significant. In addition, local recurrence was more common among patients with thickness 1.1–2.0 mm (2.8%) compared to thickness <1.0 mm (1.8%); this difference was also not statistically significant. The data demonstrated that local recurrence of melanoma with thickness <2 mm is a rare event, with an unclear association with both tumor thickness and lateral excision margin, and no apparent impact on overall survival.

8.4.2 Intergroup Melanoma Surgical Trial [1983–1989] [12]

The Intergroup Melanoma Surgical Trial investigated the optimal lateral excision margin for patients with primary melanomas of intermediate thickness, defined as 1–4 mm. The group enrolled a total of 740 patients with thickness 1–4 mm, including 468 patients (Group A) with melanomas on the trunk or proximal extremity, who were randomized to either 2 cm or 4 cm excision margins and 272 patients (Group B) with melanomas on the head, neck, or distal extremities, who all received 2 cm excision margins. Narrow margins were selected for Group B, as it was technically not feasible to obtain 4 cm margins given the anatomic location.

Among Group A (patients randomized to either 2 cm or 4 cm margins), there were no differences in rates of local recurrence or overall survival. Ten-year disease-specific survival was 70% and 77% for patients with 2 cm or 4 cm margins, respectively ($p = 0.074$). Among the 238 patients with a 2 cm lateral margin, the incidence of local recurrence was 0.4% as a first relapse and 2.1% at any time. Among the 230 patients who underwent surgical excision with a 4 cm margin, the local recurrence rates were 0.9% as a first relapse and 2.5% at any time. A wider lateral surgical margin did not reduce the risk of local recurrence. Based on these findings, the authors concluded that a 2 cm margin was safe for intermediate-thickness melanoma.

In the Intergroup trial, local recurrence was found to be associated with a high mortality rate, with a 5-year survival rate of only 9% (as a first relapse) or 11% (any time) compared with 86% 5-year survival for patients without local recurrence ($p < 0.0001$). Ten-year survival for all patients with local recurrence was only 5%. Given the apparent implication of local recurrence, the authors asserted that a 2 cm excision margin, rather than 1 cm is recommended whenever anatomically feasible, as the rate of local recurrence as first relapse was 0.6% for patients in the Intergroup trial with melanoma 1–2 mm who underwent excision with 2 cm margins, compared to 4.2% for patients in the WHO trial with melanoma 1–2 mm and excision margins of 1 cm. Comparisons across trials may not be valid and thus no definitive conclusions can be made.

Given the observed impact of recurrence on survival, the authors sought to identify subgroups of patients with intermediate-thickness melanoma who were at high-risk for local recurrence. Two clinical characteristics were significantly associated with an increased rate of recurrence: increasing thickness of the primary tumor and presence of ulceration. For patients in Group A (i.e., with trunk or proximal extremity melanoma), the local recurrence rates (any time) increased from 1.0% for melanoma 1.0–2.0 mm in thickness, to 4.6% for melanoma 2.1–3.0 mm in thickness, and to 4.1% for melanoma 3.1–4.0 mm in thickness. Ulceration of the primary tumor was also associated with a dramatic increase in local recurrence rates. There was a six-fold increase in local recurrence (any time) in Group A patients (1.1% for non-ulcerated melanomas versus 6.6% for ulcerated melanomas). A similar trend was observed for Group B patients, as there was an eight-fold increase in local recurrence (2.1% versus 16.2%) ($p < 0.001$). In addition, the rate of local recurrence varied by anatomic location, as the local recurrence rate was 1.1% for proximal extremity, 3.1% for trunk, and 5.3% for distal extremity and 9.4% for head or neck.

Multivariate prognostic factors analysis among the group of 740 patients found that only two factors were related to significantly poorer survival: presence of tumor ulceration ($p < 0.001$) and the head and neck site ($p = 0.02$). Size of the surgical margin (2 cm versus 4 cm) did not correlate with local recurrence rates. Tumor ulceration (risk ratio 6.3, $p < 0.0001$) and head/neck site (risk ratio 9.4, $p < 0.01$) were significantly associated with an increased risk of recurrence. Ulceration was the only significant and independent factor associated with recurrence among Group A patients with melanomas on the trunk or proximal extremity (risk ratio 4.3, $p < 0.03$).

Beyond assessing the optimal excision margin for intermediate-thickness melanoma, and the epidemiology of local recurrence in this group, the authors evaluated varying options for the

initial management of regional lymph nodes. Patients were thus randomly selected to receive an elective lymph node dissection (ELND) or observation of their clinically uninvolved nodes. The results of this aspect of the trial are presented in a later chapter, Sentinel Lymph Node Biopsy and Nodal Surgery.

8.4.3 Swedish Melanoma Study Group [1982–1991] [15]

The Swedish Melanoma Group conducted a multicenter study to compare recurrence and survival outcomes among patients with primary melanoma (0.8–2 mm) located on either the trunk or extremities who were randomized to 2 cm or 5 cm lateral margins. A total of 989 patients were randomized, with median follow-up of 11 years. No statistically significant differences in survival were observed between the two treatment groups. The rate of local recurrence was very low, occurring in <1% of patients (8 of 989), with no difference based on lateral excision margin. Given that no difference in local recurrence or survival was found between the two treatment groups, the authors concluded that tumors with thickness of 0.8–2 mm could be managed with an excision margin of 2 cm as safely as with a margin of 5 cm.

8.4.4 The French Cooperative Group [2003] [16]

With a similar design to the Swedish Melanoma Study Group, the French Cooperative Group, representing nine European Centers, prospectively randomized 337 patients with tumor thickness ≤2.0 mm to undergo excision with a 2 cm or 5 cm margin. Ten-year disease-free survival rates were 85% for patients with a 2 cm margin and 83% for the group with a 5-cm margin. There was also no difference in the 10-year overall survival rates (87% versus 86%). Local recurrence was identified in five patients (1.5%), with one recurrence (0.6%) in the 2 cm arm and four recurrences (2.4%) in the 5 cm arm. While local recurrence was rare, recurrence of any type was identified in 55 of 326 patients (16.9%), with regional recurrence and distant metastasis identified in 24 and 14 patients, respectively. The authors concluded that a surgical excision with a 2 cm lateral margin is adequate for primary melanoma with thickness ≤2 mm.

Both the Swedish Melanoma Group Study and the French Cooperative Group found equivocal rates of local recurrence, disease-free survival, and overall survival among patients with thin to intermediate melanoma (<2 mm or 0.8–2 mm in thickness, respectively), randomized to excision with a lateral margin of either 2 cm or 5 cm. Both trials provided convincing evidence for the use of narrow margins among patients with melanoma with thickness <2 mm. However, the clinical significance was somewhat limited, as the WHO Melanoma Program Trial had previously shown that 1 cm margins were safe for a similar group of patients.

8.4.5 United Kingdom Melanoma Study Group [1992–2001] [17, 20]

The United Kingdom Melanoma Study Group conducted a prospective, randomized clinical trial comparing outcomes for 1 cm versus 3 cm surgical excision margins among 900 patients with melanoma of the trunk or limbs and tumor thickness ≥2 mm. Among the six landmark trials, this was the only clinical trial to include patients with melanoma >4 mm (i.e., T4 disease), and this group comprised about 25% of the total study enrollment. At 60-months follow-up, the authors reported that a 1-cm margin was associated with a significantly increased risk of locoregional recurrence, comprising local recurrence (within 2-cm of scar or graft), in-transit recurrence (beyond the first 2-cm of scar or graft to the regional nodes), and nodal recurrence. However, disease-specific mortality and overall survival at 60-months follow-up were similar in the groups.

Extended follow-up (median 8.8 years) provided more decisive results. Among all 900 patients, there were 494 total deaths and 359

deaths attributable to melanoma. Disease-specific mortality was greater in the narrow margin group, as there were 194 deaths attributed to melanoma in the 1 cm margin group compared to 165 in the 3 cm group (unadjusted hazard ratio 1.24, 95% confidence interval 1.01–1.53; $p = 0.04$). Based on these findings, and previously reported data regarding the increased risk for regional recurrence, the authors concluded that a 1 cm excision margin is inadequate for melanoma with thickness > 2 mm on the trunk and limbs.

The UK Melanoma Study provided decisive evidence that a 1 cm lateral excision margin was inadequate for melanoma of thickness >2 mm. The results deviate markedly from the trend observed in related prior clinical trials, as this was the first study to demonstrate worse survival outcomes among patients who underwent excision with narrow lateral margins, compared to wider excision margins. In particular, the Intergroup Melanoma Surgical trial found that a 2 cm lateral margin was safe relative to a 4 cm margin in a similar but not identical study population, as patients with melanoma >4 mm were excluded from the Intergroup trial. Unfortunately, the Intergroup trial did not publish subgroup analysis for patients with melanoma 2–4 mm, and thereby reconciliation of the somewhat varying results cannot be completed. It remained unclear whether a 2 cm or 3 cm margin was needed for patients with melanoma >2 mm.

8.4.6 Swedish Trial for T3/T4 Melanomas [1992–2004] [18, 21]

To further investigate the safe lateral margin for patients with melanoma >2 mm in thickness, a second randomized clinical trial was completed in Sweden, with collaboration from institutions in Denmark, Estonia, and Norway. Between 1992 and 2004, a total of 936 patients with melanoma on the trunk or upper or lower extremities of thickness >2 mm were randomized to excision with a 2 cm or 4 cm lateral margin. Local recurrence and survival were assessed.

Results published in 2011 with a median follow-up of 6.7 years (IQR 4.3–9.5) found no difference in melanoma-specific mortality ($p = 0.95$) nor overall mortality ($p = 0.64$). Additionally, local recurrence was greater in the 2 cm margin group (4.6% versus 1.9%, $p = 0.06$), but there was no difference in the overall rate of locoregional recurrence ($p = 0.96$) or survival, as above. The data suggest that a 2 cm resection margin is safe for patients with melanoma >2 mm.

The group published updated results in 2019, reinforcing their initial findings. At a median follow-up of 19.6 years, no difference in overall survival nor melanoma-specific mortality was observed between the two groups. A total of 621 deaths were reported, with 397 attributed to melanoma—192 (48%) in the 2-cm group and 205 (52%) in the 4-cm group (unadjusted HR 0.95, 95% CI 0.78–1.16, $p = 0.61$). Local recurrence was not assessed in the long-term follow-up.

While the Intergroup trial and the UK Melanoma study provided potentially conflicting results, the Swedish Trial for T3/T4 Melanomas provided some clarity, demonstrating that lateral excision margins of 2 cm are sufficient for melanoma with thickness >2 mm.

8.5 Evidence for Wide Local Excision: Approach to the Deep Margin

While there are multiple randomized trials evaluating the appropriate lateral excision margin, there are currently no prospective data to inform the optimal depth of excision. Unfortunately, the randomized studies performed to assess the optimal lateral margins did not standardize the depth of excision. Four of the six trials permitted surgical excision to extend down to or to include the deep fascia, and one study did not specify the extent of depth of surgical resection in the methodology [9]. Given this variation in surgical management, data from the clinical trials cannot inform the optimal depth of the deep resection margin.

There are two retrospective studies [22, 23] evaluating whether removal of the deep muscle fascia is associated with disease recurrence and/or survival. The first report by Olsen et al. was published in 1964 and included 112 patients with wide local excision of melanoma, with or without removal of the deep fascia. They found a higher rate of regional metastasis, but no difference in the rate of recurrence, with removal of the fascia [22]. The authors postulated that the deep fascia served as a barrier to regional but not local recurrence. However, the extent of peripheral margins was variable (3 to 50 mm) and elective regional lymph node dissection was completed in some patients, thereby vastly undermining the reliability of the study conclusions. A subsequent study by Kenady et al. [23] assessed outcomes of 202 patients with either stage 0 or stage 1 primary melanoma who underwent excision, with or without removal of deep fascia. At 5-year follow-up, no difference in the rate of recurrence, location of recurrence, or melanoma-specific survival was observed between the two groups.

More recent data from the Melanoma Institute Australia [24] provides preliminary evidence that the anatomic depth of surgical resection may influence recurrence and survival. The group performed a retrospective evaluation of 2131 patients with melanoma 1–2 mm thick in order to assess if pathologic margins were a predictor of recurrence and survival outcomes. The deep pathologic margin was a strong independent predictor of local and in-transit recurrence free survival ($p = 0.003$). In addition, when comparing a <8 mm deep pathologic margin to the ≥8 mm group, there was a significant difference in disease-free survival on univariate ($p < 0.001$) and multivariate ($p = 0.017$) analysis. The findings underscore the potential importance of obtaining adequate deep margins. However, this analysis has not been validated in a randomized study.

Given that melanoma staging (and prognosis) is based on Breslow thickness, it is intuitive that the depth of surgical resection might have a critical impact on recurrence and other outcomes. However, as indicated, there is no evidence-based standard and there is wide variability in current surgical practice. In collaboration with the American College of Surgeons, a group of researchers from the Mayo Clinic conducted a survey of surgeons operating on patients with melanoma to evaluate standard practice with regard to excision depth [25]. The authors found that while the most common surgical technique reported was "resection down to, but not including, the muscular fascia" (64% of respondents), there was significant variability, with about 35% of surgeons reporting a different standard depth. Variation based on provider specialty was also observed among the survey respondents, with surgical oncologists most likely to perform a deep resection as a standard part of their practice (27 [21.4%] versus 10 [8.1%] of general surgeons; $p = 0.004$). Based on the survey results, Mayo Clinic performed an internal review and found a 50:50 split between surgeons resecting the muscular fascia as a routine and those resecting down to, but not including the muscular fascia. As a result, the institution created a consensus practice for all primary, intermediate-thickness melanoma, namely, to routinely resect down to, but not include the muscular fascia (unless in an area of very thin subcutaneous tissue) until such time as evidence-based guidelines become available.

8.6 Current Recommendations [26]

Current guidelines regarding optimal surgical excision are based primarily on the combined findings of the landmark series of randomized clinical trials. While clinical staging is based on Breslow thickness, ulceration status, and other factors, surgical excision is dictated by tumor thickness alone, with the extent of the lateral margin directly based on thickness.

For melanoma in-situ, excision of the lesion or biopsy site with a 0.5–1 cm margin of clinically normal skin and a layer of subcutaneous tissue is adequate. While melanoma in-situ lesions are not invasive, recurrence may present as invasive melanoma, and subsequent treatment of any invasive lesions should follow current guidelines for invasive cancer.

For invasive melanomas ≤1 mm thick, current guidelines recommend a narrow 1 cm margin. This recommendation is based on the WHO Melanoma Program Trial #10, which found no significant differences in the rate of local recurrence, disease-free survival, or overall survival for patients with melanoma <1 mm, who underwent resection with 1 cm and 3 cm excision.

For invasive melanomas 1–2 mm thick, current NCCN guidelines recommend a 1–2 cm lateral margin, with the standard consensus to obtain a 2 cm lateral margin whenever anatomically feasible and when the surgical defect can be closed primarily without a skin graft.

Four of the six trials evaluated patients inclusive of this subgroup. The WHO trial evaluated patients with melanoma ≤2.0 mm and on subgroup analysis among patients with thickness 1–2 mm, found that narrow excision (1 cm margin) did not negatively impact survival relative to a wide excision (3 cm margin). However, there was a non-statistically significant trend toward an increase in local recurrence in this subgroup, though study power was inadequate to provide a more definitive assessment of the relative risk for local recurrence between the two groups. Conversely, the Swedish Melanoma Study evaluated patients with thickness 0.8–2 mm and found that a 2 cm margin was safe relative to wider excision. Both the Intergroup Melanoma Surgical Trial (patients with thickness 1–4 mm) and the French Cooperative Group (patients with thickness <2 mm) found that a 2-cm margin was safe relative to a wider margin (4-cm margin in the Intergroup Melanoma Surgical Trial and a 5-cm margin in the French Cooperative Group).

Based on this available evidence, the NCCN recommends a lateral margin of 1–2 cm for patients with melanoma of thickness 1–2 mm, with a preference for 2 cm as technically feasible. The optimal margin cannot be specified further, as no randomized trial has directly compared outcomes for 1 cm versus 2 cm margins. However, the currently active MelMarT trial (see next section) is comparing recurrence and survival outcomes of 1 cm versus 2 cm excisions margins among all patients with melanoma >1 mm and thus, with adequate enrollment, subgroup analysis should be possible in order to provide more definitive guidance for this group.

For invasive melanomas 2–4 mm thick, guidelines necessitate a 2 cm lateral excision margin. This recommendation is based on complementary findings from the Swedish Trial for T3/T4 Melanomas and the United Kingdom Melanoma Study. As the name implies, the Swedish Trial for T3/T4 Melanomas evaluated outcomes for patients with melanoma >2 mm thick who were randomized to undergo excision with either 2 cm or 4 cm margins, and found no difference in local recurrence, melanoma-specific survival or overall survival at follow-up of nearly 20-years. Conversely, the trial from the United Kingdom compared 1 cm versus 3 cm excision margins in this population and found that a 1-cm margin was associated with a greater recurrence rate and an increase in melanoma-specific death relative to a 3-cm margin.

For lesions of any Breslow thickness, the recommended margins may be modified to accommodate anatomic or functional considerations, particularly for certain anatomic locations such as the distal extremity or face. By itself, the inability to perform primary closure should not prevent obtaining indicated clinical margins, as alternate surgical techniques for closure exist, as will be discussed in a subsequent section.

8.7 Ongoing Research: Australia and New Zealand MelMarT Trial [2015–2016] [7]

While current guidelines for the safe and optimal surgical excision margins for melanoma of varying thickness are derived from the six landmark trials (detailed above), some surgeons contest that current guidelines, specifically those recommending 2 cm margins for melanoma of thickness >2 mm, hasten unnecessary morbidity, hospital length of stay, post-operative complications, need for reconstructive surgery, and other negative consequences. In particular, a group of surgeons from Australia and New Zealand are concerned that the recommendation for 2 cm margins is driven by the findings of the United

Kingdom Melanoma Study, which observed that a 1 cm surgical margin was associated with increased locoregional recurrence and worse melanoma-specific trial. The group asserts that these results may be misleading, especially as multiple prior randomized trials found low rates of local recurrence as first relapse, ranging from 0.3% to 1.0% [12, 14–18]. Given the results of the Swedish Trial for T3/T4 Melanomas, which showed the safety of a narrow, 2 cm margin for patients with melanoma >2 mm, the authors are conducting a randomized clinical trial to compare 1 cm versus 2 cm margins for patients with melanoma >1 mm in Breslow thickness. The pilot study was published in 2018, showing the feasibility of the trial, with 400 patients enrolled and 12-month follow-up.

8.8 An Alternative to Clinical Margins: Pathologic Evaluation

Current guidelines regarding the excision of primary melanoma utilize clinical margins; however, a group of researchers from the Melanoma Institute Australia have proposed and studied an alternate approach to determining safe excision margins. As melanomas may extend beyond clinically identified margins, the assessment of histopathologic margins may be a more accurate indicator of appropriate surgical margins. Haydu et al. performed a retrospective evaluation of 2131 patients with melanomas 1–2 mm thick (T2) in order to assess if histopathologic margins were a good predictor of recurrence and survival outcomes [24].

Pathologic lateral margins <8 mm were associated with increased recurrence and disease-free survival. Significantly higher total recurrence rates were seen in the <8 mm pathologic margin group compared with the ≥8 mm group (38.5% versus 24.8%, $p = 0.002$). Five-year cumulative disease-free survival for patients with a pathologic excision margin <8 mm was 75.3% compared with 82.6% for the ≥8 mm pathologic excision group ($p = 0.03$). However, no melanoma-specific survival benefit was observed for ≥8-mm pathologic excision margin group, with a melanoma-specific survival of 90.3% compared with 88.0% for the <8 mm excision group ($p = 0.213$). While study conclusions may be limited given its retrospective nature, the study provides preliminary evidence for evaluating the peripheral pathologic margin as part of standard surgical management of melanoma. If the peripheral pathologic margin is <8 mm, regardless of the clinical margin utilized, there may be a role for performing wider excision.

While peripheral excision margins did not seem to influence local recurrence, in-transit recurrence, or melanoma-specific survival, the authors found that the deep margin was a strong independent predictor of local recurrence and disease-free survival, as described.

To facilitate additional research and practice changes, the authors recommend that pathologists routinely measure and document the distance of the melanoma from the peripheral and deep margins of the specimen, as recommended by internationally accepted pathology reporting guidelines [27]. Interestingly, guidelines regarding pathologic reporting from the National Comprehensive Cancer Network (NCCN) recommend inclusion of deep and peripheral margin status, namely whether the margin is positive or negative, but do not specifically recommend reporting the size of the deep and peripheral margin.

8.9 Surgical Technique [8, 28]

For most primary cutaneous melanoma lesions, surgical excision can be achieved via elliptical excision with primary closure, Wide Local Excision (Fig. 8.1). After prepping and draping the patient in a traditional sterile fashion, the intended surgical incision should be carefully measured and marked using a ruler and pen. Clinical margins should be measured from the edges of the biopsy site or from the periphery of any residual disease. An elliptical incision with a length-to-width ratio of about 3 to 1 facilitates closure of the wound. As possible, the long axis of the incision should be oriented along the ipsilateral lymphatic drainage

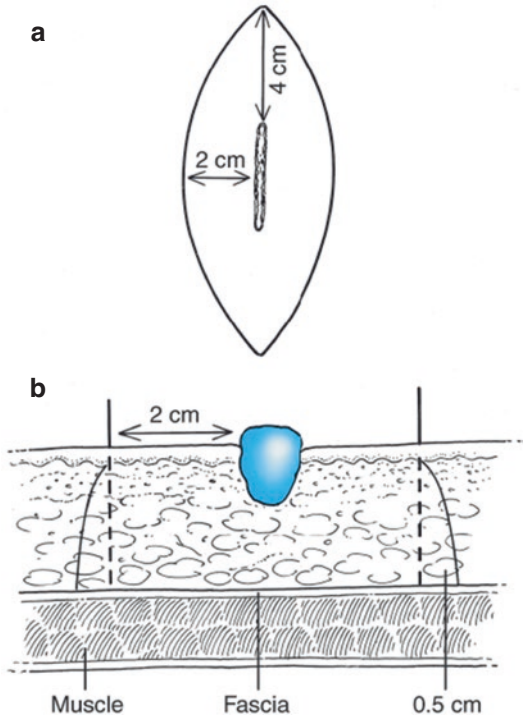

Fig. 8.1 Wide Local Excision of Melanoma

such that subsequent regional lymph node dissection, if needed, is more easily performed. On the upper and lower extremities, the incision should be oriented along the length of the extremity, such that the apices of the wound have minimal tension, facilitating primary closure.

Surgical excision should be carefully performed to maintain proper margins circumferentially, with particular care to avoid beveling toward the melanoma. In most patients, the wide excision should be carried to the underlying deep fascia, which does not need to be excised. Extending the deep margin to the deep fascia may not be necessary in obese patients or for certain difficult anatomic locations; however, the excision should include at least the superficial fascia.

Following excision of the tumor and surrounding tissue, orientation of the specimen should be indicated for the pathologist to facilitate complete assessment and any needed follow-up.

For most lesions, tension-free closure of the resulting defect can be accomplished via a standard simple advancement flap, raised just above the fascia. After assuring meticulous hemostasis, the wound is typically closed with deep dermal absorbable suture followed by a series of interrupted nylon sutures, generally vertical or horizontal mattress. For wounds with minimal tension, a subcuticular absorbable suture may be used to close the skin in lieu of nylon.

For lesions on the face or other difficult anatomic locations, excision with the indicated margins (based on Breslow thickness) should be performed and if primary wound closure is not feasible, alternate techniques for healing should be pursued. Specific options for closure/reconstruction will depend on the individual anatomic and patient characteristics.

For wounds with a smaller defect or in certain locations, secondary closure, or closure via secondary intention may be indicated.

If primary closure cannot be accomplished, there are several options including autologous skin grafts, rotational or free flaps, and closure by secondary intention. Patients with appropriate donor sites may be eligible for split-thickness or full-thickness skin grafts. Historically, the use of a full-thickness skin graft was dissuaded given unproven concerns that a full-thickness skin graft hindered the ability to detect recurrence and even resulted in greater local recurrence and poorer survival. However, this concern has been disproven. With that said, for patients with uncertain margins at the index surgery, a temporary closure, with an allograft, biologic graft, negative pressure wound dressings, or standard gauze dressings should be utilized, with deferment of a permanent graft until negative margins are confirmed. Common sites in which a full-thickness skin graft may be necessary include lesions of the head and neck, as well as the distal extremities. Relative to other options for secondary closure, full-thickness skin grafts have notable advantages with regard to cosmesis and durability. Typical donor sites for a full-thickness graft harvest include the skin from a natural body crease such that the donor site incision can be concealed. To the extent possible, thickness, texture, pigmentation, and the presence or absence of hair should be matched.

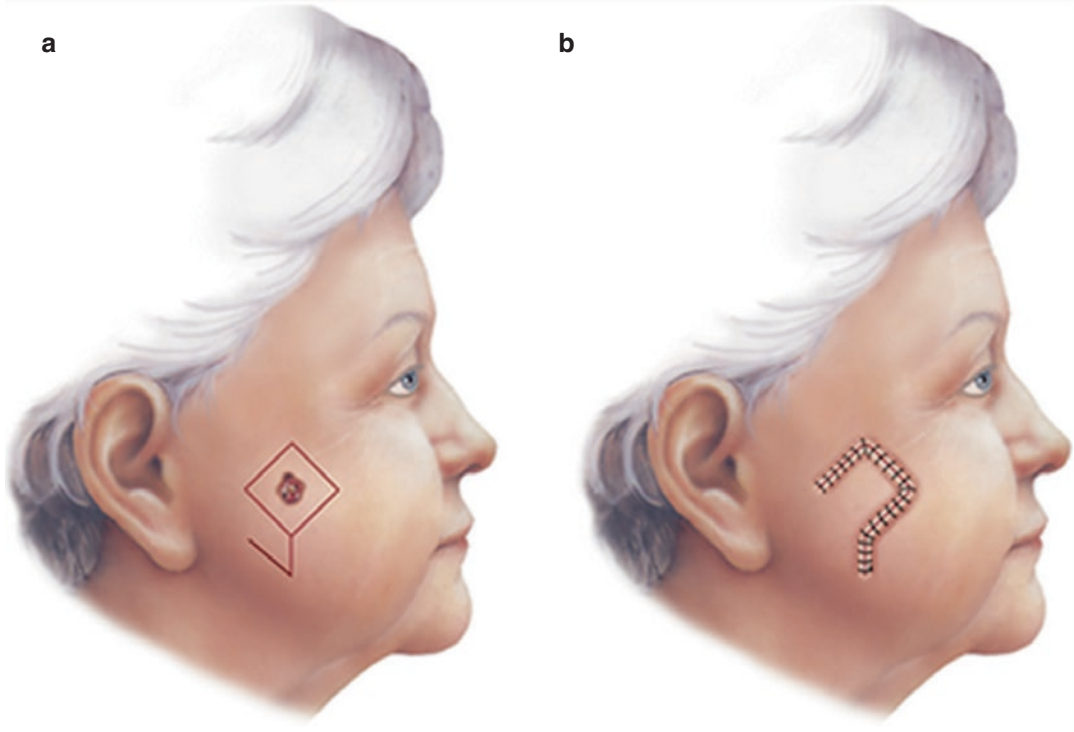

Fig. 8.2 A rhomboid flap following a melanoma excision on the right cheek

Skin grafts can be appropriate for coverage of some defects, but certain sites and defects may require more advanced soft tissue coverage via a regional or distant flap. With regard to melanoma surgery, a rhomboid flap is a relatively common option for wound reconstruction. The defect is excised in the shape of a rhomboid and designed such that the donor site scar is oriented in the direction of the less tense skin. The flap is rotated into the defect, and the donor site is closed primarily in a straight line (Fig. 8.2).

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9 Evolution of Neoadjuvant Therapy in Melanoma

Bilal Fawaz, Gordana Rasic, and Teviah E. Sachs

9.1 Introduction

Patients with resectable stage III melanoma have a significant risk of recurrence when treated with surgery alone [1]. Therapeutic lymph node dissection (LND), when employed, is done for patients who present with the macroscopic disease, which is or will become symptomatic. In most cases, LND does not improve overall survival (OS) but rather limits locoregional morbidity and leads to improved quality of life. Stage III patients make up a heterogenous population with regards to prognosis. The OS rate at 5-years decreases precipitously within stage III disease, with an OS of 93% in stage IIIA patients, compared to 32% in stage IIID [1]. Patients with palpable or macroscopic nodal involvement have the poorest prognosis, with a 5-year OS of 30% [2]. Adjuvant radiotherapy is recommended in high-risk cases to improve locoregional disease-free survival, but no impact on OS has been observed [3]. Given the variable outcomes with a mostly standardized therapeutic approach, modification of the treatment algorithm for stage III melanoma should be undertaken.

The introduction of targeted inhibitors of cellular growth proteins—such as BRAF and MEK—resulted in a dramatic improvement in progression-free survival (PFS) and OS in patients with stage IV melanoma [4]. Immune checkpoint inhibitors, targeting PD-1 and/or CTLA-4, similarly demonstrated impressive clinical efficacy in metastatic melanoma [4]. Building on the success in stage IV patients, the agents were subsequently investigated as adjuvant treatment in stage III melanoma [5–9]. The resulting improvement in survival outcomes led to the adoption of systemic adjuvant therapy as the standard of care in stage III melanoma [10].

The success of adjuvant systemic therapy also raised the question of whether the same agents may yield similar or even superior efficacy in the neoadjuvant setting. Investigation in preclinical murine models of various advanced-stage melanoma suggested a superior clinical benefit to neoadjuvant immunotherapy compared to adjuvant therapy, with sustained elevation of tumor-specific cytotoxic CD-8+ T-cells in the postoperative period [11]. Preclinical studies have suggested that neoadjuvant application of systemic therapy may yield superior results to adjuvant only use. This has led to the extensive

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investigation into the use of immunotherapy and targeted therapy in this clinical setting [12–21].

9.2 Background

Neoadjuvant systemic therapy (NAST) has numerous potential benefits when compared to adjuvant treatment. Immunotherapy, in particular, relies on the presence of tumor antigens to induce a potent tumor-specific T-cell response. Drug exposure when the tumor antigen burden is at its highest has the potential to result in a broader and more potent anti-tumoral response [11, 12]. NAST additionally aims to lower the risk of disease recurrence through early targeted treatment of occult metastatic disease, as well as minimize surgical morbidity due to pre-operative tumor shrinkage [12]. Some studies have also shown that the presence of neoadjuvant pathologic response correlates with superior outcomes [13, 14]. This may help identify patients at risk of having poor outcomes, for which clinical trial enrollment with novel agents or additional adjuvant treatment should be considered.

Despite the clear potential benefits, NAST does have some potential disadvantages. Given the absence of indicators to predict treatment response, NAST may delay potentially curative surgery in the subset of patients who will not respond. Targeted agents and immunotherapies also have a considerable rate of adverse events, some with significant long-lasting morbidity, including gastrointestinal effects, endocrine and neurological impairments and even mortality [13–20]. Due to the presence of a higher tumor burden in the neoadjuvant setting, the rate of adverse events with immunotherapy may be worse as compared to adjuvant treatment due to increased cross-reactivity between tumor antigens and self-antigens. Lastly, a theoretical risk exists for microsatellite lesions within the primary tumor site, i.e., "skip areas," after the pre-operative introduction of systemic therapy, which could make complete surgical excision more difficult to attain.

Given the high-risk clinical scenario and the current lack of consensus on which treatment is more efficacious (targeted therapy vs. immunotherapy, monotherapy vs. combination therapy) or even the timing of treatment (neoadjuvant vs. adjuvant vs. combined method), a multidisciplinary team approach should be utilized for all patients with advanced melanoma [12]. The International Neoadjuvant Melanoma Consortium (INMC) was established in 2016 to standardize treatment approaches and clinical trials in the neoadjuvant setting [12]. The consortium includes a multi-disciplinary team of physicians, translational research scientists, statisticians, and patient advocates aiming to establish an organizational framework to improve the generalizability of neoadjuvant study results [12]. Among other recommendations, the INMC suggests limiting enrollment to patients with clinically detectable stage III disease who are deemed surgically resectable. These patients are the most likely to recur following surgery alone, and therefore are the patients with the most potential gain from neoadjuvant therapy. The recommended duration of neoadjuvant treatment is 6–8 weeks, with well-defined primary endpoints [12].

9.3 Neoadjuvant Immunotherapy

9.3.1 Combination Therapy

As discussed in detail in the "Systemic Therapy in Advanced Melanoma" chapter, the advent of immunotherapy has revolutionized the treatment of metastatic melanoma [3–9]. PD-1 and CTLA-4 inhibitors have also garnered attention recently in the neoadjuvant setting. The first study comparing adjuvant vs. neoadjuvant combination therapy with ipilimumab (CTLA-4 inhibitor) plus nivolumab (PD-1 inhibitor) was published in 2018 [13]. The OpACIN trial was a randomized phase Ib trial including 20 patients with high-risk palpable stage III melanoma. Patients were randomized 1:1 to receive either surgery followed by four cycles of ipilimumab/nivolumab (adjuvant therapy group) or two cycles of ipilimumab/nivolumab followed by surgery and then two

additional cycles of immunotherapy (neoadjuvant therapy group).

After a median follow-up of 25.6 months, a significant pathologic response was noted in the tissue specimens of the 7/9 evaluable patients (78%) in the neoadjuvant group, with 6 patients achieving a pathological complete response (pCR, $n = 3$) or near pCR (<10% viable tumor cells; $n = 3$) [13]. Responses were sustained, with no recurrence at a median follow-up of 25.6 months, suggesting that pathologic response may be used as a surrogate marker for outcomes. Two patients in the neoadjuvant arm recurred at 2 years, compared to four patients in the adjuvant arm. Additionally, the author demonstrated superior expansion of anti-tumoral T-cell clones in the neoadjuvant arm, further supporting preclinical studies [13].

Despite the observed efficacy, treatment was discontinued in 90% of patients due to grade 3 or 4 adverse events (AEs). Four patients developed severe AEs, including Steven-Johnson syndrome, colitis, polyradiculopathy, and type 1 diabetes. Eight patients developed chronic endocrinopathies requiring long-term hormonal replacement [13].

Given the significant rate of toxicity observed in the study above, Rozeman et al. sought to identify the optimal dosing for combination immunotherapy in the OpACIN-neo trial that aimed to minimize toxicity while still achieving comparable clinical efficacy [14]. The treatment duration was limited to 6 weeks (two cycles), followed by complete surgical resection. The investigators randomized 86 patients into one of three groups: group A, the control group, received the standard ipilimumab/nivolumab dosing: two cycles of ipilimumab 3 mg/kg plus nivolumab 1 mg/kg; group B received low-dose ipilimumab (1 mg/kg) with nivolumab 3 mg/kg; group C received two cycles of ipilimumab 3 mg/kg, followed by nivolumab 3 mg/kg every 2 weeks, instead of concurrent administration [14].

The pathologic responses were comparable between all three groups, with 24/30 patients (80%) demonstrating a response in group A, 23/30 patients (77%) in group B, and 17/26 patients (65%) in group C. Pathological complete response was noted in 14 patients in group A (47%), 17 patients in group B (57%) and six patients in group C (23%). After a median follow-up time of 17.6 months, only 1/64 patients (2%) with a pathologic response relapsed, compared to 62% (13/21) of the non-responders.

The trial demonstrated important morbidities and response failures. In group A, one patient died after 9.5 months of treatment initiation due to immune-related encephalitis. A patient in each of group B and C developed distant metastasis by 6 weeks. Three patients (1 in group A, 2 in group C) had their lymph node dissections delayed due to immune-mediated adverse events (iAEs), and one patient in group C did not undergo surgery due to iAE [14]. Within the first 12 weeks, high-grade AEs were noted in 40% of group A patients, 20% of group B patients, and 50% of group C (resulting in early discontinuation of accrual in this group). The most common high-grade AEs included transaminitis and colitis [14]. The authors, therefore, concluded that low-dose ipi combined with full-dose nivo might be more appropriate for broader clinical use due to its high overall response rate (77%; pCR 60%) and relatively low rate of adverse events (20%) [14].

The question remained, however, as to the necessity of lymph node dissection with its inherent morbidity, in patients who responded favorably to combination therapy as demonstrated in the OpACIN-neo trial. The PRADO extension cohort was established to answer this question. The goal of the PRADO trial was to determine whether certain stage III patients may forgo therapeutic lymph node dissection (TLND) after responding positively to neoadjuvant immunotherapy [15]. Specifically, the authors hypothesized that patients with a pCR or near pCR in the index node (the largest node identified prior to therapy) could be spared TLND. Non-responders (defined as >50% viable tumor cells) would still receive additional adjuvant therapy after TLND to improve outcomes [15]. In total, 70/99 patients (77%) achieved a pathological response in the index node. 60/99 patients achieved a pCR or near pCR, and TLND was omitted in a total of 58

patients. The rate of grade 3–4 iAEs was 24% at 12 weeks, similar to the low-dose group in the OpACIN-neo trial [14, 15]. A conclusion regarding the safety of this approach is still forthcoming, as the data on the 24-month recurrence-free survival rate is pending at the time of this writing (Clinical trial information: NCT02977052) [15].

Another randomized phase II study involving 23 patients compared combination therapy with ipilimumab 3 mg/kg and low-dose nivolumab 1 mg/kg to monotherapy with nivolumab 3 mg/kg [16]. In the nivolumab monotherapy group, both the overall response rate (ORR) and pCR were 25%, with minimal toxicities reported. Response rates in the combination group were promising, with an ORR of 73% and pCR in 45% of patients [16]. However, the rate of high-grade adverse events in the combination group was 73%, and one of 12 patients in the nivolumab monotherapy developed disease progression due to operational delays. The trial was terminated early as a result [16].

9.3.2 PD-1 Monotherapy

Limited studies exist on PD-1 inhibitor monotherapy in the neoadjuvant setting, given the established superior efficacy of combination therapy for stage IV melanoma [4]. Amaria et al., as discussed above, similarly demonstrated superior outcomes with ipilimumab/nivolumab combination therapy for stage III patients when compared to nivolumab monotherapy (ORR 73% vs. 25%, respectively; pCR 45% vs. 25%, respectively) [16]. However, standard combination therapy is also associated with significant high-grade adverse event rates that limit its clinical utility.

To limit therapeutic toxicity and avoid significant delay of surgical management, Huang et al. conducted a study investigating a single dose of neoadjuvant pembrolizumab (PD-1 inhibitor) for stage III and IV melanoma [17]. The investigators hypothesized that the immune response at 3 weeks would correlate with disease-free survival (DFS). Twenty-seven patients were enrolled in this single-arm phase II trial, all of whom received a single 200 mg dose of pembrolizumab, followed by resection 3 weeks later, then 1 year of adjuvant single-agent pembrolizumab. The overall 1-year DFS was 63%, and 8/27 patients (29.6%) achieved either a pCR or near pCR. None of the responders experienced a relapse after a median duration of 25 months [17]. Treatment was well-tolerated, with a <30% rate of high-grade AEs. The authors concluded that single-dose neoadjuvant PD-1 inhibitor is a safe and effective treatment in the management of metastatic melanoma [17].

9.3.3 Commentary

While monotherapy with PD-1 inhibitors resulted in a more favorable toxicity profile, response rates with combination CTLA-4 and PD-1 inhibition are significantly higher [13–17]. The OpACIN-neo trial demonstrated impressive clinical efficacy and manageable toxicity utilizing low-dose ipilimumab (1 mg/kg) plus standard-dose nivolumab (3 mg/kg) in the neoadjuvant setting [14]. While this therapeutic approach appears to strike the right balance between clinical efficacy and toxicity, randomized controlled trials (RCTs) are still needed to confirm its superiority when compared to monotherapy with either agent. RCTs comparing this regimen in both the neoadjuvant and adjuvant setting would help to clarify the optimal timing of systemic therapy.

9.4 Neoadjuvant Targeted Therapy

Targeted inhibitors of cellular growth factors commonly implicated in melanoma development, such as BRAF and MEK, were the next line of agents investigated as NAST. After scattered case series and reports demonstrated positive results with pre-operative vemurafenib, two-phase II trials were published investigating the safety and efficacy of combined BRAF/MEK inhibition for high-risk, surgically resectable tumors [18–21].

The first of the two trials, which was conducted by Amaria and colleagues, included 21 patients with high-risk, resectable stage III or oligometastatic stage IV, BRAF-mutant melanoma [20]. Patients were randomized to receive either standard of care or 8 weeks of neoadjuvant dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor), followed by up to 44 weeks of adjuvant combined therapy [20]. The Standard of care at the time of study enrollment was complete surgical resection, including oligometastatic disease if present, followed by either observation or adjuvant treatment with interferon or ipilimumab. The control arm of the trial was terminated early after significantly more patients in the experimental group experienced event-free survival at 12 months compared to standard of care (10/14 patients, or 71%, vs. 0/7 patients, respectively) [20]. The median event-free survival was 19.7 months in the neoadjuvant/adjuvant group compared to 2.9 months in the control group. None of the patients with pCR experienced a relapse. Treatment was well-tolerated, with most adverse events being low-grade chills, headache, and pyrexia. No grade 4 events or treatment-related deaths were observed [20].

NeoCombi was the second of the two trials that investigated neoadjuvant BRAF/MEK inhibition in stage IIIB or IIIC BRAF-mutant melanoma [21]. The study was a single-arm, open-label trial in which patients received 12 weeks of neoadjuvant therapy with dabrafenib/trametinib, followed by up to 40 weeks of adjuvant treatment. Amongst all 35 enrolled patients, 17 (49%) had a pCR, and 18 (51%) had a pPR. Notably, 8/17 patients with pCR experienced disease progression after a median duration of 30.6 months post-surgery, which represents a stark departure from Amaria et al.'s results using combined immunotherapy, as well as the numerous neoadjuvant immunotherapy studies [13, 14, 16, 20]. They found that 29% of patients experienced grade three or four adverse events, but no treatment-related deaths occurred [21]. The investigators concluded that neoadjuvant dabrafenib/trametinib should be considered in high-risk, resectable stage III melanoma patients, given the high rate of pathological response and the relatively tolerable side-effect profile.

9.4.1 Commentary

Neoadjuvant targeted therapy appears to be better tolerated compared to immune checkpoint inhibition, with encouraging clinical response rates. However, treatment responses may not be durable, and pCR does not appear to correlate with outcomes as reliably as pCR after immunotherapy. It is notable that the trial by Amaria, et al., included Stage IV patients with oligometastatic disease. It should be assumed—as with other aggressive malignancies, that in many patients deemed oligometastatic, additional foci may exist without being clinically or radiographically detectable. The early recurrences in these patients, therefore, are not altogether surprising. In addition, the aforementioned trials do not allow us to determine whether the combined neoadjuvant/adjuvant approach yields any additional benefit over either neoadjuvant or adjuvant therapy alone. It also remains unclear whether BRAF-mutant stage III melanomas would benefit more from checkpoint inhibition or targeted inhibition, as no comparison trials currently exist.

9.5 Conclusion

The majority of studies published thus far are early-phase trials with heterogenous study designs, small sample sizes, and short follow-up durations. Early results are promising, but further investigation is required to define better the ideal patient population, systemic agent(s), and treatment duration. It remains to be conclusively determined whether NAST has any benefit over adjuvant therapy, combination therapy, or even treatment at disease relapse. Considering the lack of high-grade evidence, the current NCCN guidelines only recommend the consideration of NAST after a multi-disciplinary discussion, preferably as part of a clinical trial, instead of incorporating it into its official guidelines [22]. Additionally, the INMC was established to standardize neoad-

juvant melanoma trials, hoping to define and standardize study designs clearly. Ultimately, prognostic biomarkers are needed to individualize NAST and better predict clinical outcomes in high-risk, resectable metastatic melanoma. Phase III trials comparing neoadjuvant vs. adjuvant immunotherapy are currently underway. Similar studies are needed in BRAF-mutant melanomas comparing targeted therapy to immunotherapy in both the adjuvant and neoadjuvant settings. What can be said at this time conclusively is that patients with advanced melanoma now have options for treatment and potential for the durable response that were previously unimaginable until the earlier part of this century. With future studies and advancements, we may one day regard advanced melanoma as a curable disease.

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Part IV

Melanoma Management: Treatment of Regional Disease

Sentinel Lymph Node Biopsy and Nodal Surgery

10

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10.1 Introduction

For patients with primary cutaneous melanoma, the assessment and management of regional lymph nodes have changed dramatically over the past two decades. Historically, positive regional lymph nodes triggered a prompt complete lymph node dissection (CLND) [1–3]. However, treatment paradigms have evolved with efforts to minimize unnecessary morbidity associated with CLND, and supported by recent prospective data undermining its survival benefit [4–6]. The implications of a positive SLN are changing, and the approach to the nodal basin has shifted from one focused on therapeutic intervention to one emphasizing its prognostic significance.

10.2 Historical Perspective: Controversial Role for Elective Lymph Node Dissection (ELND) among Clinically Negative Patients

Historically, there was consensus among physicians that CLND was indicated for clinically detected metastasis to the regional lymph nodes [7]. However, treatment of clinically negative lymph nodes was controversial. Several retrospective studies [8–11] observed a small but significant survival advantage of performing an immediate elective lymph node disease (ELND) in patients with no clinical evidence of regional metastases, rather than observing and performing a delayed lymph node dissection (LND) following the development of clinically evident regional disease. As early as 1979, Balch et al. [11] published results from a review analysis of 394 patients with clinical stage I melanoma. Following multifactorial analysis, two pathological factors (tumor thickness and ulceration) and two clinical factors (initial surgical treatment and anatomic location) were identified as major prognostic variables. More specifically, the analysis revealed that wide local excision with immediate ELND conveyed a survival benefit. This supported their clinical observation that patients with wide excision plus ELND had an 8-year survival rate of nearly 80%, whereas no patients with excision alone survived more than 8 years.

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To further assess the role of ELND in clinically negative patients, two studies compared recurrence rates and survival outcomes among patients who had pathologic evidence of regional metastasis, but variable clinical nodal status. Roses et al. [8] completed a retrospective review of 213 patients with pathologic Stage II malignant melanoma (157 with clinically negative/histologically positive nodes who underwent ELND and 56 with clinically positive/histologically positive nodes who underwent therapeutic LND). There was a marked difference in survival between the two groups. Five-year survival was 44% and 21% for clinical stage I and clinical stage II patients, respectively ($p < 0.0001$). Similar results were observed for 10-year survival (28% versus 12%). The authors asserted that lymphadenectomy performed at a time when the disease is microscopically but not clinically detectable confers a survival benefit.

Similar findings were found by Milton et al. [10] in a retrospective study of 1319 patients with primary melanoma and clinically negative regional lymph nodes, whose first definitive surgical treatment was either wide excision of the primary lesion or wide excision plus ELND. Among patients with clinically negative disease who underwent ELND, about 5% (18/328) had histologic evidence of nodal metastasis. Five-year survival for patients with clinical stage I/pathological stage II disease was nearly twice as good as patients with clinical stage II/pathological stage II (61% versus 32%, respectively). In addition, in men with lesions of intermediate thickness, defined as 1.6–3.0 mm in the study, 5-year survival among patients undergoing ELND, regardless of pathologic findings, was higher than for patients with wide excision alone (72% versus 53%). A similar survival benefit was not identified in other subgroups.

Both studies demonstrated a significant difference in long-term survival between clinical stage I and stage II patients who underwent wide local excision plus ELND. However, the extrapolation that ELND is beneficial and/or indicated for all patients with clinical stage I disease is flawed. While survival outcomes may be better in patients with clinically negative disease rather than patients who presented with gross nodal disease, it is not sound to compare the two groups. Patients with clinical evidence of regional metastasis at the time of presentation are inherently undergoing resection at a more advanced stage. Plus, the tumor itself may represent a more aggressive form of melanoma, thereby resulting in a later stage at presentation. Nonetheless, related studies from this era found that the pathologic status of nodes was a significant and important prognostic factor for survival among patients with the resectable disease [9, 12, 13]. While a small portion of patients with clinical stage I disease may have pathologic evidence of regional metastasis and thus receive therapeutic benefit from ELND, this fact alone does not justify immediate ELND for all patients with invasive melanoma.

While retrospective cohort studies provided imperfect evidence, a series of prospective trials [14–18] were conducted and failed to identify a survival benefit of immediate ELND among all patients with clinical stage I melanoma. Interestingly, the trial results were generally consistent; among all patients, outcomes favored patients who received immediate ELND, but the advantage was not statistically significant. That said, the trials did identify some subgroups of patients with clinically negative disease for whom immediate ELND appeared beneficial with regard to local recurrence and overall survival, as presented in the following sections.

As early as 1967 to 1974, the WHO Melanoma Group conducted a prospective trial of 553 patients with clinical stage I melanoma of the extremities, who were randomized to either excision of the tumor with immediate regional ELND or excision of the primary tumor with regional LND at time of appearance of regional metastases. Based on equivocal 5 and 10-year survival rates published in 1977 [14] and 1982 [15], the authors concluded that ELND does not improve the prognosis for malignant melanoma and is not recommended when patients can be followed at three-month intervals. No subset of patients benefitted from immediate dissection.

As part of the Intergroup Melanoma Surgical Trial, Balch et al. [16] compared 10- and 15-year survival rates for a prospective group of 740 patients with stage I or II intermediate thickness melanomas (1–4 mm) randomized to either ELND or clinical observation of the nodes. Overall, 10-year survival was not different between patients with ELND and nodal observation (77% versus 73%, respectively, $p = 0.12$). However, subgroup analysis by three independent predictors of survival, specifically tumor thickness, anatomical site, and ulceration, revealed a survival benefit of immediate ELND for certain prospectively defined subgroups. In particular, ELND conferred a 10-year survival benefit for patients with nonulcerated melanomas (84% versus 77%, $p = 0.03$), patients with tumor thickness of 1.0–2.0 mm (86% versus 80%, $p = 0.03$) and patients with melanoma located on the limb (84% versus 78%, $p = 0.05$). The authors asserted that the findings regarding ulceration are actually intuitive, as ulcerated melanomas have a high risk of harboring a distant microscopic disease that would offset any benefit of enhanced regional control. Likewise, no benefit was observed for the subgroup of patients with thick melanoma, as there is a strong association between thickness and ulceration.

A subsequent trial [19], conducted by the WHO Melanoma Group between 1982–1989, compared the efficacy of immediate ELND versus clinical observation with LND at the time of clinical detection among 252 patients with a trunk melanoma >1.5 mm in thickness. Among all patients, the authors found no statistically significant difference in five-year survival (51.3% for observation and delayed LND versus 61.7% for immediate ELND, $p = 0.09$). Consistent with findings from prior retrospective studies [8, 10], the authors found that patients with occult regional node metastases (identified at the time of immediate ELND) had improved 5-year survival compared to patients in whom dissection was delayed until the appearance of regional metastasis (48.2% versus 26.6, respectively, $p = 0.04$). Multivariate analysis showed that routine use of immediate ELND had no impact on survival (hazard ratio 0.72, 95% CI 0.5–1.02).

Lastly, a group of researchers from the Mayo Clinic [18] conducted a similarly designed study among 171 patients with stage I melanoma, randomized to ELND and nodal observation. Ultimately, the observation group was stratified into two groups: delayed lymphadenectomy for patients with subsequent evidence of clinical regional metastasis and no lymphadenectomy for patients without progression of the disease. No significant difference was found among the three treatment groups with respect to melanoma-specific survival or metastasis-free survival.

10.3 Historical Perspective: Evidence for a Sentinel Lymph Node in Melanoma

Despite extensive inquiry into the role of ELND for clinically negative disease, its use remained controversial, given both an uncertain long-term survival benefit and the significant morbidity associated with performing ELND [20–22]. Still, since survival was found to be better following ELND for clinically negative and pathologically positive nodes than for clinically positive and pathologically positive nodes, there was a push to be able to accurately predict the presence of occult regional metastasis at the time of diagnosis. Building on preliminary observations from other cancer disciplines [23, 24], researchers sought a novel approach for assessing regional nodes, namely via an investigation into the existence of a sentinel lymph node (SLN) [25, 26].

Initially, it was believed that there was an anatomically determined path by which lymph drained from the primary tumor to the regional lymph nodes [23, 24]. While this theory proved to be unreliable, it opened the door for the investigation into the functional drainage of lymph from the site of the primary tumor to a regional nodal basin. In an effort to characterize the pattern of lymphatic drainage from primary melanoma, a group of researchers performed a pilot study among 57 patients with melanoma, in which they performed lymphoscintigraphy, by injecting a radioactive colloidal gold into the area of the primary melanoma, followed by

radionucleotide scanning 24 h after initial injection [25]. The patients then underwent regional lymphadenectomy and the presence or absence of metastases to the lymph nodes was correlated with the distribution of colloidal gold in the regional lymph node sites. Among the 57 patients who underwent preoperative gold scanning, 17/57 (29.8%) had nodal metastatic disease at the time of regional lymphadenectomy, and no lymph node metastases were found at sites other than those identified via lymphoscintigraphy. Introduced in 1977, radioactive gold scanning appeared to be a promising technique for the identification of lymphatic drainage; however, it did not expedite the process for detecting metastasis nor reduce the extent of regional dissection needed to remove metastatic nodes.

As techniques for detecting lymphatic drainage improved, it became apparent that lymphatics drained to a particular set of lymph nodes, rather than an entire nodal basin. With the notion of SLNs appearing more credible, Morton et al. hypothesized that detection of this set of nodes would permit accurate pathologic regional assessment, thereby negating the need for a CLND. Replicating techniques that they initially developed in feline studies, Morton and his group [26] used vital dyes to complete intraoperative identification of sentinel lymph nodes, defined as the lymph nodes on the direct drainage pathway from the primary lesion. Following careful excision of the sentinel nodes, en bloc lymph node dissection of the regional basin was performed in the standard fashion. The accuracy of the procedure was then evaluated by comparing the frequency of metastases in the sentinel lymph nodes with the incidence of metastases in the lymph nodes in the remainder of the lymphadenectomy. At least one sentinel node was successfully identified in 194 of 237 lymphatic basins, and metastases were identified in 47 (18%) of 259 sentinel nodes, while non-sentinel nodes were the exclusive site of metastasis in two (0.06%) of 3079 non-sentinel nodes from 194 lymphadenectomy specimens.

The results confirmed the hypothesis that when cutaneous melanoma metastasizes via the lymphatics, it almost exclusively involves the SLNs of the regional basin. Morton's technique identified, with a high degree of accuracy, patients with early-stage melanoma who have nodal metastases and are likely to benefit from CLND. The results were initially presented at the annual Society of Surgical Oncology Symposium in 1990, where they were met with significant skepticism, and despite the apparent rigor and significance of the study, the manuscript was not published for nearly 2 years. Nonetheless, Morton's research carved a path for the sentinel lymph node biopsy (SLNB) to emerge as the gold standard for regional staging in melanoma.

10.4 Role of Sentinel Lymph Node Biopsy (SLNB) in the Management of Melanoma

Traditionally, performing an SLNB was thought to serve two critical functions in the management of primary melanoma. First, determining the pathologic status of the nodal basin, especially in a minimally invasive manner, was believed to provide prognostic information, which would help inform cancer staging and appropriate treatment. The evidence underlying the prognostic value of a positive SLN has emerged over time and is associated with the thickness of the primary tumor, as reviewed in the following section. Secondly, it was believed that the pathologic status of regional lymph nodes should dictate appropriate management of the regional lymph nodes, with CLND thought to be indicated for patients with regional metastatic disease. However, recent studies have scrutinized the role of CLND among patients with regional metastases, providing new evidence to inform additional management following positive SLN, and thereby potentially undermining some of the value of performing SLNB. Current guidelines regarding the indications for performing an SLNB in the management of melanoma are based on available retrospective and prospective data, and are specific to tumor thickness, as reviewed below.

10.5 Prognostic Value of Sentinel Lymph Node Biopsy

At its core, SLNB is critical for the accurate staging of invasive melanoma. Multiple single-institution retrospective studies and several prospective studies have shown the independent prognostic value of SLN status among patients with cutaneous melanoma [20, 27–29]. Historically, the prognostic significance of the SLN was established for intermediate-thickness melanomas, with uncertain extension to thin and thick melanoma. Studies in the last 20 years have provided more conclusive evidence for the prognostic significance of SLNB across all melanoma groups.

The following section reviews the most pertinent research evaluating the prognostic value of SLNB, as it pertains to primary melanoma with tumors of varying thickness.

10.5.1 Intermediate-Thickness Melanoma (1–4 mm)

With regard to intermediate-thickness melanoma, multiple retrospective studies [30–32] have shown the accuracy and prognostic value of SLN status, independent of other prognostic measures such as tumor ulceration. Notably, a group of surgeons in the United States, in conjunction with the American Joint Committee on Cancer, performed a retrospective, cohort study of nearly 15,000 cN0 patients, using the AJCC Melanoma Staging Database [28]. Their analysis found a prognostic superiority of SLNB (with CLND if metastases were present) in patients with melanomas >1 mm thick relative to ELND or clinical exam alone. Five-year survivals were 90.5%, 77.7%, and 69.8%, respectively, for patients without the regional disease, staged by SLNB (n = 2552), ELND (n = 2014), or clinical exam alone (n = 5192). This corresponds to a 68.5% and 26.2% reduction in mortality in patients staged to be N0 by SLN compared with patients staged to be N0 by clinical exam or ELND, respectively. While the relative prognostic superiority of SLNB to clinical exam is expected (given the removal of occult regional disease with both SLNB and ELND), the relative superiority of SLNB to ELND is less intuitive. The authors concluded that part of this survival benefit is caused by stage migration, as a result of more accurate staging with SLNB. Fewer patients with stage III disease are missed with SLNB compared with exam or even ELND. Histologic evaluation of a single or a small number of nodes with SLNB is more accurate, given enhanced scrutiny, which is not possible given the number of nodes assessed with ELND.

In addition, findings from two prospective randomized trials, namely the First Multicenter Selective Lymphadenectomy Trial (MSLT-1) and the Sunbelt Melanoma Trial helped establish the prognostic significance of SLN biopsy for patients with intermediate-thickness melanomas. With 10-year follow-up data published in 2014, the landmark MSLT-1 trial evaluated outcomes in 2001 patients with melanoma >1 mm thick who were randomized to undergo wide excision and nodal observation with delayed CLND for development of clinical nodal disease, or wide excision and SLNB with immediate CLND for nodal metastases detected on SLNB [27]. In the SLNB group, patients with sentinel-node metastases had poorer outcomes than patients with negative sentinel nodes. For patients with intermediate-thickness melanomas, the 10-year melanoma-specific survival rate was 62.1 ± 4.8% among those with SLN metastases compared with 85.1 ± 1.5% among those with tumor-free SLN (hazard ratio for death from melanoma, 3.09; 95% CI 2.12–4.49, $p < 0.001$). Multivariate analysis (which also included Breslow thickness, ulceration, and site of tumor) revealed that SLN status was the strongest predictor of disease recurrence or death from melanoma. The trial provided conclusive evidence that SLN biopsy-based staging of intermediate-thickness melanoma offered important prognostic value.

The Sunbelt Melanoma Trial [20, 33] was designed to compare outcomes following CLND with adjuvant high-dose interferon alfa-2b therapy (HDI) versus CLND alone among patients with primary melanoma ≥1 mm and regional metastasis staged by SLNB. However,

the trial also provided critical evidence for the prognostic value of SLNB. Based on analysis of more than 850 patients with SLNB and median follow-up of nearly 7 years, the authors found that the recurrence rate was greater among patients with histologically positive SLN compared to patients with negative SLN (15.5% versus 6.0%, respectively, $p < 0.05$). In addition, patients with positive SLN were more likely to have distant metastases (as opposed to locoregional recurrence) than those with negative SLN (67% versus 46%, respectively, $p < 0.05$).

10.5.2 Thin Melanoma (≤1 mm)

Historically, thin melanoma has been associated with an excellent prognosis after wide excision and no further treatment was thought to be indicated [34–36]. Accordingly, the prognostic significance of SLNB in thin melanoma was thought to be minimal. However, several large long-term series have since demonstrated the prognostic value of SLN metastases in thin melanoma [37–39]. A group of Italian researchers evaluated the role of SLNB in nearly 500 patients with thin melanoma and found that while the incidence of positive SLN was low (4.9%), sentinel node positivity remained a predictor of poorer disease-free survival and overall survival [37]. Five-year overall survival was 93% for patients with negative sentinel node and 81% for patients with positive sentinel node ($p = 0.001$). Similar findings were identified following a retrospective review of 1250 patients with SLNB and thin melanoma included the Sentinel Lymph Node Working Group database from 1994 to 2012 [38]. SLN metastases were again detected in approximately 5% of patients, and with a median follow-up of 2.6 years, the authors found that melanoma-specific survival was significantly worse for patients with positive versus negative SLN ($p = 0.01$). A third study of more than 1500 patients [39], published in 2008, found nearly identical results, with a 10-year rate of melanoma-specific survival of 98 ± 1% and 83 ± 8% for patients with positive versus negative SLN, respectively ($p < 0.001$). Based on these findings, it is clear that the status of the SLN is significantly linked to survival in patients with thin melanoma, and SLNB provides critical prognostic information and likely improves staging in thin melanoma.

10.5.3 Thick Melanoma (≥4 mm)

For several years after SLNB became standard practice for patients with intermediate thickness melanoma, its prognostic value among patients with thick melanoma was uncertain. Given the relatively high rate of initial distant metastases among patients with thick melanoma, it was believed that the status of regional nodes was less important. However, a consistent prognostic association between SLN status and survival has since been confirmed in this group.

Using SEER data from 2004 to 2011, Kachare et al. found that SLN status was a robust predictor of survival among patients with thick melanoma, as a negative SLNB had a five-year disease-specific survival of 75.3% versus 44.1% with a positive node ($p < 0.0001$) [40].

In a retrospective study of 131 patients with thick melanoma, Gershenwald et al. found that SLNB was positive in 39% of patients. While the presence of ulceration and SLN status were both independent prognostic factors for disease-free and overall survival, SLN status was the most powerful predictor of overall survival by univariate and multivariate analyses [29]. Post-hoc analysis of data from the Sunbelt Melanoma Trial, which included 240 patients with thick melanoma, revealed similar results [41]. In particular, patients with negative SLNs had significantly better median disease-free survival (46.5 versus 31.0 months, $p = 0.04$) and overall survival (55.5 versus 43.0 months, $p = 0.04$) compared with patients with positive SLNs.

On multivariate analysis, sentinel lymph node status, as well as male sex, increasing Breslow thickness, and ulceration were associated with worse overall survival. Nearly identical results were observed among 298 patients with thick melanoma at two Italian centers [37]. Collectively, the results indicate that SLN metastases confer

prognostic value among patients with thick melanoma; however, performing SLNB may not provide a therapeutic advantage, as survival is poor for most patients with thick melanoma, as discussed in the following section.

10.6 Survival Benefit of Performing Sentinel Lymph Node Biopsy

While the prognostic significance of SLN metastases was proven for melanoma of all thicknesses, the therapeutic advantage of performing SLNB is a distinct matter. Quantifying the impact of performing SLNB (and ensuing indicated interventions) on long-term disease-specific survival is critical for determining the appropriateness of performing SLNB in patients with melanoma. Principal prospective data emerged from MSLT-1 [27], which evaluated survival and outcomes among patients randomized to either SLNB versus nodal observation, as previously described. While no significant treatment-related differences in the 10-year melanoma-specific survival were seen in the overall study population, the survival impact of performing SLNB, as assessed in MSLT-1 and other studies, is dependent on tumor thickness. Characterizing the therapeutic value of SLNB depends on a review of available data in each of the subgroups of melanoma.

10.6.1 Intermediate Thickness Melanoma (1–4 mm)

For patients with intermediate melanoma, there is mixed evidence that performing SLNB itself confers a survival benefit. Ten-year data from MSLT-1 revealed that biopsy-based management was associated with a difference in disease-free survival between the SLNB and observation groups (HR, 0.76; $p = 0.01$), but not melanoma-specific survival (HR, 0.84; $p = 0.18$) in the entire study population [27]. However, among patients with nodal metastases and intermediate melanoma, the 10-year melanoma-specific survival rate was 62.1 ± 4.8% in the SLNB group compared with 41.5 ± 5.6% in the observation group (those who later went on to develop clinically detected nodal disease) (HR, 0.56; $p = 0.006$), thereby suggesting that early detection of non-clinically significant, microscopic nodal metastasis may confer a survival benefit in this subset of patients.

A retrospective study by Kachare et al. [42] analyzed SEER data from 2003 to 2008 to compare outcomes among patients with intermediate melanoma who underwent wide excision with SLNB or wide excision alone. Compared with observation, SLNB was associated with a modest advantage in melanoma-specific survival (HR, 1.18; $p = 0.009$). A similarly designed study [35] assessed SEER data from 2004–2011 for patients with intermediate thickness melanoma arising in the head and neck, and found no significant association between SLNB and improved disease survival (five-year disease-specific survival was 89% and 88% for patients with SLNB versus nodal observation, log-rank $p = 0.30$). A review of data from the Melanoma Institute Australia [43] found that patients who underwent SLNB rather than observation had significantly better melanoma-specific survival ($p = 0.011$) and distant metastasis-free survival ($p = 0.041$).

10.6.2 Thin Melanoma (<1 mm)

It is well established that survival for patients with melanoma is directly related to tumor thickness [44] and historically, thin melanoma was associated with an excellent prognosis. However, outcomes are not uniform, as some aggressive thin melanoma are capable of metastasis, resulting in locoregional and distant recurrence. Several large series, with long-term follow-up, have highlighted this variable prognosis, with reported 10- and 20-year overall survival rates of 80–97% and 64%, respectively [34, 35]. Nonetheless, nodal metastases are rare, with an SLN positivity rate of 5%, according to a recent systematic review and meta-analysis of 60 studies and more than 10,000 patients [45]. Thus, the therapeutic advantage of SLNB for all patients

with thin melanoma has not been demonstrated at a population level, and accordingly, early NCCN guidelines stated that SLNB was not recommended for routine use in this group [46].

However, given the likelihood of a high-risk group of patients with thin melanoma, and the lack of other highly prognostic clinical and pathologic characteristics, there was a push to identify factors associated with SLN metastases [36]. Multiple studies investigated this link, and a large systematic review and meta-analysis found that thickness ≥0.75 mm, Clark level IV/V, mitoses, and microsatellites significantly increased the odds of SLN positivity [45]. Additionally, ulceration was noted to be a significant predictor of SLNB metastasis [38]. Theoretically, for patients with high-risk thin melanoma, SLNB confers a therapeutic advantage to nodal observation alone, though this has not been directly investigated. Some data indicates that while the presence of certain features may be associated with a statistically significant increase in the risk of SLN metastasis, the association is not clinically meaningful nor independent [47, 48].

10.6.3 Thick Melanoma (>4 mm)

Given the high rate of initial distant metastases and the overall poor prognosis of thick melanoma, relative to intermediate and thin melanoma, it was historically controversial whether early nodal surveillance via SLNB served a therapeutic advantage for patients with thick melanoma. Results from available retrospective studies provide compelling evidence that while SLNB provides prognostic information, it does not confer any therapeutic advantage among patients with thick melanoma [40, 49, 50]. A review of SEER data from 2003 to 2010 among patients undergoing either wide local excision alone or excision plus SLNB for clinically negative melanoma >4 mm found that performing SLNB was not associated with disease-specific survival ($p = 0.20$) [40]. In addition, a large single-center, a retrospective study comparing SLNB versus observation among 1211 patients with thick melanoma found that SLNB was associated with improved disease-free survival, but not melanoma-specific survival after adjustment for established prognostic factors [50]. Similar findings were found in a retrospective study at the University of Turin, Italy, which compared outcomes across three groups: negative SLNB, positive SLNB and SLNB not performed (nodal observation). Multivariate analysis confirmed a better prognosis for SLN-negative patients compared with patients in the observation group; however, patients in the observation group had the same prognosis as patients with positive SLN, when adjusted for known confounders [49].

10.7 Current Guidelines for Performing a Sentinel Lymph Node Biopsy

Based on available evidence, the NCCN, as well as the American Society of Clinical Oncology and the Society of Surgical Oncology have published guidelines regarding the clinical indications for performing SLNB in patients with invasive melanoma [46]. The recommendations weigh the prognostic significance of SLNB, its potential therapeutic advantage, as well as the risks associated with the procedure. This analysis shifts based on certain clinical features and thus, guidelines are based on two primary features: Breslow thickness and presence of ulceration.

For thin melanoma (thickness <1.0 mm), SLNB should be considered for two groups of patients: (a) patients with Breslow depth <0.8 mm and one or more high risk features, including ulceration and high mitotic index; and (b) patients with Breslow depth 0.8–1.0 mm, regardless of the presence of ulceration or other risk factors. Recommendations are based primarily on studies identifying the clinical factors associated with SLN positivity [45]. Other clinical factors and patient factors such as age have been shown to mediate this risk [51, 52] and ultimately, the decision to perform SLNB in these two groups should follow the discussion with the patient regarding the relevant risks and benefits of surgery [46].

For patients with Breslow depth <0.8 mm and no evidence of ulceration, routine SLNB is not recommended, given the low probability of the patient having positive SLNs.

For patients with intermediate melanoma (thickness 1–4 mm), SLNB is recommended for all patients given its prognostic significance and survival benefit, as shown in MSLT-1 [27] and multiple studies reporting outcomes in this group [35, 42, 43]. However, patient factors should be considered in the decision to offer SLNB, particularly in older or frail patients.

For patients with thick melanoma (thickness >4.0 mm), SLNB may be considered, after a thorough discussion of the risks and benefits. While its prognostic significance has been shown in multiple studies, both MSLT-1 [27] and multiple retrospective studies [40, 49, 50] did not identify a survival benefit of performing SLNB compared to nodal observation among patients with thick melanoma. Most notably, MSLT-1 found no difference in 10-year melanoma-specific survival among patients in the SLNB group compared with routine nodal observation with screening ultrasonography [27]. Performing SLNB at diagnosis may be unnecessary, given the limited associated survival benefit. However, for patients with regional metastasis, and no evidence of distant disease, early detection of regional metastasis via SLNB may offer important opportunities for adjuvant treatment [46].

10.8 Technical Consideration: Sentinel Lymph Node Biopsy [53]

Performance of SLNB in melanoma relies on preoperative lymphatic mapping. While the relevant lymphatic drainage pathway from melanoma on the extremities is fairly predictable (to the ipsilateral axillary nodes for upper extremity and ipsilateral inguinal or popliteal nodes for the lower extremity), lesions on the trunk, head, and neck may have variable drainage. For this reason, a preoperative lymphoscintigram is imperative and should be reviewed before proceeding to the operating room in order to anticipate the relevant nodal basin. Typically, the patient will receive an injection of radiocolloid on the day before or the morning of the operation, with subsequent lymphoscintigram. In the rare event that lymphatic mapping fails, the operation may be postponed with an attempt at reinjection for mapping at a later date.

Radiotracer lymphatic mapping is supplemented by the injection of blue dye in the operating room. A small intradermal injection is administered just outside the lesion to be excised, but within the anticipated surgical margins, to avoid permanent blue tattooing of the skin.

Intraoperatively, an incision is made over the relevant nodal basin, the nodal basin is explored, and a combination of a radio probe and inspection is used to identify sentinel lymph nodes. The number of sentinel nodes will vary between patients. Nodes are excised until there are no remaining radioactive or blue nodes. Any lymph node with radioactivity that is less than 10% of the hottest node is not considered a sentinel node. All nodes should be handled with care to avoid fracture and cautery artifact. Lymphatics and vessels should be secured with ties or clips. Routine drains are not needed.

10.9 Management of a Positive Sentinel Lymph Node

Traditionally, patients with invasive melanoma and pathologically positive SLN were managed with CLND of the regional nodal basin [54]. The objectives of CLND were two-fold: prevent the development of distant disease and perform accurate staging. However, over the past 30 years, the treatment standard of performing a CLND for any patient with a positive SLN has evolved secondarily to multiple retrospective studies [2, 54] and a series of prospective trials [30], which have reinforced the prognostic accuracy of SLNB alone and undermined the presumed survival benefit of immediate CLND for patients with evidence of regional disease as identified by SLNB.

Three randomized trials evaluated the role of SLNB and CLND in the treatment of regional nodes:

- Multicenter Selective Lymphadenectomy Trial I (MSLT-I) [1, 27]
- German Dermatologic Cooperative Oncology Group-Selective Lymphadenectomy Trial (DeCOG-SLT) [4, 5]
- Multicenter Selective Lymphadenectomy Trial II (MSLT-II) [6]

Each of the trials and their impact on the treatment of regional lymph nodes are reviewed below.

Discussed in detail in previous sections, MSLT-I compared melanoma-specific survival among patients randomized to either (a) wide local excision with subsequent clinical observation or (b) wide excision and SLNB. Complete dissection was performed upon nodal recurrence for the observation arm and upon discovery of positive SLN for the SLNB arm. MSLT-I confirmed the role of SLNB in establishing long-term prognosis in melanoma and revealed that early nodal treatment via SLNB was associated with improved regional control and recurrence rates [27]. While no melanoma-specific survival benefit was observed for the overall cohort, biopsy-based management and early nodal dissection as dictated by SLNB, was associated with improved distant-free survival and melanoma-specific survival for patients with intermediate-thickness melanoma and regional metastasis. In addition, among patients with intermediate thickness melanoma and nodal metastases, early detection via SLNB and immediate CLND resulted in significantly improved survival compared to observation with delayed CLND when recurrence was noted.

Hence, the impact of CLND on melanoma survival for patients with SLN positive disease remained controversial. Two prospective randomized controlled trials, DeCOG-SLT and MSLT-II, were designed to investigate whether CLND improves survival for patients with SLN metastases.

Conducted from 2006 to 2014, DeCOG-SLT [4, 5] compared survival outcomes in 1256 patients with positive SLNB who were randomly assigned to CLND or observation. The final results, with a median follow-up of 72 months, showed that compared to clinical observation, immediate CLND in SLN positive patients did not provide a survival benefit. Five-year distant metastatic free survival was 67.6% and 64.9% for immediate CLND and observation, respectively. No difference was observed in five-year recurrence-free survival (HR 1.01) nor overall five-year survival (HR 0.99). Grade 3 and 4 adverse events occurred in 32 patients (13%) in the CLND arm. No subset of patients was identified that might benefit from CLND, indicating that CLND should not be routinely performed in patients with SLN metastasis.

Building on the group's first trial, MSLT-II was designed to evaluate whether CLND was indicated for patients with SLN metastases and intermediate-thickness melanoma. Patients with nodal metastases detected via SLNB were randomly assigned to immediate CLND or nodal observation with routinely scheduled ultrasonography. Immediate CLND was not associated with increased melanoma-specific survival among the nearly 2000 enrolled patients. In the per-protocol analysis ($N = 1755$), the mean (±SE) 3-year rate of melanoma-specific survival was similar in the CLND group and the observation group (86.1 ± 1.3% and 86.1 ± 1.2%, respectively, $p = 0.42$ by the log-rank test) at a median follow-up of 43 months. Immediate CLND did increase the rate of regional disease control at 3 years (92 ± 1.0% versus 77 ± 1.5%, $p < 0.001$ by the log-rank test), which was thought to underlie a slightly higher rate of disease-free survival observed in the dissection group relative to the observation group (68 ± 1.7% and 63 ± 1.7%, respectively, $p = 0.05$ by the log-rank test). The trial found that rather than performing CLND, careful observation of the regional nodes with routine ultrasonography was safe for patients with melanoma and SLN metastasis. Together, DeCOG-SLT and MSLT-II changed published practice guidelines (from the NCCN and the

ASCO/SSO) with regard to how sentinel metastases should be managed among patients with intermediate thickness melanoma.

10.10 Current Guidelines for Performing a Complete Lymph Node Dissection

Since incorporating SLNB in the standard treatment of melanoma, the management of regional metastasis, as identified via SLNB, has changed dramatically. Based on the findings of DeCOG-SLT and MSLT-II, as well as better options for adjuvant targeted and immune therapies [31, 32, 55], the necessity of CLND in patients with positive SLN is not evident.

In 2018, the ASCO and SSO published updated guidelines regarding the role of CLND among patients with positive SLN [46]. Based on a review of all published data, the expert panel published two statements regarding CLND among patients with positive SLNB. First, the group stated that for patients with the low-risk micrometastatic disease, CLND or careful observation with routine clinical exam and ultrasonography are options, with careful consideration of clinicopathological factors. For high-risk patients, careful observation may be considered only after a thorough discussion with patients about the potential risks and benefits of foregoing CLND. Importantly, high-risk features are defined on the basis of the exclusion criteria for MSLT-II. Specifically, this includes: extracapsular spread or extension, concomitant microsatellites of the primary tumor, more than three involved nodes, and more than two involved nodal basins and immunosuppression of the patient. For patients undergoing close observation, CLND should be heavily considered if recurrence is noted in the regional nodes and there is no distant disease.

The consensus group provided two cautions. First, there were relatively small numbers of patients with higher SLN burden (>1 mm) in both trials and results may thus not be generalizable to patients with more than a low-risk micrometastatic disease in the nodal basin. Second, in both trials, the observation group received frequent follow-up evaluations, including the use of serial nodal ultrasound. Accordingly, the results may have limited applicability in settings where patients are unable to undergo reliable follow-up.

The guidelines are guarded compared to the published conclusions of DeCOG-SLT and MSLT-II. While this caution may be advisable given the relatively limited evidence, further prospective research is warranted to qualify the safety of careful observation in patients with positive SLN, in order to limit unnecessary morbidity associated with CLND.

10.11 Technical Considerations: Regional Lymph Node Dissection

A full discussion of the technical aspects of regional lymphadenectomy is beyond the scope of this chapter. The most common lymph node dissections performed for melanoma are the axillary and inguinal node dissections. Regional lymphadenectomies involve the removal of an entire nodal basin using relevant anatomic landmarks. The packet of lymph nodes is generally excised en bloc with the associated fat pad, and individual nodes are identified and sectioned by the pathologist. Routine placement of bulb suction drains is common.

10.12 Emerging Considerations for Management of Nodal Disease

DeCOG-SLT and MSLT-II were primarily designed to investigate the clinical significance of a positive SLNB among patients with invasive melanoma; however, one of the other impetuses for pursuing alternative management strategies to CLND was the significant morbidity associated with CLND. In the past 5–10 years, several institutions have demonstrated the safety and feasibility of

minimally invasive approaches to inguinal lymph node dissections in patients with melanoma [56–58], which could potentially alter the risk and benefits of performing CLND.

A multicenter, phase I/II clinical trial (SAFE-MILND) was completed across ten institutions to evaluate the use of a minimally invasive inguinal lymph node dissection (MILND) for patients with melanoma among a group of surgeons newly adopting the procedure. Enrollment of 88 patients was completed between 2012 and 2014, and preliminary results published in 2017 were promising, with a lymph node retrieval that met or exceeded current oncologic guidelines and published benchmarks, and a favorable morbidity profile, relative to open inguinal lymphadenectomy [58].

A randomized, prospective trial was also initiated at Emory University in 2008 [56, 57]; however, the randomization portion of the trial was aborted as there was inadequate accruement. Nonetheless, the study provided some novel results regarding outcomes following videoscopic inguinal lymphadenectomy (VIL). Among 63 patients with melanoma who underwent VIL, the median overall survival was 68.8 months, and the recurrence-free survival was 18.5 months. Most complications were minor (defined as Clavien-Dindo 1 or 2), and included seroma (N = 18), wound infection (N = 24), and skin necrosis or dehiscence (N = 6). Less than 7% (4/63) of procedures performed were converted to an open dissection. The results demonstrated decreased morbidity and oncologic noninferiority of VIL relative to open CLND, suggesting that VIL was a valid surgical approach for patients requiring lymphadenectomy.

10.13 Conclusion

The management of regional lymph nodes in melanoma has evolved rapidly as landmark clinical trials have provided an intellectual framework for understanding the rationale and expected outcomes of lymph node surgery. Sentinel lymph node biopsy should be considered a staging procedure that provides important prognostic information. While the discovery of the micrometastatic disease in sentinel lymph nodes no longer supports the performance of completion lymphadenectomy for all patients, the information gained from sentinel lymph node biopsy impacts decisions about adjuvant systemic therapy, which has been shown to improve survival for patients with stage III melanoma. Complete regional lymphadenectomy retains a role in patients who have a clinically evident or bulky nodal disease.

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11 Adjuvant Systemic Therapy for Stage III Melanoma

Adam Lerner and Debjani Sahni

11.1 Introduction

For decades, nodal metastases were managed surgically in an attempt to halt disease spread in melanoma patients presenting with regional disease. More recently, however, two large, prospective, randomized trials demonstrated prognostic significance, rather than a need to pursue surgical therapeutic intervention, when there is pathologic confirmation of regional lymph node involvement in patients with cutaneous melanoma. Stage III disease in melanoma is now considered to be a marker for potential clinically and radiologically inapparent systemic micrometastases that are the primary determinants of a patient's melanoma-specific survival [1, 2]. While completion lymph node dissection of sentinel lymph-node positive disease may modestly influence locoregional control and disease-free survival (68 vs 63% at 3 years in one study), it does not significantly impact melanoma-specific survival (86 ± 1.3% vs 86 ± 1.2%), and its associated significant morbidity must also be taken into account in therapeutic decision making [1].

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11.2 Heterogeneity of Stage III Melanoma

In discussing current options for adjuvant treatment of stage III melanoma to reduce the incidence of systemic relapse, it is first important to acknowledge the prognostic heterogeneity of patients with stage III disease. Patients with clinically recognized, palpable adenopathy, or "macrometastases," have a much higher incidence of systemic relapse than those with "micrometastatic" nodal disease, apparent only upon pathologic evaluation of non-palpable lymph nodes. In one study of 2313 patients with stage III disease, 81% had micrometastases, and 19% had clinically detectable macrometastases. The 5 year OS was 67% for those with micrometastatic nodal disease vs. 43% for those with macrometastatic nodal disease [3].

Within the micrometastatic lymph node group, prognosis varied widely based on the number of tumor-containing lymph nodes, Breslow thickness, ulceration, and the anatomic site of the primary melanoma. While patients with micrometastasis to a single lymph node and a non-ulcerated primary melanoma of <2 mm had a 5 year OS of 87.1%, patients with four or more involved lymph nodes and an ulcerated primary of 6 mm or greater had a 5 year OS of 22.7% [3]. Given this wide variability, there are some stage III melanoma patients in which considering such prognostic information will be critical to both the

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patient and the oncologist in weighing the risks and benefits of utilizing adjuvant systemic therapy to reduce the likelihood of relapse.

11.3 Early Adjuvant Therapy: Interferon α-2b

Consistent with studies described in the chapter on the systemic management of patients with metastatic melanoma, from 1980 onward, more than three decades of treatment of stage III melanoma patients with chemotherapeutic agents, cytokines, or vaccines intended to stimulate an effective immune response to melanoma failed to substantially alter the outcome of these patients. Perhaps the most intensively studied therapy during this period was high-dose adjuvant interferon α-2b (IFN), given as 20 million IU/m^2/day intravenously for 4 weeks, followed by ten million IU/m^2 3 times a week subcutaneously for 48 weeks. In Eastern Cooperative Oncology Group (ECOG) trial 1684, 287 stage IIB or III melanoma patients were randomized to high-dose IFN (HDI) or observation. Recurrence free survival (RFS) was 1.72 vs 0.98 years, and median overall survival (OS) 3.82 vs 2.78 years, respectively, in these two arms [4]. These data supported regulatory approval of HDI therapy for stage IIB and stage III melanoma patients.

As HDI therapy was associated with a substantial number of side effects that made such treatment difficult to tolerate, a second randomized trial (E1690) was carried out comparing the outcome of three groups: the HDI regimen described above, a low-dose IFN (LDI) regimen and observation [5]. Among 642 patients accrued to this trial, HDI therapy showed improvement in RFS (HR 1.28) relative to observation but LDI did not. Neither HDI nor LDI significantly improved OS, although a retrospective analysis suggested that crossover of patients on the observation arm to HDI therapy off protocol may have subsequently influenced the OS result. A pooled analysis of ECOG and Intergroup trials of HDI ultimately failed to show a significant impact of HDI therapy on OS [6].

11.4 Adjuvant Checkpoint Inhibitor Therapy and Targeted Therapy in Advanced Melanoma

The detailed mechanism of action of immune checkpoint therapy and targeted therapies are discussed in the chapter, "Systemic therapy in melanoma."

11.4.1 Adjuvant Checkpoint Inhibitor Therapy in Stage III Melanoma: Ipilimumab

As the clinical efficacy of checkpoint inhibitors or BRAF/MEK inhibitor combination targeted therapy in patients with advanced melanoma became apparent after 2011, clinical progress in the care of patients with resected stage III melanoma resulted from subsequent trials that examined the efficacy of such therapies when used in the adjuvant setting.

As in the case of patients with advanced melanomas, the anti-CTLA-4 monoclonal antibody ipilimumab was the first checkpoint inhibitor to be studied in the setting of resectable stage III melanoma. In the EORTC 18071 clinical trial, 951 such patients were randomized to ipilimumab or placebo therapy [7]. As per protocol, patients treated with ipilimumab received 10 mg/kg every 3 weeks for four doses, then every 3 months for up to 3 years. It is noteworthy that only 13% of patients completed the 3 years of treatment and 39% of patients stopped therapy after the first four doses due to adverse events.

With a median follow-up of 5.3 years, the 5-year RFS was 40.8% with ipilimumab and 30.3% with placebo. The corresponding 5-year overall survival of patients randomized to ipilimumab or placebo was 65.4 vs 54.4%, respectively (HR 0.72; $p = 0.001$) [8]. In 2015, the Food and Drug Administration (FDA) approved ipilimumab therapy for patients with resected stage III melanoma on the basis of these studies.

As previously observed in patients with metastatic melanoma, the toxicity observed in stage III patients treated with ipilimumab in this trial

was frequent and occasionally substantial [8]. Grade 3 or 4 immune-related toxicity was observed in 41.6% of ipilimumab-treated patients. Five patients died of toxicity that was attributed to ipilimumab therapy: three from colitis, one from myocarditis, and one from multiorgan failure associated with Guillain–Barre syndrome. Given the toxicity of ipilimumab and its apparent lesser efficacy when compared with anti-PD-1 based therapies (see below), adjuvant ipilimumab is no longer recommended in NCCN guidelines for stage III melanoma.

11.4.2 Adjuvant Checkpoint Inhibitor Therapy in Stage III Melanoma: Anti-PD-1 Agents

The introduction of anti-PD-1 therapy soon established that these agents were more active and less toxic than IFN or ipilimumab in the care of patients with resectable melanoma. In a randomized study of 906 stage IIIB, IIIC, and IV patients with fully resected melanoma (roughly 18% of patients were stage IV), treatment with nivolumab vs ipilimumab for up to 1 year resulted in a 12-month recurrence-free survival of 70.5% vs 60.8%, respectively [9].

Similar to systemic therapy for unresectable melanoma, grade 3–4 toxicity was significantly lower (14.4%) in nivolumab-treated patients than in those treated with ipilimumab (45.9%), and treatment discontinuation due to toxicity was also comparably lower (9.7 vs. 42.6%, respectively). One year of treatment with anti-PD-1 therapy became the standard of care in patients with fully resected melanoma.

11.4.3 Targeted Therapy in Stage III Melanoma

Combination BRAF/MEK inhibitor targeted therapy regimens have demonstrated efficacy in patients with BRAF-mutated stage III resectable melanoma. In a double-blind, placebo-controlled trial of patients with resectable BRAF V600E or V600K mutated melanoma, treatment with dabrafenib plus trametinib for 1 year led to 3-year relapse-free survival of 58% in the combination therapy group vs. 39% in the placebo group. The corresponding overall 3-year survival rates were 86 and 77%, respectively [10]. While these targeted therapy studies suggest a comparable early disease control rate to anti-PD-1 inhibitor therapy for resected stage III patients, we are unable to draw firm conclusions as the data are from separate studies.

11.5 Choice of Therapy

Faced with a stage III melanoma patient whose tumor has a BRAF mutation, what is the best form of adjuvant systemic therapy to initiate? Similar to stage IV disease patients, we still have no definitive answer for this. Until trials directly comparing targeted therapy with anti-PD-1 inhibitor therapy are performed, it is likely that most practitioners will prescribe a year of checkpoint inhibitor therapy as first-line adjuvant therapy in stage III disease. This is largely based on the observation that the 5-year durable disease-free survival for advanced melanoma patients who have received checkpoint inhibitor treatment is inferred to be markedly better than the 5-year results obtained with targeted therapy [11, 12].

11.6 A Change in the Paradigm of Care for Stage III Melanoma

The studies outlined above document a sea of change in the care of patients with resectable stage III melanoma. The nodal disease is now recognized as not the proximate cause of melanoma mortality, but rather a critically important marker for the presence of the systemic micrometastatic disease that will actually dictate a patient's disease-specific survival. Instead of aggressive resection of all nodes draining a primary melanoma, surgical care now focuses on the sensitive detection of metastatic nodal disease through the use of sentinel

lymph node procedures, thereby enhancing identification of those patients who may benefit from systemic adjuvant therapy. Even more importantly, while still far from perfect, the checkpoint inhibitor and targeted systemic adjuvant therapies we can now offer to patients with stage III melanoma clearly improve long-term survival, justifying their use in most stage III patients. As noted above, a year of adjuvant treatment with an anti-PD-1 directed therapeutic is currently the standard of care for a newly diagnosed stage III melanoma patient. That said, this approach to the adjuvant systemic therapy of stage III melanoma may well change in the years ahead in this rapidly evolving area of clinical research.

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12 Adjuvant Radiation Therapy for Stage III Melanoma

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12.1 Background

Regional nodal metastases are the most common site of metastatic melanoma. Patients with clinical evidence of nodal involvement are managed with upfront therapeutic nodal dissection. Prior to the availability of effective systemic immunotherapy and BRAF/MEK targeted therapy the role of Radiation therapy (RT) in the management of node-positive melanoma was in the adjuvant setting following surgical resection to reduce the risk of regional recurrence. Much less frequently RT was used as definitive therapy for local and locally advanced melanoma (owing to the relative radioresistance of the disease). Because of this relative radioresistance and the high propensity of melanoma for distant spread, the addition of adjuvant RT to surgical resection has long been questioned. A number of randomized studies have attempted to determine which high-risk local features help identify patients that would most benefit from aggressive local and regional therapy [1, 2]. While adjuvant RT is associated with improved local and regional control, studies have failed to demonstrate a survival benefit, and thus its role after surgery has been controversial with some centers using it regularly and others choosing not to do so and prioritizing systemic therapy. Following the demonstration of significant improvement in progression-free and overall survival with systemic immunotherapy and targeted therapies, these agents have become prioritized as the primary adjuvant treatment modality in Stage III and Stage IV disease. In this new era of effective systemic therapy there do remain scenarios however where adjuvant RT should be considered including:

1. After regional lymph node dissection of macroscopic lymph node disease
2. After previous Regional Lymph Node Dissection (RLND) has failed in the regional field
3. After resection of desmoplastic or other melanoma subtypes with neurotropism
4. As adjuvant treatment after resection of brain metastases when there is no other or low volume distant disease

RT also continues to play an important role in the palliative care setting to alleviate pain or bleeding from melanoma primary or metastases with unresectable disease, satellite, or in-transit disease, and residual local disease resistant to

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systemic therapy. As melanoma remains a disease with high rates of morbidity and mortality it is important for clinicians to appreciate and understand the full armamentarium at their disposal to help achieve optimal outcomes for their patients.

12.2 Regional Metastases of Melanoma

12.2.1 After Regional Lymph Node Dissection

Before recent breakthroughs in systemic therapy adjuvant RT for high-risk resected regional disease required careful evaluation with recommendations to offer treatment made on an individual basis. Early studies determined relapse rates following surgical resection alone for regionally metastatic melanoma [3, 4]. Nodal failure following regional lymph node dissection (RLND) alone has been historically reported between 15 and 20% but maybe as high as 30–50% with the presence of certain high-risk features [5]. The factors found to have the greatest influence on the risk of regional relapse and thereby benefit from adjuvant RT include:

1. Larger size of lymph node involvement
2. A higher number of involved nodes
3. Presence of gross or pathologic extranodal extension (ENE)
4. The location of nodal disease, with a higher risk of relapse in parotid and neck disease compared with the axilla and groin

These early studies helped identify high-risk features for relapse which then lead to several attempts to evaluate the role of adjuvant RT after RLND in high-risk patients. A small randomized study at Mayo Clinic by Creagan et al. published in 1978 failed to show a benefit from adjuvant RT [6] and reinforced the idea that melanoma is a radioresistant malignancy with a limited role for RT in its definitive management. However, there were significant shortcomings with this study including a small sample size of 56 patients, short follow-up, and inadequate RT dose. In the following decades, a number of single-arm and retrospective studies with higher patient numbers and higher total radiation dose and dose per fraction did show increasing rates of local control substantiating the hypothesis that adjuvant RT holds efficacy in the treatment of regional melanoma [1, 4, 7]. The Radiation Therapy Oncology Group (RTOG) designed and opened a trial, RTOG 93-02, to compare patients undergoing cervical lymphadenectomy with or without adjuvant RT; however, this closed early because of insufficient patient accrual and results have not been reported. The Trans-Tasman Radiation Oncology Group (TROG) designed a Phase II study with 234 patients receiving adjuvant RT following lymph node dissection at pathologic high risk for recurrence defined as >1 positive lymph node, positive ENE, recurrence after prior LND, or tumor spill at the time of surgery. Adjuvant RT was prescribed at 48 Gy in 20 fractions of daily RT. Systemic therapy given at the time of RT was discouraged. The initial report of toxicity by Burmeister et al. in 2002 indicated that late toxicity with this regimen was very acceptable with the authors concluding this regimen could form the basis of a randomized trial [8]. Results of this Phase II study were published in 2006 by Burmeister et al. and demonstrated a 5-year regional control rate of 91%. The 5-year PFS was 27% and OS 36% [9]. Significantly worse PFS and OS were observed in patients with >2 lymph nodes. Updated findings of toxicity revealed 9% grade 3 lymphedema of patients treated to the axilla and 19% of those treated to the inguinal nodes. No grade 4 toxicity was observed. This data-guided development of the international multi-center phase III cooperative group trial ANZMTG 1–02/TROG 02.01 that randomized 217 patients across 16 centers to observation vs. adjuvant RT for patients at high risk of nodal relapse after lymph node dissection. High risk was defined as at least 1 positive node in the parotid basin, 2 or greater positive nodes in cervical or axillary nodal basins, 3 or greater nodes in the inguinal chain, or presence of ENE or one node greater than or equal to 3 cm in size. These eligibility criteria were based on a pre-

dicted minimum risk of a lymph node relapse rate of at least 20%. RT was delivered to the nodal basin to a total dose of 48 Gy in 20 fractions. The primary endpoint was defined as regional relapse and relapses in the observation arm could be offered RT salvage. There were 250 patients randomized to the adjuvant RT (123 patients) groups and the observation group (127 patients) combined. Two patients withdrew consent, 31 had a major eligibility infringement, and two patients were lost to follow-up. Although the study did two analyses, one with an intent-to-treat that included 248 patients, the relevant data with the eligible population of 217 was presented. Initial results with a 40-month median followed up were published in 2012 and updated results with 6-year median follow-up published in 2015 showed that the observation group had more overall regional relapses 39 of 108 evaluable (36%) vs. 23 of 109 evaluable (21%) in the RT treated group (adjusted hazard ratio 0.52 [95% CI 0.31–0.88, $p = 0.023$] [10, 11]. No differences were noted for relapse-free survival (HR 0.89 CI 0.65–1.22; $p = 0.51$) or overall survival (HR 1.27, 95% CI 0.89–1.79; $p = 0.21$). Lymph node site did not demonstrate a significant difference in rates of relapse among both groups. Five-year OS for the RT group was 40% whereas the observation group was 45%, though the results were not significant. In terms of survival, a greater number of positive nodes (hazard ratio 1.35, 95% CI 1.09–1.68, $p = 0.006$) and the presence of ECE (hazard ratio 1.71, 95% CI 1.36–2.15, $p < 0.0001$) were the only factors associated with adverse survival. Toxicity and quality of life were also analyzed in the study as secondary endpoints. In the RT group, 20% developed grade 3 acute toxicity consisting primarily of skin dermatitis with grade 4 toxicity being rare with just 2 patients affected. At 5 year follow-up there were no differences in lymphedema as measured by upper limb volume between the two groups (10.5% vs 7.0% increase $p = 0.25$). In the lower limb, however, there was a non-statistical increase in limb size after RT compared with observation (mean volume ratio 15.0% vs 7.7% increase $p = 0.14$). In quality of life reporting, there was no significant difference between the two groups at 3,6,12,24, and 60-month reporting time points except for physical well-being at 3 months. Other studies have also held suggestions that RT to the lower limb is an additional risk factor on top of surgery for increased lymphedema especially after lower limb and groin dissection. Figure 12.1 is an example of adjuvant radiotherapy for melanoma to the regional axilla (Table 12.1).

Many studies have demonstrated that high-risk features of regional relapse also correlate with increased rates of distant metastasis [24–26]. This is reflected in the current AJCC eighth ed. Staging system with Stage IIIA, IIIB, IIIC melanoma demonstrating 10-year melanoma-specific survival of 77%, 60%, and 24%, respectively. Adjuvant RT in regional disease has not demonstrated efficacy to improve overall survival whereas adjuvant immunotherapy has and therefore should take priority over RT as the standard of care for adjuvant management of regionally metastatic melanoma. Furthermore, updated data from the EORTC 1325 and EORTC 18071 suggest that adjuvant immunotherapy may improve not just distant control but also local control, although the benefit appears more modest. At 1.5-year follow-up locoregional recurrence only in the EORTC 1325 in placebo vs treated arms was 16.7% vs 11.6% (HR 0.69 [0.44–1.09]) and in EORTC 18071 was 18.5% vs 16.7% (HR 0.85 [0.6–1.22]). Results have also been reported at 5 years for EORTC 18071 and was 24.7% vs 21.1% [34]. In EORTC 1325 study, the authors have also demonstrated that compared to the placebo arm, the reduction in the hazard of recurrence or death in the pembrolizumab arm was greater ($p = 0.028$) after onset of immune-related adverse event (irAE) (HR –0.37, 95% CI: 0.24–0.57), which were primarily endocrine disorders, than without/before an irAE (HR = 0.61, 95% CI: 0.49–0.77) [35]. This resulted in a 63% risk reduction of recurrence in the treated group that developed irAE's versus a 44% reduction in the overall group versus placebo. These systemic therapy study protocols did not allow adjuvant

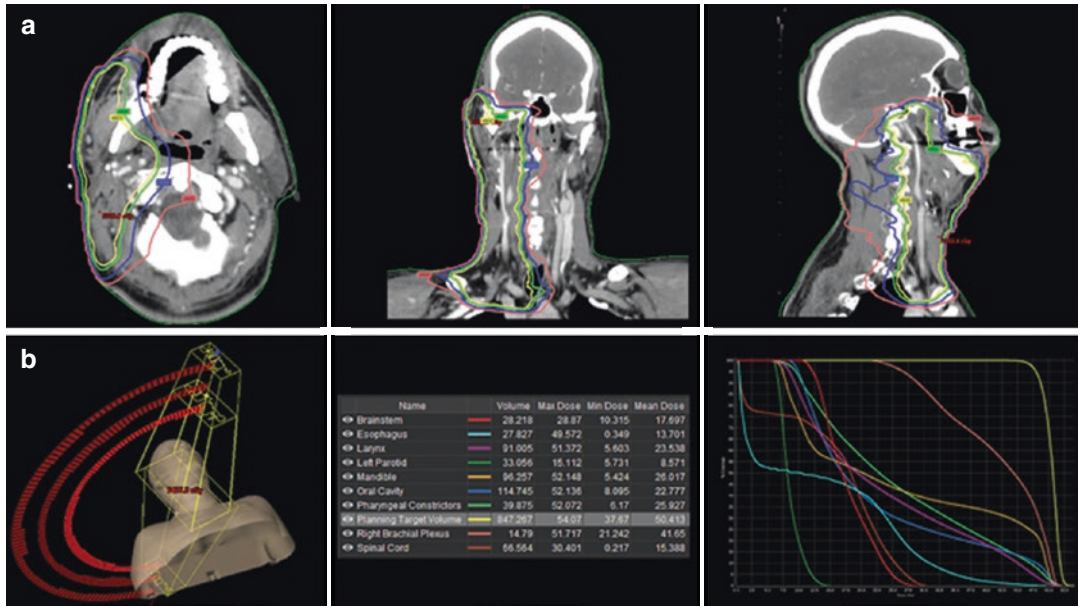

Fig. 12.1 (**a**) Intensity-modulated radiation therapy (IMRT) treatment plan with isodose lines in axial, coronal, and sagittal planes for adjuvant right neck treatment after neck dissection in a patient with stage IIID melanoma of the right cheek with 6 of 26 lymph nodes positive, largest node 2.4 cm in size, with extranodal extension and a 1-mm deep margin. Prescription dose was 48 Gy in 20 fractions and radiation therapy was given concurrently with immunotherapy. (**b**) IMRT beam entry (3 partial arcs), dose-volume histogram legend with structure volumes (in cc) and max, minimum, and mean doses (in Gy), and dose-volume histogram for select structures

RT [36–38] and so the question does remain whether the addition of RT would add further benefit. In EORTC 1325 hazard ratios for recurrence were higher for patients with high-risk lymph node metastases (Stages IIIB and IIIC, macroscopic nodes, and ≥4 positive nodes) than for those with low-risk lymph-node metastases (Stage IIIA, macroscopic nodes, and ≤=3 positive node), at least raising the question of whether RT may play some role in improving locoregional control [37]. If RT were to be added to the treatment paradigm with immunotherapy, the optimal timing of adjuvant RT and immunotherapy is yet to be determined (Table 12.2).

A number of institutional prospective studies have also been run in the metastatic setting utilizing SBRT and concurrent immune systemic therapy to attempt and induce the abscopal effect – the phenomenon in which localized treatment of a tumor causes shrinking of not only the treated tumor but also of tumors outside the scope of the localized treatment. These early studies are focused on safety and efficacy and much uncertainty still remains on how to best enhance the abscopal response clinically. Lessons learned from the practice-changing PACIFIC trial in non-small cell lung cancer (NSCLC) provides unique insight into the safety of fractionated thoracic RT with concurrent systemic chemotherapy followed by systemic immunotherapy [39]. Specifically, this trial randomized Stage III NSCLC patients to standard definitive chemoradiation with or without adjuvant durvalumab (PDL-1 inhibitor) and demonstrated a significant PFS and OS benefit with the addition of adjuvant durvalumab. The overall toxicity profile was similar between durvalumab and placebo group with similar rates of any grade 3– adverse events (30% vs. 26%). If RT is to become an integral part of management in melanoma, new clinical trials will need to be designed to establish the additional benefit along the paradigm of other non-melanoma cancer trials. This may take considerable time to develop as systemic therapy advancements have yet to plateau. Breast cancer management also serves as an analogy where RT retains an important role in

high-risk patients post-mastectomy despite considerable advancement in effective systemic therapies [40].

Patients not fit for surgical lymph node dissection of melanoma nodal metastases represent a challenging clinical scenario, but one that studies prior to effective systemic therapy has shown impressive efficacy to definitive RT. This is best documented in the cervical neck nodes from head and neck primary disease. In one investigation from MD Anderson Cancer Center, 36 patients underwent cervical node irradiation (30 Gy in 6 Gy per fraction treated twice per week) [15]. The 5-year rate of complications was reported at 10% and the 5-year rate of local and regional control rate was 94% and 94%, respectively. The strategy was applied to a group of elderly patients with major comorbidities that underwent limited node excision for biopsy but with persistent macroscopic neck disease [33]. The 5-year regional control, DFS, OS rates were 69%, 44%, 50%, respectively.

In summary, adjuvant management of melanoma is rapidly evolving, considering effective systemic immune and targeted therapies which have shown to reduce distant as well as regional recurrence and have led to improvements in PFS and OS. The role of RT in this setting needs to be refined at the appropriate time in the form of new clinical studies particularly in patients with high-risk features that were defined in the ANZMTG 1–02/TROG 02.01 randomized study, which established the efficacy of RT in the adjuvant setting in reducing locoregional recurrence. At present, multidisciplinary tumor boards must weigh the use of RT to assist in disease control of select cases where it may be felt to benefit the patient.

12.2.2 After Previous RLND Has Failed in Field

Data in this setting is sparse but the options for control in regionally relapsed disease are limited and RT is often part of the treatment regimen. Follow-up data from ANZMTG 1–02/TROG 02.01 showed 26 isolated regional relapses in the observation group (20.5%) which occurred at a median time of 7 months after RLND [11]. Twenty of these patients underwent salvage surgical dissection followed by RT, 4 had surgery only, one had RT only, and one had no further treatment. Twenty-three of the 26 patients achieved successful regional control. Owing to more aggressive biology in relapsed patients, survival was only 34% at 5 years and 18 patients relapsed with distant disease. These data are prior to the era of effective systemic therapy and more granular data about salvage therapy in the multigroup systemic therapy trials should be forthcoming. The Phase III placebo-controlled study of adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated melanoma which reported a 3-year relapse-free survival of 58% vs 39% ($p < 0.001$) and overall survival benefit reported a safety population analysis which included a breakdown of treatments administered after melanoma recurrence [38]. Of the 148 relapses analyzed in the treatment arm 52% underwent surgical resection and 41% received RT but specifics of patients that received either or both therapies and/or further systemic therapy were not published. The contemporary role of RT in the salvage setting is best decided in a multidisciplinary tumor board setting. New trials in the current era will be needed to evaluate the role of RT especially as the benefits of systemic immune and targeted therapies begin to plateau.

12.3 After Resection of Desmoplastic or Other Melanoma Subtypes with Neurotropism

While there are no randomized trials investigating the role of adjuvant radiation in patients with desmoplastic melanoma subtypes, there are several large retrospective studies and a single-arm phase II study evaluating its role. Desmoplastic melanoma is an uncommon histology that accounts for less than 4% of cutaneous melanomas and is characterized by dense fibrous stroma, resistance to chemotherapy, and a lack of actionable driver mutations, and is highly associated with UV light-induced dam-

age [41]. It is frequently associated with neurotropism and higher rates of local recurrence owing to its relative aggressiveness [42]. In a large retrospective pathologic and clinical outcomes series from the Melanoma Institute of Australia, 671 patients with neurotropic melanomas (72% with desmoplastic histology) were compared with a control cohort of 718 non-neurotropic melanomas [43]. Neurotropic melanomas were found to be three times as likely to have a borderline margin of excision increasing their risk of local recurrence by four-fold. Of the neurotropic melanoma group, 82 patients received hypofractionated RT to 48 Gy in 2.4 Gy per fraction daily over 4 weeks. With a 3.5-year median follow-up, adjuvant RT decreased the risk of local recurrence by half when margins were less than 8 mm (HR, 0.48; 95% CI, 0.27–0.87). Overall risk of recurrence also showed significant reduction with adjuvant RT (HR, 0.51; 95% CT, 0.29–0.87) especially at the primary site (HR, 0.3; 95% CT, 0.13–0.69) but not at distant sites (HR, 0.60; 95% CT, 0.29–1.24; $p = 0.17$). Adjuvant RT was not found to improve overall or melanoma-specific survival ($p = 0.31$ and 0.55, respectively).

A 130-patient series of resected desmoplastic melanoma from MD Anderson also showed considerable local control benefit in the 71 patients who received adjuvant hypofractionated RT in 6 Gy per fraction over 3 weeks [44]. Local recurrence at a median follow-up of 6.6 years was 24% for the surgery alone group and 7% for the patients that received adjuvant RT. Those patients with perineural invasion had significantly better local control than those who did not (91% vs 63% at 10 years; $p = 0.02$).

The NCCTG N0275 Alliance Cooperative Group enrolled 20 patients on a prospective Phase II trial evaluating resection followed by adjuvant RT also to 30 Gy in 6 fractions for patients with desmoplastic melanoma [45]. Over 50% of patients had a primary site in the head and neck and the median thickness of the primary disease on pathology was 3.0 mm. At 4 year follow-up there were just 2 recurrences (both in the head and neck) for a local control rate of 90% and no patients developed in transit or distant relapses (Table 12.3).

Based on these studies that demonstrate improved local control, adjuvant RT should be considered for patients with desmoplastic melanoma, especially for those with thicker primary (>3 mm) and those with neurotropism that has not been widely excised (>8 mm margin). Dose and fractionation can be chosen based on anatomical location with standard fractionation used to minimize toxicity when the primary site is head and neck, the most common location of desmoplastic melanoma. As with nondesmoplastic melanoma, the role of adjuvant RT would need to be reevaluated if new generation adjuvant systemic therapies show benefit for this histologic subgroup but to date, this has not been studied.

Appendix

Table 12.1 List of radiotherapy studies for melanoma

Institution/Author/Year/ PMID	Study type	Patient #	Median follow-up (months)	Radiation fractionation and technique	Outcome
Mayo Clinic Creagan et al. 1978 [6] PMID: **363255**	Single-institution prospective randomized [adjuvant]	56 27 RT 29 no RT	N/A	25 Gy in 14 (3–4 weeks) Supervoltage RT	3 relapses in RT vs 1 relapse in control No difference in DFS, OS
Danish Cancer Society Overgaard et al. 1985 [12] PMID: **4044346**	Single-institution prospective randomized [adjuvant]	14	N/A	27 Gy in 3 (1.5 weeks) 40 Gy in 8 (4 weeks) High-voltage 60Co or electron	69% complete or persistent regression of tumor Overall response rate of 97%
Danish Cancer Society Overgaard et al. 1995 [13] PMID: **7776772**	Multi-center prospective randomized [adjuvant]	70 (128 lesions) 65 lesions RT only 63 lesions RT + hyperthermia	3	24–27 Gy in 3 (8 days) ± hyperthermia Electrons, high-voltage photons	2-year LRC: 28% RT vs 46% RT + hyperthermia, $p = 0.008$ 2-year LRC: 37% overall 5-year OS: 19%
Univ. of Wales Bowsher et al. 1986 [3] PMID: **3790922**	Single-institution retrospective [no RT]	86 (72% therapeutic RND, 28% prophylactic RND)	Therapeutic: 54 Prophylatic: 52	Not applicable	33% cervical node recurrence, 13% axillary node recurrence, 9% inguinal node recurrence
LDS hospital Sause et al. (RT OG 83–05) 1991 [1] PMID: **1995527**	Multi-center prospective randomized [not specified]	126	N/A	32 Gy in 4 (4 weeks) 50 Gy in 20 (4 weeks) Electron, high-voltage photons	23.8% complete remission34.9% partial remission No difference found for doses
LDS hospital Monsour et al. 1993 [2] PMID: **8377499**	Single-institution retrospective [no RT]	48	24	Not applicable	LC: 48% Recurrence in 25 patients
MD Anderson Ang et al. 1994 [4] PMID: **7960981**	Single-institution prospective phase II [adjuvant]	174 79 elective RT 32 adjuvant RT 63 postoperative RT	35	30 Gy in 5 (2.5 weeks) 9–12 MeV electron	5-year LRC: 88% 5-year OS: 47%
MD Anderson Ballo et al. 2002 [14] PMID: **11958890**	Single-institution retrospective [adjuvant]	89 37 RT 51 RT + systemic therapy	63	30 Gy in 5 (2.5 weeks) 6 MV photon fields	5-year LRC: 87.00% 20% nodal relapse 5-year OS: 50% 5-year DFS: 46%
MD Anderson Ballo et al. 2003 [15] PMID: **12655537**	Single-institution retrospective [adjuvant]	160	78	30 Gy in 5 (2.5 weeks) Low-energy electron	10-year LC: 94% 10-year RC: 94% 10-year LRC: 91% 10-year DSS: 48% 5-year complication-free survival: 90%

(continued)

Table 12.1 (continued)

Institution/Author/Year/ PMID	Study type	Patient #	Median follow-up (months)	Radiation fractionation and technique	Outcome
MD Anderson Ballo et al. 2004 [16] PMID: **15576833**	Single-institution retrospective [adjuvant]	40	22.5	30 Gy in 5 (2.5 weeks) High-energy electron, megavoltage photon (≥6MV)	3-year RC: 74% 5% LN basin recurrence 3-year DFS: 35% 3-year OS: 38%
MD Anderson Bonnen et al. 2004 [7] PMID: **14716775**	Single-institution retrospective [adjuvant primary, elective nodal]	157	68	30 Gy in 5 (2.5 weeks) 36 Gy in 6 (3 weeks)50 Gy in 25 (5 weeks) 60 Gy in 30 (6 weeks) 9–12 MeV electron field	5-year RC: 89% 9 local recurrence, 15 nodal recurrence, 57 distant recurrence 5-year DSS: 69% 5-year DMFS: 63%
MD Anderson Ballo et al. 2005 [17] PMID: **15952196**	Single-institution retrospective [adjuvant]	36	63.6	30 Gy in 5 (2.5 weeks) High-energy electron, megavoltage photon (≥6MV)	2 regional recurrence, 14 distant recurrence 5-year RC: 93% 5-year DMFS: 59%
MD Anderson Beadle et al. 2009 [18] PMID: **18774657**	Single-institution retrospective [adjuvant]	200 95 axilla RT 105 supraclavicular fossa RT	59	30 Gy in 5 (2.5 weeks) 6MV photon fields	5-year axillary control: 88% No difference in RT sites 5-year OS: 51% 5-year DFS: 43% 5-year DMFS: 46%
MD Anderson Guadagnolo et al. 2010 [19] PMID: **19787786**	Single-institution retrospective [adjuvant]	16 Bilateral cervical metastases	5	30 Gy in 5 (2.5 weeks) Photon field, electron field, IMRT	1-year RC: 64% 31% nodal relapse 2-year OS: 27%
Queensland radium institute Burmeister et al. 1995 [20] PMID: **7638990**	Single-institution prospective [adjuvant]	57 26 RT 31 no RT	15	Variety of schedules (not specified)	Response rate: 84% 12% recurrence (RT patients) Median OS: 20 months (RT), 18 months (no RT) 65% distant recurrence
Univ. hospital Zurich Huguenin et al. (palliative) 1998 [21] PMID: **9607358**	Single-institution prospective [palliative]	90	6.2	20 Gy in 5 (1 week) 30 Gy in 10 (2 weeks) 6–18 MV photons linac, electrons, 100-kV X ray	Relief of pain in 26/40 cases 55% patients with persistent neurologic dysfunction improved with treatment

Roswell park Cancer institute Lee et al. 2000 [22] PMID: **10661355**	Single-institution retrospective [adjuvant systemic therapy]	338 149 systemic therapy 189 no systemic therapy	54	Not applicable	10-year nodal recurrence: 30% Recurrence risk: Cervical 43%, axilla 28%, inguinal 23% No difference for adjuvant systemic therapy 10-year OS: 30% 10-year DSS: 36%
Princess Alexandra hospital, Univ. of Queensland Burmeister et al. (TROG 9606) 2006 [9] PMID: **17064803**	Multi-center prospective phase II randomized [adjuvant]	234	58.4	48 Gy in 20 (4 weeks) Photon field, electron field	5-year RC: 91% 6.8% regional recurrence 5-year OS: 36%
Princess Alexandria hospital, Univ of Queensland Burmeister et al. 2012 [10] PMID: **22575589**	Multi-center prospective phase III randomized [adjuvant]	250 123 RT 127 no RT	40	48 Gy in 20 (4 weeks) Photon (axilla, inguinofemoral) photon +Electron (H&N)	20 RT recurrence vs 34 no RT recurrence, HR 0.56, $p = 0.041$ 59 RT deaths vs 47 no RT deaths
Princess Alexandria hospital, Univ of Queensland Pinkham et al. 2013 [23] PMID: **23773393**	Single-institution retrospective [adjuvant]	277 121 RT 156 no RT	23	48 Gy in 20 (4 weeks) Modality N/A	Overall axillary control rate: 87% 17 RT recurrence, 20 no RT recurrence Overall median survival: 56 months
Princess Alexandria hospital, Univ of Queensland Barbour et al. 2015 [24] PMID: **25582744**	Single-institution retrospective [adjuvant]	173 66 RT 113 no RT	32	48 Gy in 20 (4 weeks) 3D-CRT photon, single lateral electron field	RT: 17% nodal, 60% distant recurrence No RT: 10% nodal, 38% distant recurrence 5-year overall regional recurrence: 23%
Univ. of Florida Chang et al. 2006 [25] PMID: **16973303**	Single-institution retrospective [adjuvant]	56	52.8	30 Gy in 5 (2.5 weeks) 60 Gy in 30 (6 weeks) Photon fields	5-year LRC: 87% 12% local recurrence, 5% regional recurrence, 43% distant recurrence 5-year CSS: 57% 5-year OS: 46%
Roswell Park Cancer Institute, MD Anderson Agrawal et al. 2009 [26] PMID: **19701906**	Multi-center retrospective [adjuvant]	615 509 RT 106 no RT	60	30 Gy in 5 (2.5 weeks) 50–54 Gy in 25–27 (5–5.5 weeks) Appositional electron field, photon field	Regional recurrence: 10.2% RT vs 40.6% no RT Distant recurrence: 55.4% RT vs 73.6% no RT 5-year overall RC: 81% 5-year DSS: 48%

(continued)

Table 12.1 (continued)

Institution/Author/Year/ PMID	Study type	Patient #	Median follow-up (months)	Radiation fractionation and technique	Outcome
Univ. of Ljubljana Strojan et al. 2010 [27] PMID: **19910139**	Multi-center retrospective (Cancer registry of Slovenia) [adjuvant]	83 43 RT 40 no RT	25.2	Median 60 Gy in 30 (6 weeks) 30 Gy in 5 (2.5 weeks) most common 5–6 MV linac, 60Co photon beams, 9–15 MeV electron	2-year RC: 78% RT vs 56% no RT, $p = 0.015$ 8 regional recurrent RT vs 1 pt. local + distant 2-year OS: 36.1%
Lille-Nord de France Univ. Bibault et al. 2011 [28] PMID: **21294913**	Single-institution prospective [adjuvant]	86 60 RT 26 no RT	73	Median 50 Gy in 25 (5 weeks) >50 Gy (30 pts), <50 Gy (30 pts) 3D-CRT	5-year RC: 80% (>50 Gy) vs 35% (<50 Gy), $p = 0.004$ 22.5% local recurrence overall Median overall survival: 31.8 months
Univ. of Melbourne Henderson et al. (ANZMTG 1–02/TROG 02.01) 2015 [11] PMID: **26206146**	Multi-center prospective phase III randomized [adjuvant]	250 123 RT 127 no RT	73	48 Gy in 20 (4 weeks) Photon (axilla, inguinofemoral) photon+Electron (H&N)	Recurrence: 23 (21%) RT vs 39 (36%) no RT (HR 0.52, $p = 0.023$) 5-year OS: 40% RT vs 45% no RT (HR 1.27, $p = 0.21$) No difference in OS or RFS
Penn State Univ. Baker et al. 2016 [29] PMID: **27636187**	Multi-center retrospective (SEER database) [adjuvant]	638 319 RT 319 no RT	26.2	N/A	3-year OS: 48% RT vs 60% no RT
Emory Univ. Danish et al. 2016 [30] PMID: **27575390**	Multi-center retrospective (NCDB) [adjuvant]	912 118 RT 794 no RT	66	N/A	5-year OS: 41.1% RT vs 34.4% no RT
Asan medical center Kim et al [31] 2017 PMID: **28739713**	Single-institution retrospective [adjuvant]	62 28 RT 34 no RT	34	50 Gy in 25 3D-CRT, 6–15 MV photon	5-year RFS: 92% RT vs 63% no RT
Moffitt Cancer Center, Univ. of South Florida Strom et al. 2017 [32] PMID: **24142775**	Single-institution retrospective [adjuvant]	410 83 RT 327 no RT	69	30 Gy in 5 (2.5 weeks) 54 Gy in 27 (5 weeks) Electrons, photons	5-year RC: 94.1% RT vs 69.5%, no RT $p = 0.003$ 5-year OS: 46.8% overall
Melanoma institute Australia Kroon et al. 2018 [33] PMID: **30116948**	Single-institution retrospective [adjuvant]	28	22	48 Gy in 20 (4 weeks) 33 Gy in 6 (3 weeks) 54 Gy in 27 (5.5) Modality N/A	5-year RC: 69% 11 (39%) distant recurrence 5-year OS: 50% 5-year DFS: 44%

Table 12.2 List of immunotherapy studies and melanoma

Institution/ Author/Year/ PMID	Study type	Patient #	Median follow-up (months)	Drug and dosage	Outcome
Melanoma Institute Australia Long et al. 2017 [38] PMID: **28891408**	Multi-center prospective phase III randomized controlled [immunotherapy]	870 438 treatment 432 control	33.6	Dabrafenib: 150 mg (twice daily, 12 months) Trametinib 2 mg (once daily, 12 months)	3-year RFS: 58% treatment vs 39% control (HR 0.47, 0.39–0.58, $p < 0.001$) 3-year OS: 86% treatment vs 77% control (HR 0.57, 0.42–0.79, $p = 0.0006$)
Moffitt Cancer Center Antonia et al. 2017 [39] PMID: **28885881**	Multi-center prospective phase III randomized controlled [immunotherapy]	709 473 treatment 236 control	14.5	Durvalumab: 10 mg (every 2 weeks, 12 months)	Response rate: 28.4% treatment vs. 16.0% control; $p < 0.001$ Risk of death decreased in treatment: HR 0.52; 95% CI, 0.42 to 0.65; $P < 0.001$
Gustave Roussy center campus grand Paris Eggermont et al. 2018 [37] PMID: **29658430**	Multi-center prospective phase III randomized controlled [immunotherapy]	1019 514 treatment 505 control	15	Pembrolizumab: 200 mg (every 3 weeks for 18 doses)	Recurrence: 24.7% treatment vs 21.1% control 1-year RFS: 75.4% treatment vs. 61.0% control Less risk of death in treatment: HR 0.57; 98.4% CI, 0.43 to 0.74; $P < 0.001$

Table 12.3 List of radiotherapy studies on desmoplastic melanoma

Institution/ Author/Year/ PMID	Study Type	Patient #	Median follow-up (months)	Radiation Dose + Type of radiation	Outcome
UCLA Vongtama et al. 2003 [46] PMID: **12784232**	Single-institution retrospective [desmoplastic malignant]	44 14 RT 30 no RT	64.7	44–66 Gy with 1.8 Gy fractionsmedian 50 Gy 6–10 MeV electrons	Recurrence in 0/14 RT vs 4/7 no RT, $p = 0.005$ 48% overall recurrence 5-year OS: 87%
Princess Alexandra hospital, Univ. of Queensland Foote et al. 2008 [47] PMID: **18366400**	Single-institution retrospective [desmoplastic]	24	36	48 Gy in 20 (4 weeks) 60 Gy in 30 (6 weeks) Electron, photon	17% recurrence 3-year OS: 83%

(continued)

Table 12.3 (continued)

Institution/ Author/Year/ PMID	Study Type	Patient #	Median follow-up (months)	Radiation Dose + Type of radiation	Outcome
Royal Prince Alfred Hospital Chen et al. 2008 [48] PMID: **18823042**	Single-institution retrospective [desmoplastic neurotropic]	128 27 RT 101 no RT	40.5	33 Gy in 6 (3 weeks) 48–50 Gy in 20–25 (4–5 weeks) 54 Gy in 27 (5.5 weeks) 60–64 Gy in 30–32 (6 weeks) Orthovoltage, MV photon, electron	Recurrence RT vs no RT: 7.4% vs 5.9% local 18.5% vs 14.9% nodal 11.1% vs 16.8% distant
MD Anderson Guadagnolo et al. 2014 [44] PMID: **24142803**	Single-institution retrospective [desmoplastic]	130 71 RT 59 no RT	79.2	30 Gy in 5 (2.5 weeks) 36 Gy in 6 (3 weeks) 60 Gy in 30 (6 weeks) Appositional electron fields, photon fields, IMRT	10-year LRC: 92% RT vs 70% no RT, $p = 0.002$ Recurrence: 7% RT vs 24% no RT, $p = 0.009$ 17% overall recurrence 5-year OS: 69% No difference in OS
Moffitt Cancer Center Strom et al. 2014 [32] PMID: **24142775**	Multi-center retrospective [desmoplastic]	277 113 RT 164 no RT	43.1	30 Gy in 5 (2.5 weeks) 59.4–68 in 33–34 (7 weeks) 6–12 MeV electron, photon	5-year LRC: 95% RT vs 76% no RT, $p = 0.015$ Recurrence: 7% RT vs 17% no RT positive resection margin: 14% vs 54%, $p = 0.004$
Mayo Clinic Rule et al. 2016 [45] PMID: **27368067**	Single-institution prospective phase II [desmoplastic]	20	52	30 Gy in 5 (2.5 weeks) 6–20 MeV (9 median) electron	Recurrence (2-year): 10% 5-year OS: 77%
Melanoma Institute Australia Varey et al. 2017 [43] PMID: **28731051**	Multi-center retrospective (MIA database) [neurotropic]	1335 617 neurotropic (72% desmoplastic) 82 RT 718 non-neurtropic control	42	48 Gy in 20 (4 weeks) Modality N/A	Half risk of local recurrence for RT in <8 mm margin (HR, 0.48; 95% CI, 0.27–0.87, $p = 0.02$) Less recurrence risk with RT (HR, 0.51; 95% CI, 0.29–0.87, $p = 0.01$); local (HR, 0.30; 95% CI, 0.13–0.69, $p = 0.005$); regional (HR, 0.41; 95% CI, 0.17–0.98, $p = 0.05$) No difference between neurotropic and non-neurotropic, HR 0.79 (0.55–1.15), $p = 0.22$; no effect of RT on survival
Boston Medical Center Abbott et al. 2018 [49] PMID: **30383720**	Multi-center retrospective (NCDB) [desmoplastic]	2390 308 RT 2082 no RT	41.8	N/A	5-year OS: 71.8% RT vs 75.3% no RT, $p = 0.725$ 5-year OS: 74.8% overallMVA shows RT advantage in OS (HR 0.75, $p = 0.030$)

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Part V

Melanoma Management: Treatment of Systemic Disease

13 Systemic Therapy of Advanced Melanoma

Adam Lerner, Vanessa Furtado, and Debjani Sahni

13.1 Earlier Treatments for Melanoma Predating 2011

13.1.1 Chemotherapy

In 1970, treatment with a relatively new alkylator of that era, dacarbazine, resulted in a 19% response rate in 110 evaluable advanced melanoma patients, when given intravenously as 250 mg/m^2 daily for 5 days every 3 weeks [63]. Over the following decades, over 30 randomized trials in melanoma patients examined the relative efficacy of dacarbazine given alone or in combination with other chemotherapeutic agents or biological modifiers such as cisplatin, vinblastine, vindesine, carmustine, bleomycin, procarbazine, tamoxifen, alpha-2b interferon or interleukin 2. Although modest increases in response rate for subsets of advanced melanoma patients were observed with some combination therapy regimens, none of these studies demonstrated substantially improved survival relative to treatment with dacarbazine alone, and in most cases, the combination regimens were associated with considerable toxicity [21]. Dacarbazine was initially administered in divided doses, but the development of more potent anti-emetic agents ultimately allowed this drug to be given as a single intravenous dose at 850–1000 mg/m^2 once every 3 weeks, with equal activity and with reduced impact on quality of life for the patient and their family.

The impact of dacarbazine therapy on the clinical course of patients with advanced melanoma is modest at best. Radiologic responses are noted in 13–20% of patients, with most responses being partial. Occasional durable complete responses have been reported. In two large randomized multicenter trials that utilized dacarbazine alone as one of their treatment arms, median survival was 6.3–10 months with dacarbazine administered as 1000 mg/m^2 every 3 weeks or 200 mg/m^2 D1–5 every 4 weeks, respectively [10, 24]. While a randomized trial assessing the impact of chemotherapeutic agents such as dacarbazine has never been carried out using a placebo or non-treatment arm, long-term follow-up in some of these early studies showed that <2% of patients with metastatic melanoma treated with dacarbazine alone were alive 6 years following initiation of such therapy [31]. These results stand as an important benchmark to be compared with the 5 year survival results observed with current BRAF/MEK inhibitor or checkpoint inhibitor systemic therapies discussed later in this chapter.

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13.1.2 Early Efforts at Immunotherapy in Melanoma

Early research had inferred a host immune response to primary cutaneous malignant melanoma was associated with improved survival. In one study of patients with primary melanoma with a vertical growth phase, brisk, non-brisk and absent tumor-infiltrating lymphocyte counts were associated with 10 year survival rates of 55%, 45%, and 27% ($p < 0.0003$) [14]. In this study, only tumor thickness and the presence of tumor-infiltrating lymphocytes were significant and independent prognostic indicators.

Similar results from other studies, together with the very minor benefit of cytotoxic chemotherapy in melanoma, led clinical investigators to seek an alternative approach to improving the outcome of melanoma patients. This involved developing therapies intended to *positively augment* the host immune response to the patient's melanoma tumor cells. These efforts included cytokine therapy with alpha-2b interferon or interleukin 2 (IL-2), as well as vaccines derived from peptides and melanoma cell lines, alone, or in combination with cytokine therapy.

When tested in a randomized setting, the clinical benefit of these efforts to enhance immune responses to melanoma proved to be either modest or undetectable. In a phase III study of patients with metastatic melanoma, the addition of interferon alpha-2b to high dose IL-2 led to no improvement in overall survival relative to a group of patients randomized to receive high dose IL-2 alone [78]. In a study in which earlier stage IIB and III melanoma patients were treated with either high dose interferon alpha-2b or a GM2 ganglioside vaccine (GMK), the estimated 2 year overall survival in eligible patients was 78% in the interferon arm and 73% in the GMK arm [53]. When high dose interferon alpha-2b therapy was compared with a shorter, more intensive biochemotherapy regimen (utilizing a combination of high dose IL-2, high dose interferon and cisplatin, vinblastine, and dacarbazine chemotherapy) in high-risk stage III N2A and stage III N3 melanoma patients, the overall survival at 5 years was comparable in the two arms (56% in both groups), but greater toxicity was seen in the biochemotherapy arm [28]. In another large, randomized trial, fully resected stage III or stage IV melanoma patients were treated with either BCG combined with an allogeneic melanoma cell line vaccine or BCG alone. This study was terminated at the interim analysis as no improvement in survival was detected in the experimental arm [25]. Another trial compared the treatment of locally advanced stage III or stage IV melanoma patients that expressed HLA-A*0201 with high dose IL-2 alone or in combination with a gp100:209–217(210M) peptide vaccine. While this study demonstrated an improved response rate, disease-free survival, and a trend towards overall survival ($p = 0.06$) in the experimental IL-2/peptide vaccine arm, the percentage of patients alive at 4 years remained low and roughly equal in both arms [73].

13.2 Melanoma Therapy Revolution: 2011 Onwards…

13.2.1 A Change in Immunotherapy Paradigm: Checkpoint Blockade

Studies of murine and human B and T-cells have demonstrated an astonishing somatic VDJ mutation mechanism by which millions of different clonal B and T-cell receptor antigen-binding sites are generated randomly after birth in the germinal centers of lymph nodes and the thymus, respectively. As a result of this process, the adaptive B and T-cell immune response is almost limitless in its ability to respond to proteins expressed by an ever-changing universe of infectious microorganisms. With this as a background, and with the benefit of 20:20 hindsight, it is perhaps not surprising that the lack of an effective host immune response to metastatic melanoma did not ultimately lie in an inadequate immunogenic stimulus, either in the quantity of the antigen expressed, or the presence of secondary cytokine signals such as IL-2 or interferon-alpha 2B.

Instead, the consequential breakthrough in the immune therapy of cancer, and of melanoma, in particular, followed the recognition that mamma-

lian immune systems have evolved powerful mechanisms by which to rapidly downregulate immune responses to infectious organisms. Such inhibitory signaling in immune cells is, at the risk of a teleologic analysis, necessary to avoid the potentially toxic effects of an overly strong or long-lasting immune response to infectious organisms, with attendant collateral damage to the structure of the host organ in which the infection occurred [66]. Studies of chronic viral infections demonstrated a network of downregulatory mechanisms that suppress anti-viral immune responses. Recognizing that the presence of antigenically stimulatory tumors such as melanoma in some ways present the host with an immune stimulant comparable to chronic viral infection, investigators identified parallel immune system alterations in these two models, including activation of pathways that downregulate cytolytic T-cell signaling as well as the presence of T-cell exhaustion [52].

The critical insight that followed such studies was that perhaps the primary obstacle to a robust immune response to tumors was not so much a lack of an adequate immune stimulus, but rather the presence of an immune "checkpoint," constitutively active inhibitory signaling pathways in host immune cells that block an effective antitumor immune response.

13.2.1.1 Anti-CTLA-4 Therapy with Ipilimumab

The first breakthrough in immunotherapy in patients with melanoma came from studies of CTLA-4, a T-cell transmembrane protein that downregulates signaling by CD28, a co-stimulatory signal required for full T-cell activation (Fig. 13.1a). B7, the ligand for CD28, is one of several key co-stimulatory signals upregulated on antigen-presenting cells (APC) such as dendritic cells in the presence of infections or other stimuli that signal immunologic danger to the host. The requirement for co-stimulatory "second signals" (the first signal being peptide/MHC recognition by a corresponding high-affinity T-cell receptor) serves to minimize the likelihood of inadvertent autoimmune cytolytic T-cell activity against host cells. CTLA-4, which has a higher affinity for B7 than CD28, outcompetes CD28 for its ligand and effectively terminates co-stimulation of T-cells by CD28. A negative signaling intracellular pathway is simultaneously initiated in T-cells through an inhibitory binding motif in the CTLA-4 cytoplasmic domain.

In 1996, Allison and colleagues reported that injection of neutralizing antibodies against CTLA-4 protected mice against even established syngeneic tumors [58]. The locus of action of such anti-CTLA-4 antibodies was thought to be at a central site rather than the tumor itself, likely in draining lymph nodes adjacent to tumors. There, dendritic cells present both tumor antigens and appropriate co-stimulatory signals to T-cells, thereby first activating an antitumor adaptive immune response. Their work suggested that as a result of CTLA-4's ability to effectively shut off cytolytic T-cell responses to tumors, the upregulation of this molecule in cytolytic CD8+ T-cells is an important immunologic barrier to an effective host antitumor response and that a therapeutic antibody that blocked such an immunologic "checkpoint" could be of potential clinical benefit to patients with otherwise immunostimulatory tumors [58].

Consistent with such animal studies, early phase 2 clinical trials with ipilimumab, a fully human IgG1 antibody that neutralizes CTLA-4, showed substantial activity in patients with melanoma. In 2010, this work culminated in a phase III study by Hodi and colleagues comparing ipilimumab with a glycoprotein peptide (gp100) vaccine in advanced melanoma patients. The results demonstrated improved median overall survival from 6.4 to 10.1 months in patients treated with ipilimumab [43]. A separate arm where gp100 was added to ipilimumab showed no effect on survival relative to ipilimumab alone. A particularly notable aspect of these trials was the demonstration of a plateau in survival in ipilimumab-treated patients, with a subset of patients showing complete radiologic responses and a 2 year overall survival rate of 23.5%. This was a remarkable finding as it suggested for the first time that a subset of patients with metastatic melanoma may have been cured by treatment with an immune checkpoint inhibitor.

The original trials demonstrated that ipilimumab was associated with substantial, though generally manageable, immunologic toxicity, something that would prove to be a common theme in the use of checkpoint inhibitors. In the randomized trial cited above, there were 14 deaths among 676 patients in the study, seven as a result of immune-mediated toxicity. The most common forms of immune toxicity with ipilimumab alone were fatigue (42%), diarrhea (33%), rash (19%) and cough or dyspnea (14–16%) with lesser frequency of colitis, vitiligo and immune-mediated hypothyroidism and hypopituitarism. Most of these adverse effects were ultimately well controlled by tapering courses of corticosteroids or occasionally infliximab therapy. These observations suggested that under basal conditions, immune system checkpoints such as CTLA-4 prevent clinically meaningful autoimmunity in a wide variety of normal tissues. Clearly, the potential balance of benefit and harm from the use of such therapies would have to be weighed as new checkpoint blockade indications were proposed.

13.2.1.2 Anti-PD-1 Therapy with Pembrolizumab and Nivolumab

While the clinical responses observed in melanoma patients to ipilimumab therapy were of enormous conceptual import, the development of antibodies against a second immune checkpoint, PD-1, ultimately proved to be of significantly greater clinical benefit to patients with high risk or advanced melanoma.

PD-1 is a T-cell transmembrane receptor first discovered in 1994 by Honjo and colleagues, whose overall structure closely resembles CTLA-4 [47]. In particular, both proteins contain an immunoreceptor tyrosine-based inhibitory motif (ITIM) in their cytoplasmic domains that, upon receptor ligation, initiates a signaling cascade that serves to inhibit T-cell activation. PD-1 can bind to two different ligands, PD-L1 and PD-L2. While the expression of PD-L2 is relatively restricted, expression of PD-L1 is widespread in normal murine and human tissues. PD-L1 was subsequently found to be expressed on a wide variety of both solid and hematologic malignancies, albeit at varying levels [49]. Studies in animal models suggested that treatment with anti-PD-1 and anti-PD-L1 antibodies augmented host antitumor responses [42, 48]. While anti-CTLA-4 therapies act centrally to abrogate the initiation of antitumor immune responses in secondary lymphoid tissues such as lymph nodes, anti-PD-1 and anti-PD-L1 therapies act in the periphery (see Fig. 13.1b) during

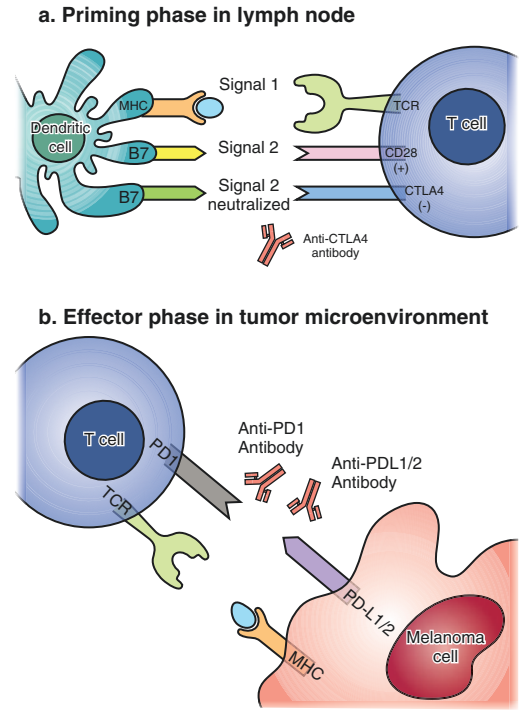

Fig. 13.1 Mechanism of action of immune checkpoint therapy. Checkpoint inhibition can occur in either the priming or effector phases of T-cell activation. (**a**) Priming phase takes place within lymph nodes: First Signal: T-cells circulating through lymph nodes, recognize antigenic peptides complexed with MHC class I/II molecules on antigen-presenting cells (APCs), including dendritic cells (DCs). Second Signal: A co-stimulatory signal is required, such as the interaction of CD28 on T-cells with B7–1/2 receptors on DCs. This is required for full T-cell activation. CTLA-4 is subsequently upregulated and competes with CD28. On binding B7–1/2, CTLA-4 downregulates T-cell activation. Antibodies to CTLA-4 block this interaction and lead to potentiation of T-cell activity. (**b**) Effector phase takes place within the tumor microenvironment: the inhibitory PD-1 receptor on T-cells binds to its two ligands, PD-L1 and/or PD-L2, on melanoma cells. The interaction of PD-1 with its ligand results in T-cell inactivation. Antibodies against either PD-1 or PD-L1/2 block this interaction and augment the T-cell response against the tumor

the effector phase of the immune response directly at the tumor/T-cell interface.

In landmark clinical trials, pembrolizumab and nivolumab, two different monoclonal antibodies against PD-1, showed substantial activity in patients with advanced melanoma [37, 68]. Subsequent randomized trials demonstrated that each of these two anti-PD-1 therapeutics had substantially greater clinical activity than the anti-CTLA-4 antibody ipilimumab, together with less associated immune toxicity [56, 69]. Pembrolizumab therapy (given every 3 weeks) was associated with a 6 month progression-free survival (PFS) rate of 46%, while that of ipilimumab therapy was 26%. The corresponding estimated 12 month survival rates for these two treatments were 68% and 58%. In contrast, grade 3–5 toxicity rates were 10 and 20% for pembrolizumab and ipilimumab, respectively [69].

Several studies of advanced melanoma patients have examined the activity of atezolizumab, an anti-PD-L1 monoclonal antibody that is in widespread use for patients with urothelial, breast and non-small cell lung cancers. Forty-five patients with advanced melanoma were enrolled in a larger phase 1 study of atezolizumab in patients with locally advanced or metastatic solid tumors [38]. Among 43 patients evaluable for efficacy, 13 (30.2%) responded to treatment by RECIST criteria with a median duration of response of 62 months. Atezolizumab has most recently been investigated in a randomized trial in patients with advanced BRAF-mutant melanoma to assess its efficacy and toxicity when combined with BRAF and MEK inhibitors (see below), leading ultimately to its FDA approval for the treatment of this melanoma patient subgroup [35].

13.2.1.3 Combined Anti-CTLA-4 and Anti-PD-1 Checkpoint Inhibitor Immunotherapy

Early single-agent studies immediately raised the question of whether a combination of anti-CTLA-4 and anti-PD-1 treatment would prove clinically more beneficial than treatment with anti-PD-1 therapy alone. The nivolumab study cited above actually compared three arms: ipilimumab alone, nivolumab alone or a combination of the two antibodies [56]. Progression-free survival (PFS) was 2.9 months with ipilimumab alone, 6.9 months with nivolumab alone, and 11.5 months with combined nivolumab and ipilimumab. The combination of pembrolizumab and low dose ipilimumab also resulted in substantial clinical activity in advanced melanoma patients, with a 1 year PFS rate of 69% and 1 year overall survival rate of 89% [61].

Long-term follow-up has confirmed the survival benefit of combined checkpoint blockade relative to treatment with either ipilimumab or nivolumab alone [57]. With a median follow-up of 60 months, mean survival was not yet reached (>60 months) with combined therapy, 36.9 months with nivolumab alone and 19.9 months with ipilimumab alone. At 60 months, 52% of patients treated with combined therapy were alive, compared with 44% with nivolumab and 26% with ipilimumab.

Unfortunately, a notable disadvantage associated with combined checkpoint therapy was an increase in the frequency of significant immune toxicity. Grade 3 or 4 toxicity occurred in 59%, 23%, and 28% of patients treated with combined therapy, nivolumab or ipilimumab, respectively. Given the observed increase in treatment-related toxicity with combined anti-CTLA-4 and anti-PD-1 immunotherapy, it is important to assess whether subsets of melanoma patients can be identified that are the most likely to benefit significantly from the addition of ipilimumab to an anti-PD-1 agent. Two of the most widely studied biomarkers are tumor PD-L1 levels and BRAF V600 mutation status. While neither of these biomarkers was able to fully predict the ideal choice of therapy, a trend was observed suggesting that those patients that were either BRAF V600 mutant or expressed PD-L1 negative levels (defined as <1% membrane staining tumor cells using the 22C3 monoclonal antibody) may be the groups to derive the most benefit from combined therapy relative to treatment with nivolumab alone. The addition of ipilimumab to nivolumab had no effect in PD-L1 positive patients (DFS of 14 months in both the nivolumab alone and the nivolumab/ipilimumab cohorts). In contrast, in PD-L1 negative patients, DFS was 11.2 months with nivolumab/ipilimumab ther-

apy and 5.3 months with nivolumab alone. It should be noted that the relationship of PD-L1 level expression or BRAF mutation status and DFS were not primary endpoints in this study, and therefore, there is not yet definitive evidence that treatment choice should be based on such levels or criteria [57].

The data cited above demonstrate an 8% improvement in survival at 5 years with the use of combined checkpoint inhibitor immunotherapy relative to anti-PD-1 therapy alone in otherwise unselected metastatic melanoma patients. This is at the cost of a doubling in the rate of grade 3 to 4 immune-mediated toxicity. Where an oncologist stands on the decision as to when to choose the more active and potentially more toxic combined checkpoint antagonist regimen will depend on patient-specific factors, as well as the oncologist's and the patient's judgment as to how best to balance potential long-term benefit against the risk of immune checkpoint inhibitor (ICI) associated toxicity.

13.2.1.4 Clinical Benefit Versus Radiologic Response Following Checkpoint Inhibitor Therapy

The 6 year overall survival in patients with stage IV melanoma is <2% following single-agent dacarbazine therapy, with the great majority of patients dying quite rapidly of this aggressive disease [31]. It is striking, therefore, that in several studies done during the era of ICI therapy, the 5 year overall survival of advanced melanoma patients treated with such agents is significantly higher than the corresponding radiologic complete response rate, suggesting that RECIST criteria for radiologic response may not accurately capture the full clinical benefit of this form of therapy.

In the 5 year follow-up study of patients treated with ipilimumab, nivolumab or combined ICI therapy, 5 year OS for patients treated with combined therapy was 52%, while the complete response rate to such therapy was 22% [57]. In a retrospective study at Memorial Sloan Kettering Cancer Center (MSKCC) of advanced melanoma patients treated with single-agent anti-PD-1 therapy, overall survival at 5 years was 40.8%, but only 25.8% of patients had radiologic complete responses [6]. Consistent with this observation, long-term follow-up of the survival of patients who clearly responded to therapy but had less than a complete response (deemed <CR in this report) showed a plateau in the survival curve of about 45% of all such patients. Such a plateau in survival was not observed in patients judged to have either stable disease or progression as their best overall response. It thus appears that a significant percentage of patients that respond to checkpoint therapy but have residual disease evident by imaging nonetheless have durable responses to therapy, perhaps in many cases being cured. The long-term outcome of this important cohort of patients will need to be determined with further studies and longer follow-up.

In patients who have had either a radiologic CR or a response <CR, a critical remaining question is the length of time with which they should continue ICI therapy. This question has not been answered thus far but is an active area of clinical investigation. In the MSKCC study noted above, 72% of patients with a complete response were alive and not in need of additional therapy 3 years after completing treatment [6]. Among those who relapsed following an initial complete response, 87% of such events occurred during the first 2 years after stopping ICI therapy, a finding that has implications for radiologic follow-up after completion of treatment.

13.2.1.5 Implications and Management of Immune-Mediated Toxicity

Melanoma patients receiving ICI therapy, particularly combined anti-CTLA-4 and anti-PD-1 treatment, not infrequently develop immune-mediated toxicity (such as significant diarrhea from colitis) that requires interruption or complete cessation of their treatment and management with corticosteroids or immune-modulators such as infliximab. This has raised the question as to whether shortened courses of immunotherapy

and the use of anti-inflammatory therapy negatively affect the ultimate control of advanced malignancy. Several studies with relatively long follow-up have suggested that, at a minimum, the ultimate clinical outcomes of patients who have had to discontinue ICI therapy prematurely is at least as good as those who continue therapy [57, 72]. These and other studies suggest that, unlike older cytotoxic chemotherapy regimens, checkpoint immunotherapy may trigger a host antitumor response that lasts well beyond the final therapeutic infusion. More generally, the incremental benefit of prolonged checkpoint inhibitor therapy in advanced melanoma is poorly understood at this time and assessment of when to best stop such therapy is an active area of clinical research.

A related question is whether the development of immune-related adverse events (irAEs) is generally of neutral, positive, or negative prognostic significance in cancer patients treated with ICIs. In a large study of patients with urothelial malignancies treated with ICIs, the development of irAEs was of positive prognostic value [64]. AEs were observed in 64% of responding patients and 34% of those without a response. Overall survival was higher in patients with a reported adverse effect than in those without such adverse events (HR, 0.45; 95% CI, 0.39–0.53).

Another issue that faces the melanoma oncologist is whether to consider reinstituting ICIs in patients who have developed significant irAEs from their treatment that have fully resolved with anti-inflammatory therapy. While a number of guidelines have been promulgated for the management of irAEs, the specifics of when to consider stopping versus re-introducing ICI therapy in patients who have had intermediate grade toxicity is left in part to the judgment of the care provider [8, 80]. In a study of 452 irAEs associated with ICI rechallenges, 130 recurrences (28%) of the initial irAEs were observed [20]. Recurrence rates of colitis (37%), pneumonitis (34%) and hepatitis (29%) were substantial, but not strictly prohibitive of considering reinstitution of therapy, particularly if the initial toxicity was observed with combined therapy and the reinstituted therapy is with an anti-PD-1 therapeutic alone. The authors concluded that reinstitution of ICI therapy can be considered in select patients with a history of irAEs with appropriate monitoring.

13.2.1.6 CNS Metastases and Mucosal Melanomas as Indications for Combined Checkpoint Inhibitor Immunotherapy

While combined ICI therapy is not always the standard of care in melanoma patients, there are certain subsets of patients, such as those with CNS metastases, in whom combination immunotherapy seems clearly indicated. In a randomized phase 2 trial, 16/35 (46%) patients treated with combined ipilimumab and nivolumab had intracranial responses compared with 5/25 (20%) in a cohort treated with nivolumab alone [62]. This single-agent anti-PD-1 response rate with nivolumab resembles the 26% intracranial response rate observed in a single-agent pembrolizumab trial, with all responses ongoing at 24 months mean follow-up [54]. In a larger single-arm phase 2 study of 94 melanoma patients with CNS metastases treated with ipilimumab and nivolumab, the intracranial response rate was 56% (26% complete responses), with 90% of such responses ongoing at the time of analysis [81].

Patients with mucosal melanomas also appear to benefit from combined checkpoint inhibitor therapy. Compared with cutaneous melanoma, mucosal melanomas have a lower somatic mutation burden and lower BRAF V600 mutation rates. They behave in an unusually aggressive manner clinically and have historically poor outcomes after local therapy. In a small retrospective analysis of 33 mucosal melanoma patients treated with either nivolumab or pembrolizumab, the single-agent anti-PD-1 response rate was 23%, with a median progression-free survival of 3.4 months [74]. In a similar retrospective study of patients previously enrolled in trials, D'Angelo and colleagues identified 86 mucosal melanoma patients treated with nivolumab alone and 35 treated with the combination of nivolumab and ipilimumab. The respective response rates observed in such patients were 23% with

nivolumab alone and 37% with combined therapy [17]. Median PFS for mucosal melanoma patients was 3.9 months with nivolumab alone and 5.9 months with combined therapy. These response rates were significantly lower than the corresponding response rates observed in patients with cutaneous melanoma: 6.2 months for nivolumab alone and 11.7 months with combined therapy.

13.2.1.7 Advanced Age Is Not a Contraindication to Checkpoint Inhibitor Immunotherapy

The incidence of cutaneous melanoma is rising rapidly in older patients. As a result, an increasingly older melanoma population will be encountered in our clinics with time.

Increasing patient age is an independent prognostic factor with respect to the overall survival rate of patients with cutaneous melanoma [3]. According to some, aging-associated changes of the immune system and its impact on patients with melanoma should be viewed in the context of imbalances in the immune system rather than a progressive weakening of the immune system [40]. First, there is a decreased number of naive T lymphocytes from bone marrow and thymus, leading to an increase in memory cells [36]. Moreover, there are weakened effector T-lymphocyte responses when exposed to antigens [32, 82]. Lastly, there is data supporting a weaker antitumor response in the setting of enhanced Treg activity [39].

Melanoma is frequently encountered in elderly patients, many of whom have multiple medical co-morbidities. The care of such patients in an era of increasingly efficacious immunotherapy has been a challenge for oncologists, as the prospect of potentially toxic therapy in an octogenarian or nonagenarian has raised the question as to whether benefits of treatment outweigh toxicity in such medically fragile patients. There has also been concern that age-related immune dysfunction could compromise checkpoint inhibitor-mediated immune responses. In keeping with trends observed in other malignancies, recent studies examining ICI therapy in the elderly have yielded a surprisingly positive view of the balance of efficacy and toxicity in this population [22].

A study conducted in Israel identified 144 elderly patients amongst 500 melanoma patients treated with anti-PD-1 therapies between 2013 and 2018 [5]. These patients were divided into two cohorts whose age ranged from 65 to 79 (group A: n = 82, mean age = 71) and 80–100 (group B: n = 62, median age = 84). A trend towards a higher overall response rate (ORR) was found with increasing age (62.3 and 73.9% in groups A and B, respectively). A significantly higher complete response rate was observed in the older patient group (20% versus 47.9%, $p = 0.001$). PFS, OS and toxicity rates were comparable amongst all patient groups.

A Danish national cohort study of patients with metastatic melanoma treated with ipilimumab (530 patients) or pembrolizumab (562 patients) found that age was a positive prognostic factor, with improved PFS and OS in patients aged between 70 and 80 years [4]. In patients over 80, OS was not improved but this was attributed to co-morbidities rather than toxicity of therapy.

13.2.1.8 Immune Checkpoint Inhibitor Resistance in Melanoma

Although the use of ICI has dramatically altered the outcome of patients with advanced melanoma, a significant portion of such patients still ultimately succumb to this disease. This may be due to "primary resistance" where patients do not ever respond to ICI. Primary resistance can affect anywhere between 40 and 65% of patients treated with anti-PD1 therapy compared >70% of patients treated with CTLA-4 inhibitors. Another subset of patients initially responds to ICI therapy followed by disease relapse after developing resistance; this is termed "acquired resistance." Such acquired resistance is thought to develop when tumor subpopulations with specific genetic and epigenetic traits are selected during treatment for their ability to evade the immune system.

There are three key components of the immune cycle involved in the immune response to cancer:

(1) Antigen presentation and T-cell priming and activation; (2) T-cell trafficking and tumor infiltration; (3) T-cell mediated destruction of tumor cells in the tumor microenvironment. Various inhibitory processes at each of these steps can block the action of ICI, leading to either primary or acquired resistance. Not surprisingly, research over the past decade has demonstrated that the underlying mechanisms responsible for such ICI resistance are diverse, both in the immune system cell populations involved and in the cytokines, cell surface molecules and signaling pathways utilized by these cell types [30], Such work has led to a variety of clinical trials evaluating novel therapeutic strategies aimed at overcoming ICI resistance. While we continue to expand our knowledge in this area of cancer biology, it is equally important to determine which biomarkers will help identify those patients that are likely to manifest either primary or acquired ICI resistance. This is currently an unmet clinical need in the field of immunotherapy in melanoma.

13.2.1.9 Immunotherapy in the Form of Intratumoral Therapy

In contrast to the various systemic forms of immunotherapy described in the previous section, an alternate approach to immunotherapy is to enhance the immunogenicity of tumor cells through more direct localized therapies. Intratumoral therapy involves the injection of therapeutic agents into accessible tumor metastases within the body. These include lesions that are clinically visible, palpable, or that can be approached by imaging guidance. The attraction of this form of treatment is the potential for enhanced locoregional efficacy, requiring only a small amount of drug, with better bioavailability of the immunostimulatory agent at the tumor site. At the same time, systemic exposure and off-target effects are minimized, therefore reducing systemic toxicity. The effect of intratumoral therapy is both local and systemic. Locally, there is tumor lysis and the release of tumor-derived antigens. This allows an immune response to be triggered to the relevant neoantigens and tumor-associated antigens, without the need to have characterized the tumor beforehand. Additionally, it provides an opportunity to develop an antitumor immune response against the entire antigenic repertoire of a tumor. In essence, such therapy creates a highly personalized vaccine using the patient's own tumor. Following local priming of the immune system, the relevant immune cells can circulate, and a systemic (abscopal) response occurs where effector cells target tumors at non-injected distant sites of metastases. With the injection of several tumors over time, a prime-boosting effect occurs on the repertoire of the polyclonal adaptive antitumor immune response. This has the potential to address the issue of heterogeneity of cancer cell subclones within lesions [65].

Intratumoral therapy may be based on a variety of therapeutic mechanisms. The use of oncolytic viral vaccines has been particularly successful in melanoma, with talimogene laherparepvec (T-VEC) being the first oncolytic virus therapy to be approved for unresectable, metastatic melanoma. Oncolytic viral vaccines are genetically engineered, attenuated viruses that drive immune responses against tumors (see Fig. 13.2). In the case of T-VEC, an engineered herpes simplex virus-1 (HSV-1) is genetically modified to promote selective replication in tumor cells, as well as produce local GM-CSF. This causes cell lysis in tumor cells leading to the release of tumor-derived antigens. The local production of GM-CSF promotes the maturation of dendritic cells that ingest tumor antigens and present them to T-cells in a manner that leads to robust T-cell activation. The activated T-cells proliferate and migrate to distant sites to produce T-cell mediated tumor death and a systemic response in tumor metastases that were not originally injected [60]. T-VEC is a biosafety level 1 agent, meaning that it is not known to cause disease in healthy adults. However, despite the low potential infection risk, the drug requires handling and administeration with caution, including post-injection care of the injection sites, to prevent viral transmission from patient to hospital or household contacts. This needs to be taken into account and discussed with the patient prior to instituting therapy. Following careful precautions, viral infections are very rare, though occasional case reports of herpetic whit-

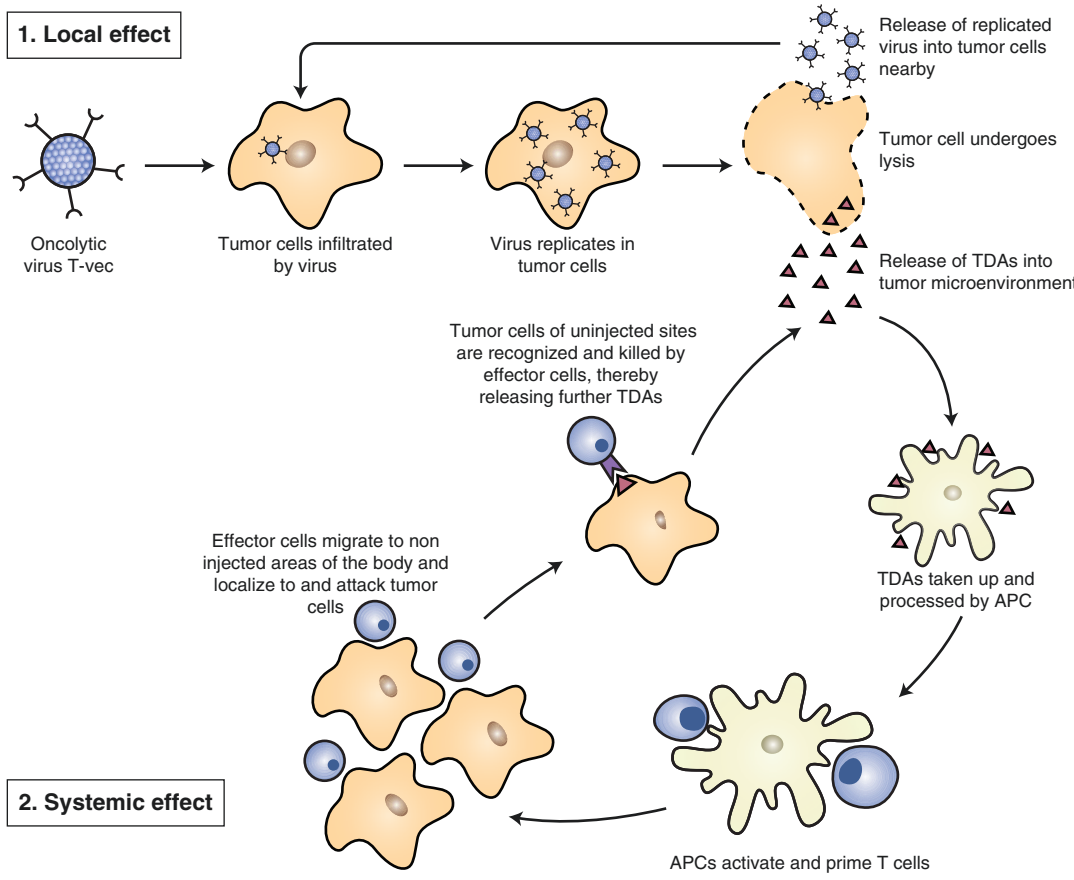

Fig. 13.2 Mechanism of action of T-VEC. Injection of T-VEC leads to selective uptake and replication of the genetically engineered herpes virus in tumor cells. The action of T-VEC is both at the local and systemic level. (**a**) Local effect: following replication within tumor cells and cell lysis, the virus is released into the tumor microenvironment together with tumor derived-antigens (TDA). The virus also produces local GM-CSF which leads to maturation of antigen-presenting cells (APC) such as dendritic cells (DC) which ingest the TDA. (**b**) Systemic effect: The DCs migrate to lymph nodes where they ultimately activate antigen-specific CD4+ and CD8+ T-cells. These proliferate and migrate to distant sites where they can lead to a systemic response to tumor cells that were not initially injected

low in healthcare workers, due to autoinoculation of the drug during administration, serve as an important reminder to take the precautions seriously [76].

The pivotal phase III trial leading to the approval of T-VEC randomized unresectable stage III or IV disease melanoma patients to receive either T-VEC or subcutaneous GM-CSF. The primary endpoint of the study was durable response rate (DRR), defined as a complete response or partial response lasting 6 months or more within 12 months of the initial injection. The T-VEC arm had a significantly improved DRR compared with the GM-CSF arm (16.3% versus 2.1%; unadjusted odds ratio, 8.9; 95% CI, 2.7–29.2; $p < 0.001$). The median time to response with T-VEC was 4.1 months (1.2–16.7). Both treatments were well tolerated with no drug-related deaths, and few cases of drug discontinuation due to adverse events. The most common side-effects were flu-like symptoms (fevers, chills, myalgia) with grade 3 or 4 adverse events documented in 11% with T-VEC and 5% with GM-CSF [1]. In a follow-up study, 48 patients (83%) who had a durable response to T-VEC showed ongoing responses with a median

duration of follow-up of 18.4 months (10.8–19.2). It is notable that despite the positive DRR demonstrated, the trial was unable to demonstrate significant superiority of survival of patients given T-VEC to those given GM-CSF. Median overall survival was 23.3 months (95% Cl, 19.5–29.6) with T-VEC and 18.9 months (95% Cl, 16.0–23.7) with GM-CSF (HR, 0.79; 95% Cl, 0.62–1.00; $p = 0.051$). As a therapeutic agent, the excitement around T-VEC was the "proof of concept." T-VEC's favorable safety profile lends itself to the possibility of combination with other drugs to increase its efficacy, without potentially increasing serious side-effects.

The greatest advantage of ICIs, discussed earlier in the chapter, is their potential for a durable response. The quandary is how to increase this response in a greater number of patients than currently offered by ICI monotherapy. The rational for adding T-VEC to ICI is that it has a complementary mechanism of action with regards to immune augmentation, and it is well tolerated. Serious adverse events are the main problem when combining ICI with each other. Data from a phase IB multicenter, open label, trial of intratumoral T-VEC with pembrolizumab showed an ORR of 67% with 43% CR in patients with unresectable stage IIIB/IV metastatic melanoma. Overall survival rates at 12-month, 24-month, and 36-month were 95.2%, 76.2%, and 71.4%, respectively. The combination of the two agents showed no increased toxicity compared to either agent as monotherapy. In a separate phase II trial, patients with IIIB-IVM1c metastatic melanoma were randomized to receive either T-VEC plus ipilimumab versus ipilimumab alone. The study showed approximately double the ORR and CR rate in the combined arm versus the single-agent arm: 39% versus 18%; odds ratio, 2.9; 95% Cl, 1.5–5.5; $p = 0.002$. The CR rate was 13% (13/98) versus 7% (7/100); PR rate was 26% (25/98) versus 11% (11/100). There were no unexpected side effects from receiving the combination drugs versus single-agent alone [13]. Thus far, the combination of T-VEC with ICI seems promising, with overall greater antitumor activity without additional safety concerns.

13.2.2 Targeted Therapy for Metastatic or Unresectable BRAF V600 Mutant Melanoma

Traditionally, melanoma has been classified by clinical characteristics, histologic morphology, and anatomic site of origin, resulting in nomenclatures such as superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma. However, over the last two decades, exploration of the molecular biology of melanoma has resulted in the identification of a number of driver oncogenes. Activating mutations in these oncogenes lead to uncontrolled growth in key signaling pathways such as the mitogen-activated protein kinase (MAPK) pathway. The Cancer Genome Atlas (TCGA) network published a study of 331 cutaneous melanomas using next generation sequencing (NGS) techniques, as a result of which a genomic classification with four subtypes (BRAF, NRAS, NF1, and triple wild-type) was proposed [83]. In general, as discussed below, such molecular classification schemes have largely supplanted the older morphology-based classification of melanoma. This is in no small part because such a classification frequently aids clinicians in choosing the appropriate therapy that is most beneficial to a patient's particular melanoma subtype.

Roughly 40% of patients with advanced melanoma have tumors harboring activating mutations within a protein kinase enzyme of the MAPK pathway, BRAF. Activating mutations in BRAF lead to constitutive activation of the MAPK pathway and a cellular growth and survival advantage (see Fig. 13.3). Eighty five percent of BRAF mutations are V600E, 8% V600K and other mutations at an individual frequency of <1% (V600R, V600M, V600D, and non V600 mutations) [12]. These observations raised the question as to whether an ATP binding site inhibitor directed at this activated kinase would be clinically beneficial in such patients. In 2010, an early phase I/II trial examining the oral BRAF inhibitor PLX4032, subsequently known as vemurafenib, reported that 26/32 (81%)

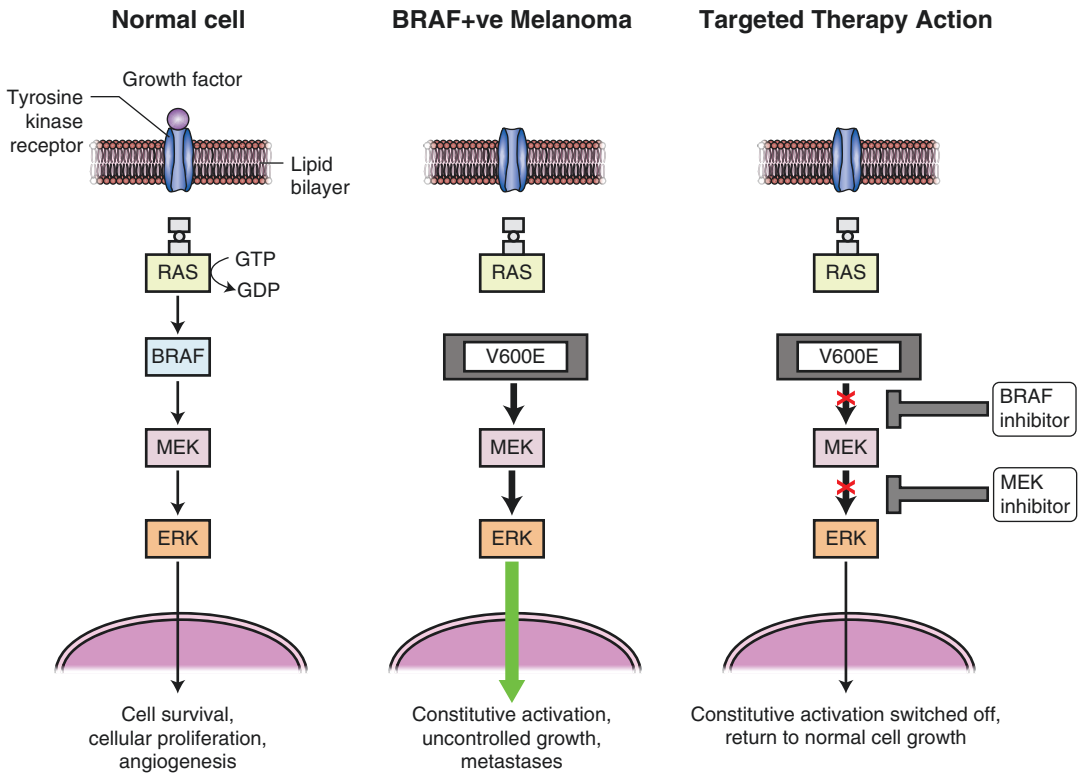

Fig. 13.3 Mitogen-Activated Protein Kinase (MAPK) pathway and targeted therapy. (**a**) Wild-type cell: Binding of tyrosine kinase receptor by external growth factor initiates signaling of the MAPK pathway. Activation of Ras sets off a cascade of activating phosphorylation events in three sequential protein kinases: BRAF-MEK-ERK. Activated ERK phosphorylates cytoplasmic and nuclear targets controlling cell growth, proliferation and differentiation. (**b**) BRAF-mutated cell: Activating mutations in BRAF leads to a ten-fold greater kinase activity than wild-type BRAF leading to constitutive activation of the MAPK pathway. This promotes cell proliferation while inhibiting apoptosis. (**c**) BRAF and MEK inhibitors were developed as targeted therapies to inhibit the action of the overactive MAPK pathway

patients with BRAF V600E mutant metastatic melanoma responded to treatment with this drug at 960 mg orally twice daily [26]. A subsequent randomized trial comparing vemurafenib to the prior standard of care for melanoma, the alkylator dacarbazine, in BRAF V600E mutant patients showed a 74% reduction in the risk of death or progression in the vemurafenib arm relative to the dacarbazine arm [11]. A second BRAF inhibitor, dabrafenib, given orally at 150 mg twice daily, not only confirmed the activity of single-agent BRAF inhibitors in patients with BRAF-mutant melanoma, but was the first drug in its class to demonstrate response in brain metastases of melanoma [12].

In the original vemurafenib trial, eight patients (15%) in the dose-escalation cohort and ten patients (31%) in the extension cohort developed well-differentiated cutaneous squamous cell carcinomas, largely keratoacanthoma-type, with a total of 35 carcinomas detected within a median of 8 weeks following initiation of therapy. Further study of these often eruptive, squamoproliferative tumors demonstrated an increased frequency of upstream HRAS mutations, a finding not usually observed (3.2%) in SCCs that occur sporadically or in patients on immunosuppressive drugs. In these BRAF wild type, HRAS-mutated cells, BRAF inhibitors were subsequently found to induce paradoxical activation of the MAPK path-

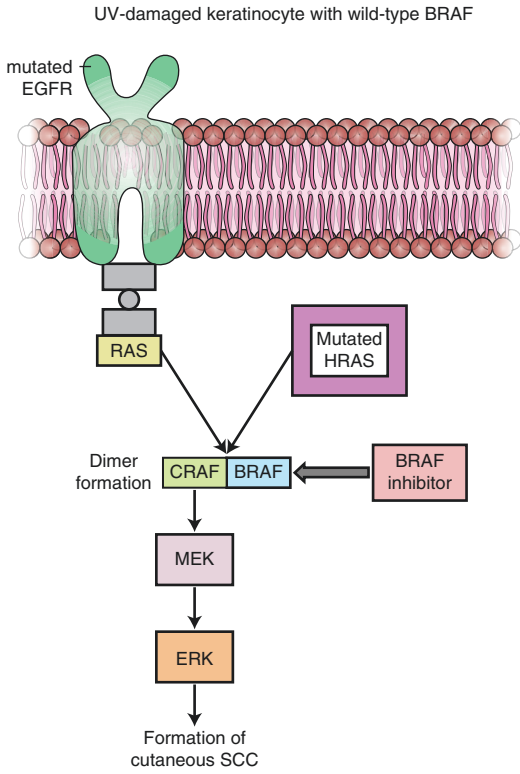

Fig. 13.4 Paradoxical activation of the mitogen-activated protein kinase (MAPK) pathway. Chronic UV damage can lead to activating mutations in the genes encoding either the epidermal growth factor receptor (EGFR) or HRas. Such activating mutations cause hyperactivity of the MAPK pathway. BRAF inhibitors (BRAFi) have two effects. (**1**) In BRAF-mutated melanoma cells, BRAFi block signaling in the MAPK pathway. (**2**) In keratinocytes harboring either mutated EGFR or HRas, these mutant upstream molecules lead to low-level CRAF activation. Paradoxically, under such conditions, CRAF is further hyperstimulated by heterodimerization with BRAF that is bound to a BRAF inhibitor. Such hyperstimulated MAPK signaling results in augmented cell proliferation and tumorigenesis

way via activation of cRAF, thus driving cell proliferation and tumorigenesis (see Fig. 13.4) [79]. Importantly, in preclinical models of this phenomenon, treatment with inhibitors of MEK, an enzyme downstream of BRAF, largely abolished BRAF inhibitor-induced proliferation of HRAS-mutated cells.

The response rate to single-agent BRAF inhibitors is well above that observed for any other class of therapy for advanced melanoma, and without question, a remarkable milestone in melanoma treatment. That said, it is important to note that many of the responses are short-lived (PFS 5.3 months for vemurafenib and 5.1 months for dabrafenib). Similarly, short PFS (4.8 months) and substantial toxicity (rash, diarrhea, and edema) were noted following monotherapy of BRAF-mutant metastatic melanoma patients with trametinib, an inhibitor of MEK [27]. Importantly, persistent MAPK pathway activation was noted in relapsed BRAF inhibitor-resistant tumors. It later became apparent from several studies that resistance to BRAF inhibitors could be attributed to a combination of multiple genetic and epigenetic alterations that ultimately led to the reactivation of the MAPK pathway downstream of BRAF [46].

The observation of MAPK pathway activation downstream of BRAF causing both squamoproliferative lesions and drug resistance over time raised the question as to whether a combined inhibition of BRAF and MEK might improve some of the side-effects and delay the development of resistance to such therapies. Such a hypothesis was supported by a randomized trial comparing the treatment of BRAF V600E-mutant melanoma patients with vemurafenib alone versus vemurafenib in combination with the MEK inhibitor cobimetinib, with PFS of 9.9 months in the combined arm versus 6.2 months in the single-agent arm [55]. A similar randomized trial comparing combined dabrafenib and trametinib with vemurafenib alone demonstrated an improvement in PFS of 11.4 months in the combination arm relative to 7.3 months in the vemurafenib only arm [70]. Remarkably, and consistent with the preclinical studies noted above, the incidence of cutaneous squamous cell carcinomas was only 1% in the dabrafenib/trametinib combination arm and 18% in the vemurafenib arm, confirming that MEK inhibition largely abrogated BRAF inhibitor-induced cutaneous SCCs. While no head-to-head trial has been performed comparing dabrafenib/trametinib with vemurafenib/cobimetinib, a non-randomized retrospective

assessment has suggested that dabrafenib and trametinib combination therapy is associated with fewer overall adverse events [18]. The combination of BRAF inhibitor and MEK inhibitor is now the standard of care for targeted therapy in melanoma.

13.2.2.1 c-Kit Directed Therapy

c-KIT is a transmembrane tyrosine kinase receptor that binds a glycoprotein ligand, stem cell factor (SCF), resulting in receptor dimerization, autophosphorylation, and signaling. In the melanocyte lineage, such c-KIT signaling enhances the migration of neural crest melanocyte precursors during development [75]. While c-KIT signaling is not critical in mature melanocytes and may even be anti-proliferative in such cells, in a subset of melanomas, juxtamembrane activating mutations of c-KIT appear to be critical for melanoma pathogenesis. Such c-KIT mutations are enriched in acral melanomas (11%), mucosal melanomas (21%) and melanomas derived from chronically sun-damaged skin (17%) but are uncommon in melanoma on the skin without chronic sun damage [16]. Additional patients in these subgroups demonstrate amplification of the c-KIT gene, often in the absence of c-KIT mutation.

Since there have been clinical trials demonstrating a benefit of KIT-targeted therapy in selected patients, the National Comprehensive Cancer Network (NCCN) has incorporated KIT-targeted therapy in their guidelines for the treatment of metastatic or unresectable melanoma. In one study of 25 patients with either activating c-KIT mutations or c-KIT gene amplification, 29% responded to treatment with the c-KIT inhibitor imatinib (400 mg a day or 400 mg bid if unresponsive). 7/13 patients (54%) with c-KIT mutations responded to imatinib therapy compared with 0/12 (0%) of those with c-KIT amplifications only [33, 44, 59]. Nilotinib was reported to have comparable potency to imatinib. Four studies have been conducted in patients with KIT-mutated melanoma with or without prior targeted KIT therapy [9, 19, 33, 59].

13.2.2.2 An Approach to Newly Diagnosed Patients with Locally Advanced or Metastatic Melanoma: Work-Up and Choice of Therapy

The initial work-up of a patient with advanced melanoma should assess a patient for the presence of metastatic disease as well as both tumor-specific and clinical characteristics that will determine both prognosis and the subsequent choice of therapy. In patients with apparent metastatic lesions, it is in many cases important to verify by biopsy that the lesions do in fact represent true melanoma metastases as a subset of patients may prove to have either a second malignancy or a benign abnormality that mimics metastatic disease. In addition, as discussed below, molecular analysis of metastatic disease can, in some cases, provide information that differs from that observed in the primary melanoma lesion that may alter therapy.

Staging will usually entail a full-body positron emission tomography/computerized tomography (PET CT) as well as a magnetic resonance imaging (MRI) of the brain with contrast. PET CT scans not infrequently detect metastases that would be missed by CT scans alone. A brain MRI is a sensitive test for detecting brain metastases of melanoma, and early recognition of such disease may have an important positive impact on the clinical outcome for such patients. Important further clinical information includes serum lactate dehydrogenase (LDH) and whether the patient is on immunosuppressive medications, either for a history of autoimmune disease or because they are organ transplant recipients. An elevated serum LDH, particularly if over two times the upper limit of normal, has been repeatedly identified as an important negative prognostic factor in patients with advanced melanoma and this observation has unfortunately remained true during the era of single and combined checkpoint inhibitor therapy [23, 50, 57]. Organ transplant recipients are at a significantly high risk of allograft rejection if treated with either anti-CTLA-4 or anti-

PD-1 therapies [77]. Patients with a prior history of autoimmune disease, particularly those on immunosuppressive therapy, are at risk for disease flares when treated with immune checkpoint inhibitor therapies, but in most cases, such flares are manageable and not a strict contraindication to therapy [34, 51].

At the time of diagnosis of either locally unresectable or metastatic melanoma, the treating physician will need to establish clearly whether a patient is a candidate for targeted therapy, whether it be used as initial treatment, or held in reserve as a later alternative form of therapy. With regards to the tumor itself, BRAF V600 and c-KIT mutation status should be determined. If the primary tumor is negative for BRAF or c-KIT mutations, an effort should be made to assess a metastatic lesion for such mutations as well, as there is a significant incidence (16–44%) of discordance between molecular analyses done on primary versus metastatic lesions [7, 41, 85]. A variety of studies now support the concept that primary melanomas are frequently heterogeneous with regard to the presence of specific targetable mutations. Metastasis allows the selective outgrowth of clones either containing targetable mutations that were not present in sufficient quantity in the primary tumor to have been detected by initial testing or, in other cases, that lack the targetable mutation that was detected in the primary tumor. Such intratumoral heterogeneity may play a role in the development of resistance to targeted therapies.

If a patient is positive for a BRAF mutation, should checkpoint inhibitor or BRAF inhibitor therapy be chosen as the initial therapy? This is a clinical question that a cutaneous oncologist frequently faces for which, at present, there is no data to guide us from randomized studies directly comparing these two therapeutic approaches. However, there is reason to consider checkpoint inhibitor therapy as the preferred initial treatment as long-term follow-up studies suggest that patients treated with checkpoint inhibitors have a significantly higher likelihood of durable response than those treated with targeted therapy. This is particularly so if patients are treated with dual checkpoint inhibitors therapy regimens such as nivolumab and ipilimumab [29, 80]. The 5 year PFS rate for patients treated with the BRAF and MEK inhibitors, dabrafenib and trametinib is 19% at 5 years [71]. In contrast, in a study comparing treatment with the anti-PD1 agent nivolumab, the anti-CTLA-4 agent ipilimumab, or the combination of these two, the 5 year PFS rate was 36% in the nivolumab and ipilimumab arm, 29% in the nivolumab arm and 8% in the ipilimumab arm [57]. Although a general preference for initial treatment with checkpoint inhibition is supported by the data cited above, there are clearly certain situations, such as poor access to an infusion center, in which targeted therapy may be the appropriate first choice for treatment.

Melanoma tumor PD-L1 levels can be established by immunohistochemistry using a variety of monoclonal antibodies. In comparison to ipilimumab therapy alone, both nivolumab monotherapy and the combination of nivolumab and ipilimumab have resulted in better response rates regardless of PD-L1 levels [45, 56, 84]. This observation suggests that even low levels of PD-L1 on tumors are biologically important and that treatment with therapeutic monoclonal antibodies directed at PD-1 or PD-L1 is potentially beneficial to all patients with metastatic cutaneous melanoma. Having said this, it is also clear that response rates to an anti-PD-1 monoclonal antibody such as nivolumab is more likely to be highly active in a patient with high levels of PD-L1 expression on their tumor than in a patient whose tumor expresses little or no PD-L1. It is, therefore, of interest that the CHECKMATE 067 trial reported better objective response rates and overall survival in PD-L1 negative patients when treated with dual agent CTLA-4 and PD-1-targeting ICIs relative to either agent alone [56, 84]. While these studies did not make the predictive strength of tumor PD-L1 levels a primary endpoint in their design and therefore need to be interpreted with some caution, an argument can be made for consideration of dual anti-CTLA-4 and anti-PD-1 therapy in metastatic melanoma patients with very low expression levels of PD-1.

13.2.2.3 Combination Targeted and Checkpoint Inhibitor Therapy of Melanoma

As noted above, the current standard of care for most patients with a BRAF-mutated advanced melanoma is checkpoint inhibitor immunotherapy, as data would suggest that such an approach affords patients the best likelihood of a lasting remission from the disease. Following the introduction of these two mechanistically disparate therapies for advanced melanoma patients, the obvious question arose as to whether a combination of BRAF-directed and checkpoint inhibitors would improve clinical outcomes relative to either treatment alone. Preclinical work demonstrated that BRAF inhibitors improved the outcome of checkpoint inhibitor therapy in murine models of melanoma, and studies in humans suggested that BRAF inhibitors enhance immune cell infiltration into patient tumors [15, 67].

Despite the scientific rationale for investigating the potential clinical benefit of combined targeted and checkpoint therapy, randomized studies to date have unfortunately not satisfactorily addressed whether such an approach will benefit patients with BRAF-mutant melanoma. One randomized study compared targeted therapy alone (vemurafenib and cobimetinib) with the same targeted therapy in combination with the anti-PD-L1 antibody atezolizumab [35]. Clinical outcomes were better with the combined therapy than with the targeted therapy alone (PFS of 15.1 vs 10.6 month, hazard ratio = 0.78, $p = 0.025$). Importantly, no major new or unexpected toxicities were identified with combined therapy. Similar results have been observed in Keynote 022, a phase II trial in which patients with advanced BRAF-mutant melanoma were treated with dabrafenib and trametinib and randomized to the addition of either pembrolizumab or placebo [2]. PFS was 16.0 vs 10.3 months for triplet and doublet therapy, respectively (hazard ratio = 0.66 and $p = 0.043$). Both of these studies were designed at a time that first-line treatment of BRAF-mutant melanoma with BRAF inhibitors was considered a standard of care. However, with the subsequent adoption of immunotherapy as first line in the treatment of advanced BRAF-mutant melanoma, the question, unfortunately, remains unanswered as to whether combined checkpoint inhibitor and targeted therapy would result in better long-term clinical outcomes than checkpoint inhibitor therapy alone.

13.3 Future Systemic Therapy for Advanced Melanoma

The last decade has ushered in a new era in the care of patients with advanced melanoma. This previously almost uniformly fatal illness can now be treated often with considerable success, with kinase inhibitors or checkpoint immunotherapy. For oncologists who cared for such patients in past years, the progress over this period has been breathtaking and a testament to the ultimate clinical value of basic research into cancer biology.

Having acknowledged this progress, it is also important to step back and note the persistent shortcomings of the systemic therapies we currently offer our patients. The 5 year overall survival for a patient with advanced melanoma treated with ipilimumab and nivolumab is 52% [57]. The five-year overall survival for a patient with advanced BRAF-mutant melanoma treated with dabrafenib and trametinib is 34% [71]. It is clear that despite the recent remarkable breakthrough in melanoma therapy, there remains much room for improvement in the treatment of this disease.

If the next generation of patients with advanced melanoma are to fare better than the numbers cited above, caregivers will need to continue to encourage their patients to enroll in clinical trials that seek to address these shortcomings. A summary of some of the most promising new forms of systemic therapy for advanced melanoma currently under study is presented in the chapter, Novel Therapies in Melanoma.

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14 Radiation Therapy in Advanced Melanoma

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14.1 Introduction

Radiation therapy (RT) plays an essential role in the setting of metastatic melanoma for the palliation of symptoms [1, 2]. Furthermore, for patients with limited metastatic disease (e.g., oligometastases), RT can be used as an alternative to surgery for local control of metastatic tumors. In this chapter, we will describe the role of RT for common metastatic disease sites, including metastases to the brain, spine, viscera, and bone. Melanoma has been considered a relatively radioresistant tumor compared to other tumors, and often requires larger doses of radiation to achieve local control or palliation compared to conventional radiation fractionation of 1.8–2 Gy per day [3–5]. With the advent of new radiation modalities over the past two decades, such as stereotactic radiation techniques to the brain and body, and with the improved prognosis of patients due to more effective systemic therapies, RT has become increasingly important in managing metastatic melanoma.

14.2 Melanoma Brain Metastases (MBM)

Brain metastases are a common site of spread for metastatic melanoma, and the management of MBM requires multidisciplinary input from neurosurgeons, neurooncologists, neuroradiologists, and radiation oncologists to determine the optimal management for each patient. Patients may be treated with a combination of neurosurgical resection, stereotactic radiosurgery, whole brain radiation therapy (WBRT), and/or systemic therapy, including intrathecal therapy or immunotherapy. The decision between these modalities for a given patient depends on the number, size, and location of the brain metastases, the burden of systemic disease, the performance status of the patient, and the past and expected future response to immunotherapy or other systemic therapy. The evolution of the management of MBM over time, as well as the role of RT for MBM, will be discussed in the following section.

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14.3 Prognostic Factors for Patients with Brain Metastases

Early studies of patients with metastatic brain disease demonstrated that the survival is determined by the number of brain metastases, patient performance status such as the Karnofsky Performance Scale (KPS), and the presence of extracranial disease [6, 7]. The Radiation Therapy Oncology Group Recursive Partitioning Analysis (RTOG-RPA) for brain metastases has also been validated in the MBM patient population to produce a melanoma-specific RTOG-RPA score [8]. More recently, molecular markers have also been integrated into prognostic indices to estimate survival for patients with MBM. Sperduto et al. developed a prognostic index for melanoma patients in the pre-immunotherapy era with brain metastases that contains five factors: age, Karnofsky performance status, extracranial metastases, number of brain metastases, and BRAF status [9]. In this study, the median survival improved from 6.7 to 9.8 months over two treatment eras (1985–005 compared to 2006–2015). Patients with the worst prognostic scores based on the five possible factors had a median survival of 4.9 months, whereas patients with the best scores had a median survival of 34.1 months. Given the wide range of survival time estimates based on these prognostic factors, tailoring the management of brain metastases in melanoma patients is paramount to maximize the quality of life and minimize potential complications of treatment for individual patients.

14.4 Whole Brain Radiotherapy and Steroid Therapy

Whole brain radiotherapy (WBRT) has long been considered the standard treatment for patients diagnosed with brain metastases [10, 11]. Melanoma brain metastases can cause symptoms or limit life due to acute mass effect, edema, and intracranial hemorrhage. Typically, 30 Gy in 10 fractions is used for WBRT. The median survival with WBRT without effective systemic therapy (i.e., systemic therapy with intracranial activity) for patients with metastatic brain disease is approximately 3–4 months. Steroid therapy with dexamethasone is often given to alleviate symptoms of edema from tumor mass effect, which can be exacerbated by a course of WBRT. Each radiation treatment is short and painless, but side effects can develop during and after the course of treatment. The most common acute side effects of WBRT are alopecia, scalp redness/irritation, and fatigue. As radiation to the brain can cause or worsen tumor-associated edema in the short-term, potential acute side effects of WBRT, especially in patients not on appropriate doses of steroids, include headaches, nausea, vomiting, seizures, or worsening of neurologic symptoms. Long-term side effects can include ongoing fatigue, neurocognitive deficits, permanent alopecia, hearing loss, and pituitary-related hormonal abnormalities. Over the past two to three decades, the management of brain metastases has been refined as a result of improved imaging with MRI technology, and we will review the studies which have evaluated the role of surgery, radiosurgery, WBRT, or a combination of treatments, in patients with MBM. Due to the potential neurocognitive side effects of WBRT, the inferior survival outcomes with WBRT alone, and the relative radioresistance of melanoma, the role of WBRT has been reexamined, especially for patients with the limited or oligometastatic disease to the brain. Table 14.1 describes the studies of WBRT for metastatic melanoma.

14.5 Patients with Single and Oligometastatic Brain Metastases

14.5.1 The Role of Surgery with WBRT

Initial studies explored the role of surgical resection of a single brain metastasis combined with WBRT to determine if this approach improved survival compared to WBRT alone. Patchell et al. showed for the first time in a randomized trial that patients with single brain

metastasis who received surgery and WBRT had a clear survival advantage compared to those receiving only WBRT (40 vs. 15 weeks; $p < 0.01$) [12]. Patients receiving surgery and WBRT also experienced lower rates of progression at the original site of metastasis (20% vs. 52%; $p < 0.02$) and more extended periods of functional independence (median 38 weeks vs. 8 weeks; $p < 0.005$). A multi-center randomized study performed in the Netherlands by Vecht et al. also randomized 63 patients to surgery and WBRT vs. WBRT alone (40 Gy in 20 fractions over two weeks, with a twice-daily treatment), and found longer overall survival and longer functionally independent survival for patients with a single brain metastasis who received surgery in addition to WBRT [13]. This finding was more pronounced in patients with stable extracranial disease (median survival 12 months vs. 7 months in this subgroup). Patients with progressive extracranial disease had a median overall survival of 5 months and a median functionally independent survival of 2.5 months regardless of the treatment given.

In contrast, a Canadian institutional study randomized 84 patients with a single brain metastasis to WBRT versus surgery and WBRT using 30 Gy in 10 fractions in both arms [14]. The study demonstrated similar overall survival of 6.3 vs. 5.6 months and no improvement in quality of life. Most patients died within the first year of treatment, and extracranial disease was a significant predictor of mortality. This study allowed the inclusion of patients with a KPS of 50 or greater, which may have adversely impacted outcomes. Of note, these studies were performed in the CT era without the ability to detect small lesions, as seen with MRI technology. Moreover, none of these studies were specific to patients with MBM, but MBM patients were among other brain metastasis patients enrolled. These initial studies, as described in Table 14.1, defined the role of surgical resection in combination with WBRT for patients with a single brain metastasis and stable extracranial disease.

14.5.2 Can WBRT Be Omitted after Upfront Surgical Resection?

Following their first study, Patchell et al. conducted another study to determine if WBRT could be omitted after surgical resection of single brain metastasis since the efficacy of post-operative WBRT after complete surgical resection was not established [15]. In this multi-center trial, 95 patients undergoing complete surgical resection (determined by post-operative MRI) of a single brain metastasis were then randomized to post-operative WBRT (49 patients) vs. no WBRT (46 patients). The primary endpoint of the study was tumor recurrence in the brain. Secondary endpoints were survival, cause of death, and preservation of functional independence. Recurrence anywhere in the brain was less frequent in the radiotherapy group than in the observation group (18% vs. 70%, $p < 0.001$). Post-operative radiotherapy prevented brain recurrence at the site of the original metastasis (10% vs. 46% $p < 0.001$), and in other sites in the brain (14% vs. 37%; $p < 0.01$). Those in the RT group were less likely to die from neurological causes (14% vs. 44%; $p = 0.003$). Overall survival and duration of functional independence, however, were not significantly different between the two arms. As a result of these findings, two schools of thought emerged regarding WBRT. There were those who believed that adjuvant WBRT should be pursued as it reduced deaths from neurological causes and recurrence of metastases in the surgical bed and elsewhere in the brain. Others, however, believed that WBRT should not be pursued in patients with limited brain metastases given the lack of a survival benefit.

Several different treatment paradigms have since been explored and they are as follows:

1. WBRT with or without dose escalation using stereotactic radiosurgery (SRS) (no surgical resection).
2. SRS with or without adjuvant WBRT.
3. Surgery or SRS with or without adjuvant WBRT.

4. Surgery with SRS to the surgical resection cavity, without WBRT.

These studies are summarized in Table 14.1. Again, it is noteworthy that most of these studies were not specific to patients with melanoma and included other cancer types as well.

14.5.2.1 WBRT with or without SRS Boost

Several trials also investigated dose escalation in the setting of the standard of care WBRT, including RTOG 95–08, and the University of Pittsburgh study [16, 17]. The treatment paradigm was that of WBRT being the standard of care, and SRS was being used to give higher tumoricidal radiation doses to patients with a limited number of brain metastases. RTOG 95–08 randomized 333 patients with 1–3 brain metastases from 55 centers to WBRT alone vs. WBRT and SRS boost [16]. The mean overall survival was similar in both arms (6.5 vs. 5.7 months, $p = 0.14$). There was no difference in time to any intracranial failure and no difference in neurological death. Local recurrence was more likely in the WBRT alone arm, compared to the WBRT+SRS arm. Patients in the WBRT+SRS group had stable or improved KPS score and decreased steroid use at six months. Acute grade 3 toxicity was 0% vs. 3%, and late grade 3 toxicity was 3% vs. 6% in the WBRT and WBRT+SRS arms, respectively. However, in the subgroup of patients with a single brain metastasis, SRS boost when added to WBRT did improve overall survival (4.9 vs. 6.5 months, $p = 0.039$). The authors concluded that WBRT+ SRS improved performance status, but without a survival advantage, other than in patients with single brain metastasis.

Kondziolka et al., from the University of Pittsburgh, randomized patients with 2–4 brain metastases to WBRT alone vs. WBRT and SRS boost [17]. The study was stopped at interim analysis at 60% accrual due to a benefit seen in the WBRT+SRS arm. The local failure at 1-year was 100% after WBRT alone, but only 8% in patients who had radiosurgery boost. The median time to local failure was 6 months vs. 36 months after WBRT alone and WBRT+SRS, respectively, ($p = 0.0005$). The corresponding median survival was 7.5 and 11 months ($p = 0.22$). The median time to any brain failure was improved in the radiosurgery group ($p = 0.002$). Interestingly, tumor control did not depend on histology ($p = 0.85$), number of initial brain metastases ($p = 0.25$), or extent of extracranial disease ($p = 0.26$), whereas survival did not depend on histology or number of tumors, but was associated with extent of extracranial disease ($p = 0.02$). There was no neurologic or systemic morbidity related to stereotactic radiosurgery. Investigators concluded that WBRT alone does not provide lasting and effective care for most patients.

14.5.2.2 SRS with or Without WBRT

Chang et al. conducted a randomized trial from MD Anderson from 2001 to 2007 to determine if WBRT could be omitted after SRS due to the concern of impaired learning and memory function after WBRT [18]. The primary endpoint was neurocognitive function, which was defined as a 5-point deterioration in the Hopkins Verbal Learning Test-revised total recall at 4 months. This trial was stopped early by the data monitoring committee because there was a high probability (96%) that patients in the WBRT showed a significant decline in learning memory function of 52% vs. 24% in the SRS alone arm. Interestingly, while WBRT added to SRS significantly improved 1-year freedom-from-CNS-recurrence (73% for WBRT+SRS vs. 27% for SRS alone, $p = 0.0003$), overall survival was actually improved in the SRS alone group (5.7 vs. 15.2 months, $p = 0.003$). This study demonstrated that SRS alone better preserves neurocognitive function compared to WBRT+SRS, but close monitoring for intracranial recurrence is necessary after SRS alone.

Aoyama et al. conducted a multi-center randomized trial in Japan of 132 patients with 1–4 brain metastases less than 3 cm in size to WBRT+SRS vs. SRS alone [19]. The primary endpoint was overall survival. The 1-year overall survivals were 7.5 months and 8.0 months in the WBRT+SRS and SRS alone groups, respectively ($p = 0.42$). Intracranial relapse was more frequent in the SRS alone arm, requiring salvage treatment,

but neurological deaths were not significantly different between arms. There were no significant differences in systemic and neurological function between arms. The authors concluded that SRS alone is a reasonable treatment as long as salvage treatment can be implemented with close follow-up.

14.5.2.3 Surgery or SRS with or Without Adjuvant WBRT

The European Organization for Research and Treatment of Cancer (EORTC) 22952-26001 trial further validated the move away from WBRT [20, 21]. In this trial, 359 patients with brain metastases with stable systemic disease or asymptomatic primary tumors and with a WHO performance status (PS) of 0 to 2 were treated with complete surgery or SRS and then randomly assigned to adjuvant WBRT (30 Gy in 10 fractions) or observation (OBS). The primary endpoint was time to WHO PS deterioration to more than 2. There were 199 patients who underwent radiosurgery, and 160 who underwent surgery. In the radiosurgery group, 100 patients were allocated to observation, and 99 were allocated to WBRT. After surgery, 79 patients were allocated to observation, and 81 were allocated to adjuvant WBRT. The median time to WHO PS > 2 was 10.0 months and 9.5 months after observation and WBRT, respectively ($p = 0.71$). Adjuvant WBRT and observation arms showed a similar median survival of 10.9 vs. 10.7 months, respectively ($p = 0.89$). Adjuvant WBRT reduced the 2-year relapse rate both at initial sites (surgery: 59% to 27%, $p < 0.001$; radiosurgery: 31% to 19%, $p = 0.04$) and at new brain sites (surgery: 42% to 23%, $p = 0.008$; radiosurgery: 48% to 33%, $p = 0.023$). Salvage therapies were more common after observation. Intracranial progression caused death in 44% and 28% in the observation and WBRT arms, respectively. This study found that adjuvant WBRT reduces intracranial relapses and neurologic deaths but did not improve the duration of functional independence or overall survival [21].

The aforementioned studies were not specific to melanoma patients, who only constituted about 5% of patients in these brain metastasis trials. As a result, Hong et al. conducted a randomized trial specific to patients with melanoma brain metastases [22]. A total of 215 patients from 24 centers with previous local treatment (surgery and/or SRS) to 1–3 brain metastases were randomized to adjuvant WBRT or observation. The primary endpoint in this study was distant intracranial failure within 12 months. Secondary endpoints included time to intracranial failure and time to deterioration in performance status. At one year, distant intracranial failure was observed in 42% and 50.5% of patients in the WBRT and observation groups, respectively, $p = 0.22$); 41.5% of patients in the WBRT group, and 51.4% of patients in the observation group died ($p = 0.28$). There was also no difference in the rate of neurologic death. The median time to deterioration in performance status was 3.8 months after WBRT and 4.4 months with observation ($p = 0.32$). Adjuvant WBRT was associated with more grade 1 to 2 acute toxicity. Unlike the many other brain metastasis studies that demonstrated distant intracranial failure being more common in the non-WBRT group, in this melanoma-specific trial the rates of distant intracranial failure were not significantly different between observation and WBRT arms. This suggests that the pattern of oligometastatic and micrometastatic disease for MBM patients may be different from other cancer histologies, or that the dose fractionation of 30 Gy in 10 fractions of WBRT may not be adequate to sterilize micrometastatic disease for patients with MBM. Based on this study for MBM, WBRT is no longer considered the default standard of care for patients with limited [1–3] brain metastases. More generally, in 2014, the American Society of Radiation Oncology released a consensus statement as part of the *Choosing Wisely Campaign* recommending against the routine practice of adding WBRT to standard SRS for limited brain metastases [23].

14.5.2.4 Surgery with SRS to the Resection Cavity

With surgery alone, patients experience a 1–2 year local recurrence rate of 46–59% at the tumor bed site, suggesting the need for adjuvant RT to lower risk of local recurrence; WBRT reduces the risk of local recurrence without improving overall sur-

vival and is associated with neurocognitive decline [15, 18, 21]. Therefore, SRS, or fractionated stereotactic radiotherapy (SRT) to the resection cavity has become an alternative adjuvant treatment to WBRT after surgery based on several phase III trials [24–26]. Mahajan et al. conducted a phase III randomized trial at MD Anderson Cancer Center in patients who had a KPS of at least 70, complete resection of one to three brain metastases, and a maximum resection cavity size of 4 cm [24]. Patients were randomized to SRS within 30 days of surgery to the resection cavity versus observation. The primary endpoint was time to local recurrence in the resection cavity. From 2009 to 2016, 132 patients (21% were MBM) were assigned to the observation group (n = 68) or SRS group (n = 64). The median follow-up was 11.1 months. The 12-month freedom from local recurrence was 43% and 72% in the observation and SRS groups, respectively [24]. Brown et al., in a multi-center study from 48 institutions in the USA, randomized patients with one resected brain metastasis and a resection cavity less than 5 cm to post-operative SRS (12–20 Gy single fraction with the dose determined by surgical cavity volume) or WBRT (30 Gy in 10 fractions or 37.5 Gy in 15 fractions) [25]. The co-primary endpoints were cognitive-deterioration-free survival and overall survival. From 2011 to 2015, 194 patients were enrolled and randomly assigned to SRS (98 patients) or WBRT (96 patients). With a median follow-up of 11.1 months, in the SRS vs. WBRT arms, median cognitive-deterioration-free survival was 3.7 months vs. 3.0 months ($p < 0.0001$); additionally, cognitive deterioration at 6 months was less common in the SRS patients (52% vs 85%). The median survival was similar (12.2 vs. 11.6 months, $p = 0.70$). The most common grade 3 or 4 toxicity was hearing impairment (3 vs 9% in SRS vs. WBRT arms). Since survival outcomes were similar, and cognitive function and grade 3–4 toxicity outcomes were superior in the SRS arm, the authors concluded that SRS is a superior standard to WBRT in the post-operative setting. Kayama et al. provided further support for the use of SRS/SRT in place of WBRT in the adjuvant setting by showing increased grade 2–4 cognitive dysfunction post-treatment in WBRT patients compared to SRS patients (16.4 vs. 7.7%; $p = 0.048$) [26].

14.5.3 Surgery or SRS?

The choice between surgery versus SRS should be evaluated in a multidisciplinary setting. There are no randomized trials that compare these modalities, and both surgery and SRS are considered equivalent modalities for local control depending on the location and size of the metastasis. In an exploratory analysis of the EORTC 22952-26001 trial of 268 patients, both modalities had comparable local control rates. However, patients undergoing surgery had higher risk of early local recurrence, while patients undergoing SRS had higher risk of late recurrence [27]. Surgery is recommended over SRS for patients with peripheral large, limited, symptomatic lesions which exert mass effect and/or cause neurological impairments [28]. In such cases, SRS without prior surgery may worsen edema and neurologic symptoms in the short term. One additional consideration is that for patients with increased intracranial pressure from mass effect or CSF outflow obstruction, but who are not good candidates for surgical resection, a ventriculoperitoneal shunt should be considered prior to initiation of radiation therapy. While surgery is effective for single, large symptomatic lesions, SRS is often used when patients have multiple [2–4] metastases and for smaller lesions that are not necessarily symptomatic [29]. For small- to medium-sized metastatic brain metastases (≤2 cm in diameter), SRS and surgery achieve comparable local control rates.

14.6 SRS in Patients with Multiple Brain Metastases

For patients with multiple lesions (up to 10), SRS is being increasingly used as an alternative to WBRT [17, 30]. Additionally, with effective systemic therapies that have activity in the CNS, it is reasonable to treat the largest brain lesions with

surgery or SRS and to observe small ones (<5–10 mm) if there is a systemic therapy that is expected to have activity in the CNS. For these patients, short interval MRI is needed to ensure that surgery, SRS, or WBRT can be used if CNS progression has occurred despite systemic therapy. SRS results in excellent local control of MBM, (e.g., 73% local control in 333 patients receiving SRS in a study by Liew et al.), though overall survival is highest in those with a single metastatic brain lesion, limited extracranial disease, and immunotherapy after SRS (median 22 months in this subgroup) [31]. Because SRS/SRT does not address micrometastatic disease in the brain, around 44% of patients will experience out of field intracranial failure after SRS/SRT [32]. Therefore, it is recommended that a brain MRI be performed every 2–3 months for the first year after treatment. Even more frequent imaging is recommended if there are known intracranial lesions that have not yet been treated with local therapy, in the hope that systemic therapy will cause a response. After the first year, a repeat brain MRI should be performed every 4–6 months indefinitely. Table 14.1 lists some of the important studies that helped establish the current roles of SRS and WBRT in the treatment of brain metastases (Fig. 14.1).

14.7 Radiation Dose Fractionation for Stereotactic Radiation

In terms of SRS/SRT dose fractionation for intact brain metastases, 20–24 Gy in a single fraction can be used for metastases with a maximum diameter of 20 mm. Of note, the prescription dose in SRS is the dose received at the periphery of the target. The dose at the center of the target is typically 15–100% higher than the prescription dose depending on the type of radiosurgery used (e.g., GammaKnife vs. CyberKnife vs. linear accelerator-based radiosurgery). Medium-sized lesions, with maximum diameters of 21–30 mm, are typically treated with 18 Gy in a single fraction. The lower dose helps protect against the increased risks of edema and radionecrosis associated with treating lesions of increased size. Lesions that are even larger, 31–40 mm, can be treated with 15 Gy, due to radionecrosis and brain edema risk, or, more commonly, with fractionated SRT, e.g. 24–27 Gy in 3 fractions or 30 Gy in 5 fractions. Spreading the dose over 3–5 fractions allows delivery of a higher biological dose to the tumor (compared to <15 Gy in a single fraction) while decreasing the risk of treatment-associated edema or radionecrosis.

Regarding stereotactic dose fractionation for treatment of resection cavities which are frequently greater than 3 cm in maximal diameter, we recommend using fractionated SRT with a 2–3 mm margin on the cavity, as opposed to single-fraction radiosurgery. In a study using post-operative SRT (where the majority of the patients had non-small cell lung cancer primaries), patients achieved best local control rates when receiving 27 Gy in 3 fractions or 30 Gy in 5 fractions to the surgical cavity compared to lower doses per fraction (24 Gy in 3 fractions or 27.5/25 Gy in five fractions) [33]. In cases of very large or irregular intact brain metastases or very large or irregular resection cavities that might not be appropriate for 5-fraction SRT, one additional alternative to WBRT is focal radiotherapy over 10 fractions with a 3D conformal or intensity-modulated radiotherapy plan, e.g. with 30 Gy in 10 fractions. This decreases some of the risks associated with SRS/SRT (particularly edema and radionecrosis), but can spare patients the toxicity associated with WBRT [34].

The most significant potential side effect of SRS is radiation necrosis, which may be symptomatic (presenting with headaches, seizures, nausea, vomiting, and/or with acute neurologic deficits) or may be asymptomatic and only detected on surveillance MRI imaging. Differentiating tumor progression or recurrence from radiation necrosis can be very difficult, but additional MRI imaging modalities such as MR perfusion and MR spectroscopy can help distinguish between the two. The decision to resect suspected progression of radiation necrosis after SRS is based on MRI findings, response to steroids, performance status, and extracranial

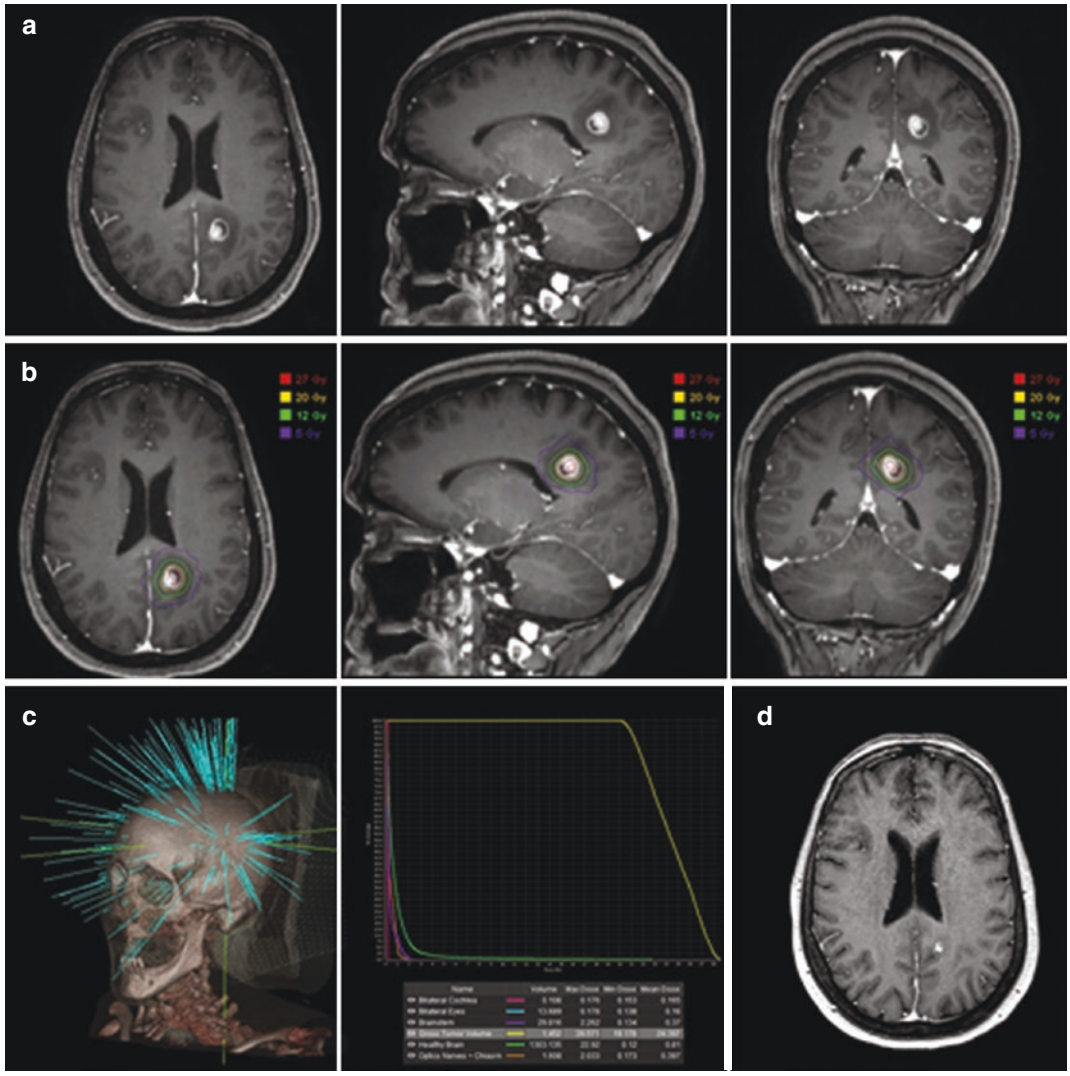

Fig. 14.1 An example of SRS to a brain metastasis. (**a**) Pre-treatment brain MRI of a 1.3 -cm peripherally enhancing melanoma brain metastasis, which demonstrated diffusion restriction and surrounding vasogenic edema in the left parietal lobe (axial, sagittal, and coronal planes). (**b**) Stereotactic radiosurgery (SRS) treatment plan with isodose lines (axial, sagittal, and coronal planes). Prescription dose was 20 Gy in a single fraction. (**c**) SRS beam entry, dose-volume histogram for select structures, and legend with structure volumes (in cc) and max, minimum, and mean doses (in Gy). (**d**) 6 -week post-treatment brain MRI showing response to treatment: now 5 mm in maximum diameter improved to 5mm from original 1.3 cm, with resolution in diffusion restriction and improvement in surrounding vasogenic edema (axial plane only). Of note, subsequent brain MRIs showed ongoing response to treatment, with only punctate focus of enhancement and no diffusion restriction or vasogenic edema

disease stability. In a retrospective review of metastatic brain lesions treated with Gamma Knife Radiosurgery (GKR), Truong et al. assessed 32 patients who underwent surgical resection for suspected progression of brain metastases from a cohort of 245 patients with 611 brain metastases treated with GKR [35]. Thirteen percent (32 out of 245) of patients and 6% (38 out of 611) of lesions required surgical resection after GKR at a median time of 8.6 months. The median survival of resected patients was 27.2 months (range, 7.0–72.5) from the diagnosis of brain metastases, 19.9 months (range, 5.0–60.7) from GKR, and 8.9 months (range, 0.2–53.1) from surgical resec-

tion. Tumor was found in 90% of resected specimens and necrosis alone in 10%. In this study, radiation necrosis was more common when the time to resection occurred >12 months from SRS. This study also evaluated the role of MRI perfusion and spectroscopy in assisting in the differentiation between radiation necrosis and disease recurrence.

Surgical salvage after SRS may offer meaningful survival improvement, for both recurrence and radiation necrosis after SRS [35]. In a large retrospective review of 271 treated brain lesions, Kohutek et al. showed that 25.8% experienced radiation necrosis, and 17.3% experienced symptomatic radionecrosis [36]. Interestingly, the rate of observed radionecrosis increased by twofold in 12 months, suggesting that SRS-induced toxicity manifests many months after treatment. Multivariate analysis from this study showed that a larger lesion size was associated with increased radionecrosis risk. Thus, consideration of tumor diameter and associated risk of radionecrosis should be included during SRS treatment decision-making for patients and clinicians. Treatments for radionecrosis include steroids, surgical resection, or bevacizumab. Suspected radionecrosis is best managed in a multidisciplinary setting.

14.8 Role of WBRT for Multiple Brain Metastases

Although the role of WBRT has dramatically decreased in the setting of limited metastases, it still remains a standard treatment option for those with multiple > 5 brain metastases, and in patients with leptomeningeal/miliary disease or with tumors in locations such as the brainstem where resection is not feasible and SRS may cause increased risk of toxicity. Moreover, new clinical strategies have been developed in recent years to limit the neurocognitive side effects associated with WBRT, specifically the use of memantine and the use of hippocampal-sparing WBRT, which utilizes intensity-modulated radiation therapy (IMRT) to limit dose to the hippocampus while treating the rest of the brain to standard 30 Gy in 10 fractions. RTOG 0614 showed that memantine during and after WBRT delayed time to cognitive decline and decreased the neurocognitive impairments previously observed to be associated with WBRT [1]. RTOG 0933 similarly showed that hippocampal-sparing WBRT may help protect against neurocognitive decline after WBRT [37]. However, there are several downsides to hippocampal-sparing WBRT, namely that it is more time- and resource-intensive to plan and administer, and that it can result in failures in the hippocampal region spared with the IMRT technique. Additionally, the case for memantine has not been explicitly studied in primary melanoma disease as past studies have focused on non-small cell lung cancer (NSCLC) primaries. That being said, both memantine and hippocampal-sparing IMRT have promise in protecting against the neurocognitive decline associated with WBRT when it is used for extensive MBM or MBM with associated leptomeningeal disease.

In summary, a growing body of evidence has made surgical resection or SRS the preferred options over WBRT for patients with a limited number [1–3] melanoma brain metastases. In the adjuvant setting after neurosurgical resection, fractionated stereotactic radiation to the resection cavity is also a preferred option over WBRT. WBRT remains an important treatment in managing patients with a high burden of intracranial disease, and in patients with innumerable lesions or miliary/leptomeningeal disease [38], or when SRS or surgical resection poses a significant risk of complications.

14.9 Extracranial Metastatic Disease

14.9.1 Overview

As with melanoma brain metastases, when assessing the utility and appropriateness of potential treatments for extracranial melanoma distant metastases, treating physicians must take into account patient prognosis, performance status, overall status and burden of disease,

associated symptoms, the potential for symptoms to develop should the metastases progress, and the individual patient's goals and values. While the mainstay of treatment for patients with melanoma distant metastases remains systemic therapy, local therapies (including radiation) play an essential role in management. Generally, radiation can be used for: (1) palliation of symptomatic lesions, (2) prophylactic palliation of lesions that are likely to become symptomatic should they progress, or (3) definitive local treatment of oligometastatic or oligoprogressive disease. Additionally, for bone or spine metastases that may require surgical intervention in weight bearing areas, radiation is routinely used in the postoperative setting to prevent a recurrence.

14.9.2 General Palliation of Extracranial Metastases and Dose Considerations

Palliative radiotherapy helps mitigate painful lesions for patients who are not suitable for surgery or more aggressive ablative radiation (due to performance status, lesion location, size, and/or number). While melanoma is considered relatively radioresistant, in a retrospective review of 84 patients treated at the Mayo Clinic from 1988 to 2000, Olivier et al. challenged the notion that radiotherapy is ineffective in palliating melanoma patients with distant extracranial metastases [39]. Of the 114 symptomatic non-central nervous system metastatic melanoma lesions treated (including visceral, skeletal, and subcutaneous metastases), 84% achieved partial improvement or complete resolution, 11% had no improvement, and only 5% exhibited progression. Furthermore, patients treated with higher doses (>30 Gy) experienced lower rates of disease progression than those treated with lower doses (≤30 Gy), suggesting that high doses result in more durable palliation for melanoma patients with extracranial metastatic disease.

There are two approaches to deciding suitable dose fractionation for palliation of symptomatic melanoma distant metastases. The first is to rely on data and experience not necessarily specific to melanoma patients. Commonly used and established palliative radiation therapy dose regimens for distant metastases for a wide range of primary tumors include 8 Gy in 1 fraction, 20 Gy in 5 fractions, and 30 Gy in 10 fractions. These dose regimens are generally very well tolerated in the treatment of a variety of metastatic sites, including bone, lymph node, and soft tissue. Moreover, both patient quality-of-life concerns and cost-effectiveness concerns provide good rationales for using the shortest effective palliative radiation treatment regimens. All of these common and reasonably short treatment regimens are considered appropriate for palliative treatment of extracranial melanoma distant metastases [5, 40, 41].

Melanoma has a unique biology, and there is some data that suggests a dose response in the palliative treatment of melanoma. Studies by Olivier et al. and Katz et al. showed better palliation with doses of at least 30 Gy, while Seegenschmiedt et al. showed better palliation with a dose of at least 40 Gy [39, 42, 43]. Other studies have failed to show such a dose response [1, 38, 44]. To further complicate matters, the biological effective dose (BED) of a given fractionation schedule depends not just on the total dose, but also on the dose per fraction. Equations that calculate BED rely on a tumor-specific constant called the alpha-beta ratio, which relates to the sensitivity of a given tumor or tissue to fractionation of radiation dose. At present, there is not a clear consensus on the actual alpha-beta ratio of melanoma [39, 45]. Randomized trials comparing different fractionation schemes for recurrent or metastatic melanoma failed to show a clear benefit of any one schedule over another [32, 46]. As a result, there are a variety of acceptable dose regimens in the palliative treatment of distant metastases of melanoma. Dosing decisions ultimately must be made on a case-by-case basis, taking into account patient-specific factors, the anatomy and proximity to adjacent organs at risk, the tolerance dose of surrounding normal tissues, and disease-specific factors.

14.9.3 Bone Metastases

Patients with bony metastases can suffer significant morbidity and complications such as hypercalcemia, pain, and pathological fracture. Palliative radiation treatment serves not only to reduce pain but also to help prevent pathological fracture. Many prospective studies (though many are not specific to melanoma patients) have validated the role of radiation in controlling pain for these patients, and several have compared dose fractionation schemes. In a randomized prospective trial of 795 patients with skeletal metastasis, delivery of 8 Gy in 1 fraction was shown to provide comparable pain control to multi-fractionated regimens [47]. Evidence that a single fraction was sufficient to achieve palliative effect makes this treatment option much more desirable with reduced cost and increased convenience. Thus, the 2011 American Society for Radiation Oncology (ASTRO) guidelines recommended 8 Gy in 1 fraction as the standard of care for palliation of uncomplicated bone metastases (i.e., no existing or impending fracture, and, in the case of vertebral metastases, no associated cauda equina or spinal cord compression). However, the 8-Gy regimen has also been associated with a greater need to repeat palliative radiation to the same site due to recurrent pain compared to multi-fractionated regimens in multiple randomized trials [48]. Decisions regarding fractionation must take into account the patient's prognosis, the burden of systemic disease, and the goals of care. It is also important to realize that ASTRO recommendations are based on trials predominantly using only a small number of melanoma patients as part of the total study population and in the pre-immunotherapy era. Based on the aforementioned studies specific to patients with melanoma, higher doses may be needed to achieve sufficient palliation in this population [39, 42, 43]. In patients with bone metastases specifically, if imaging shows existing or impending pathologic fracture, patients should be evaluated by an orthopedic surgeon for consideration of surgical intervention before radiation therapy. Post-operative radiation therapy, usually 30 Gy in 10 fractions, is given approximately 2 weeks after surgical stabilization.

14.9.4 Liver Metastases

Liver metastases have been notoriously difficult to manage, but techniques such as radioembolization and stereotactic body radiotherapy have been shown to have promise. In a study of 32 patients, Gonsalves et al. administered radioembolization therapy to treat uveal melanoma patients with liver metastases. Median overall survival and progression-free survival were 10 and 4.7 months, respectively [49]. In a larger study with 71 patients, liver radioembolization was administered with yttrium-90 (^{90}Y) microspheres; median progression-free and overall survival after salvage therapy were 5.9 and 12.3 months, respectively [50]. These findings support selective internal radiation therapy (SIRT) as a treatment for liver metastases. Liver metastases can also be treated with stereotactic body radiotherapy, particularly in the oligometastatic setting, which is discussed below.

14.9.5 Hyperthermia and Radiation Therapy

Hyperthermia, the use of heat to improve response to radiation, was clinically described by Müller in 1910 and gained momentum when a series of authors critically evaluated its effects more than 60 years later [51–54]. In 1986, the European Society for Hyperthermic Oncology began the first randomized multi-center study of 70 recurrent or metastatic melanoma patients to better understand the use of heat to complement radiation therapy. Patients either received hyperthermia (43 °C for 60 min) with radiation (24 or 27 Gy in 3 fractions) or radiotherapy alone [55]. Patients in the hyperthermia and radiation group had better complete response rates than those treated with radiation alone (62 vs 35%; $p < 0.05$) and achieved higher 2-year local control rates (46% vs 28%; $p < 0.05$). Higher dose and smaller tumor volumes were also associated with better prognosis. In practice,

hyperthermia is rarely used by radiation oncologists to improve radiation sensitivity.

14.9.6 Spinal Metastases

A multidisciplinary evaluation for the management of metastases in the spine involving interventional neurology, neurosurgery or orthopedic spine surgery, and radiation oncology is recommended. If radiographic or clinical spinal cord or cauda equina compression is present, or if spine instability is present, patients should be considered for surgical intervention. More specifically, patients with a spinal instability neoplastic score (SINS) ranging from 7–18, suggesting potentially unstable [7–12] or unstable [13–18] spine from vertebral metastases [56]. In these patients, surgical intervention should be considered before radiotherapy.

The role of surgery in spine metastases was established in phase III randomized trial by Patchell, et al. [57]. Patients with spinal cord compression due to metastatic cancer were randomized to decompressive surgery followed by post-operative RT or RT alone, 30 Gy in 10 fractions. The primary endpoint was the ability to walk. Secondary endpoints were urinary continence, muscle strength and functional status, the need for corticosteroids and opioid analgesics, and survival. After an interim analysis, the study was stopped because the criterion of a predetermined early stopping rule was met. A total of 123 patients were assessed for eligibility before the study closed and 101 were randomized. Significantly more patients in the surgery plus RT group (42/50, 84%) than in the RT alone group (29/51, 57%) were able to walk after treatment (odds ratio 6.2, $p = 0.001$). Patients treated with surgery+RT also retained the ability to walk significantly longer than those with RT alone (median 122 days vs. 13 days, $p = 0.003$). Thirty-two patients entered the study unable to walk; more patients in the surgery+RT group regained the ability to walk than in the RT alone group (10/16 [62%] vs 3/16 [19%], $p = 0.01$). The need for corticosteroids and opioid analgesics was also significantly reduced in the surgical group. Therefore, direct decompressive surgery plus post-operative RT is considered superior to RT alone in the setting of malignant cord compression.

Surgical procedures such as vertebroplasty and kyphoplasty are additional and important tools in the management of spine metastases and are able to address the structural integrity of vertebral bodies in a way that RT cannot. Just as with non-spine bone metastases that are treated with surgical stabilization, when surgery is performed for metastases in the spine, then post-operative radiation therapy, usually 30 Gy in 10 fractions, is initiated about 2 weeks after surgery.

The majority of spine metastases often involve multiple vertebral levels and/or have epidural involvement. In such scenarios, conformal RT is given to the involved vertebral bodies with a margin.

For patients with a single- or two-level vertebral spinal metastases, stereotactic body radiation therapy (SBRT) to the spine has emerged as an alternative modality. Moreover, due to the relative radioresistance of melanoma when treated with more traditional fractionation regimens, the NCCN recommends consideration of SBRT as opposed to traditional lower-dose palliative radiation regimens in melanoma histology patients, when SBRT is safe and feasible. Spine SBRT can achieve long-term tumor and pain control rates, as illustrated in a study of 500 patients by Gerszten et al., which showed tumor and pain control rates of 90% and 85%, respectively [58]. In another study specific to spinal melanoma metastases, single-fraction SBRT improved pain in 96% of the 28 patients treated; the mean dose delivered was 21.7 Gy (range: 17.5–25 Gy) [59]; the BED of this single-fractions regimen is much higher than the BED of traditional palliative regimens. Interestingly, the phase III portion of RTOG 0631, presented in abstract form at the 2019 ASTRO annual meeting, showed that patients receiving single-fraction spine SBRT (16 or 18 Gy) experienced no improved pain control compared to patients treated with conventional palliative external beam radiation therapy (8 Gy in one fraction) for limited spine metastases [60].

This may have been due to an increased risk of pathologic fracture in the SBRT arm. Of note, this study was not specific to melanoma patients, and complete phase III results have not yet been published. Multidisciplinary evaluation is recommended for spine SBRT, and careful consideration of spinal cord tolerance, vertebral body stability, and risk of pathological fracture must be considered. Potential for long-term pain or functional compromise from a pathological fracture after SBRT is a concern, and our preference is for a fractionated SBRT regimen (e.g., 24–27 Gy in 3 fractions or 30–35 Gy in 5 fractions) as opposed to the single-fraction regimen used in RTOG 0631. Additionally, we recommend consideration of vertebroplasty if there is a risk for a pathological fracture.

14.10 Radiation as Definitive Local Treatment of Oligometastatic or Oligoprogressive Lesions

In addition to the role of SBRT in treating melanoma spine metastases, as described above, it can be used as an ablative treatment of soft tissue metastases or of visceral metastases in organs such as the lungs, liver, and adrenal glands. This is a particularly apt strategy in patients with oligometastatic or oligoprogressive disease, where definitive local treatment of a metastatic site can have the potential to affect overall disease status and prognosis. SBRT appears to be effective for oligometastatic disease, regardless of histology. In a retrospective review by Stinauer et al., patients with metastatic lesions from melanoma or renal cell carcinoma who were treated with SBRT achieved impressive local control, particularly when higher doses were used [61]. Their data indicated that a prescription dose of at least 48 Gy in 3 fractions would result in >90% 2-year local control. Moreover, in patients with oligometastatic disease, i.e. 3 or fewer metastases, all of which were treated with aggressive local therapy, and possibly also systemic therapy, the median overall survival was not reached, while the entire cohort (i.e., those with oligometastases and those with more extensive disease) had a median overall survival of 24.3 months and median follow-up time for living patients of 28 months.

Moreover, SBRT local control rates compare favorably with surgical metastasectomy local control rates. For example, in retrospective analyses, Widder et al. and Lodeweges et al. showed that patients treated with lung SBRT achieved comparable local control and overall survival rates compared to those treated with pulmonary metastasectomy, even though SBRT patients were older and were more likely to have failed prior therapies [62, 63]. Of note, poor prognostic factors after lung SBRT for oligometastatic disease include histologies other than colorectal carcinoma (including melanoma), presence of synchronous oligometastases, and tumor size >3 cm [64].

Regarding SBRT dose, Salama et al. conducted a prospective SBRT dose escalation study of 61 patients (only 1 of whom had melanoma) with 1–5 metastases in the lung, abdomen, liver, head and neck, and extremity [65]. Radiation dose was 24–48 Gy in 3 fractions, and dose-limiting toxicity was not reached. One-year overall survival was 81.5%. Whether higher SBRT doses are needed in melanoma patients compared to those with other histologies is unknown, but some data, including the aforementioned Stinauer study, suggest that this may be the case [61]. Certainly, some of the benefit of SBRT compared to traditional radiation therapy is the ability to deliver higher (and ideally ablative) doses. In a retrospective study comparing conventional/hypofractionated radiotherapy with SBRT in patients with metastatic melanoma, SBRT patients treated with 1–5 fractions to 18–60 Gy experienced significantly fewer local failures than those treated with conventional radiation with 8–50 Gy in 1–20 fraction (6% vs. 31%; $p < 0.01$), further supporting the value of SBRT [66].

Perhaps most promising in terms of SBRT treatment of oligometastatic disease is the phase II, randomized SABR-COMET study of SBRT versus standard palliative treatment for those with 1–5 metastases and a controlled primary

[67]. In this study, Palma, et al. showed that SBRT to all metastatic sites was associated with a trend toward improved overall survival (median 28 months vs. 44 months, $p = 0.09$). Of note, however, 4.5% of the 66 patients in the SBRT group experienced treatment-related deaths. This study was not powered to detect an overall survival difference at the 0.05 level of significance, and phase III trials are still needed to confirm these initial findings. Moreover, SBRT must be performed at a center with appropriate experience and expertise, and care must be taken to avoid toxicity. Table 14.2 lists published studies reporting on outcomes of SBRT for extracranial metastases (Fig. 14.2).

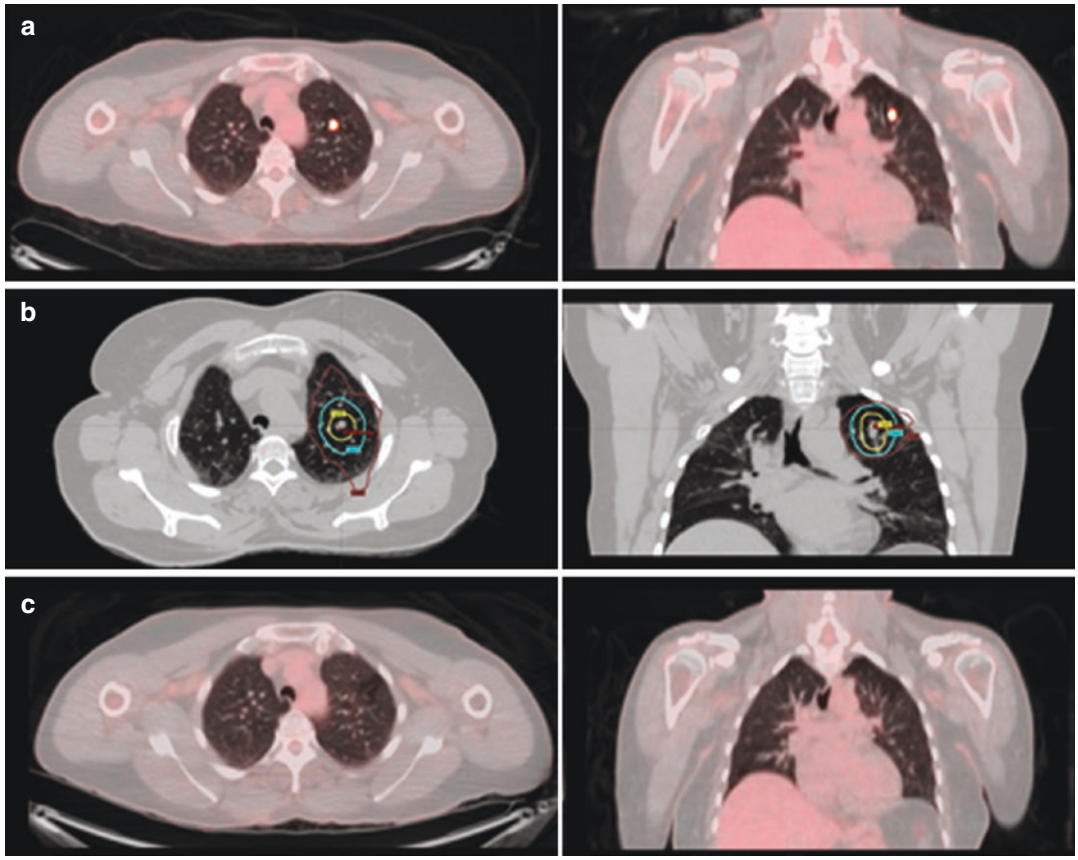

Fig. 14.2 (**a**) Pre-treatment PET scan (in axial and coronal planes) showing a 7-mm, FDG-avid oligometastatic melanoma lesion in the left lung of a patient on immunotherapy who otherwise had no active disease. Patient was treated with lung stereotactic body radiation therapy (SBRT). (**b**) SBRT treatment plan with isodose lines (in axial and coronal planes). Prescription dose was 54 Gy in 3 fractions and was given concurrently with ongoing immunotherapy. (**c**) Post-treatment PET scan (in axial and coronal planes) showing complete radiographic response

14.11 Combining Radiation and Systemic Therapies in Metastatic Melanoma

In the last decade, systemic therapies and radiation have come under the spotlight for their potential as promising combination treatments. Implications for combining systemic therapies with radiation therapy in the context of MBM are manifold. Alone, each treatment modality has its limitations: targeted therapies lose efficacy when tumor cells develop resistance, and SRS/SBRT are limited to treating local disease. By combining different therapeutic modalities, the potential benefit could be in [1] improving the efficacy of each modality through synergistic effects, including via radiosensitization, or [2] aggregating the unique advantages that each modality provides.

From immune checkpoint inhibitors to BRAF inhibitors, some studies have suggested possible synergy between systemic therapy and radiation. However, existing data do not yet definitely prove clinically significant synergistic benefit between combinations therapies, and it is possible that any potential benefits of combining systemic and local therapies for metastatic melanoma may be merely additive.

14.11.1 BRAF Inhibitors and Radiation Therapy

In vitro data from 37 melanoma cell lines suggest that there are radiosensitizing effects of the BRAF inhibitor vemurafenib [68]. Verifying the in vitro studies, Hecht et al. found that vemurafenib-treated patients had significantly more chromosomal breaks, a marker of increased radio-sensitivity. It is important to note that radiosensitization can also cause increased toxicity, and this is something clinicians must keep in mind when patients are receiving both RT and systemic therapies. In the Hecht et al. study, unwanted skin toxicities resulted from concurrent use. Patients treated with WBRT and a concurrent BRAF inhibitor had high rates of radiodermatitis compared to patients treated with WBRT only (44% vs. 8%, $p < 0.001$), though the authors conclude that the increased toxicity is acceptable [69]. The Eastern Cooperative Group (ECOG), on the other hand, recommends withholding BRAF inhibitors one day before and after SRS or three days before and after SRT [70]. In a German multi-center patterns-of-care study, BRAF and VEGF/EGFR inhibitors were never administrated concurrently with SBRT to patients with metastatic disease [71]. Since 59% of the 27 treating facilities withheld targeted agents 1 week before or after SBRT, the authors recommend that BRAF inhibitors be withheld at least 1 week before SBRT.

Does this apparent radiosensitization actually result in improved disease control outcomes? In a retrospective study of 96 patients with 314 MBM treated with SRS, patients receiving immunotherapy or BRAF/MEK inhibitors in addition to SRS had improved freedom from distant intracranial progression, freedom from extracranial progression, and overall survival compared to those receiving conventional chemotherapy before or after SRS [72]. However, local control (in the SRS field) was unchanged. The benefits of immunotherapy and BRAF/MEK inhibitors (and the absence of a local control benefit) persisted on multivariate analysis. This suggests that there may not necessarily be a synergistic benefit to BRAF/MEK inhibitors combined with SRS, but rather that the observed improvement in outcomes was due to the independent effect of the systemic therapy outside of the radiation treatment field.

14.11.2 Immunotherapy and Radiation Therapy

There is even more interest in the potential for combination immunotherapy and radiation ther-

apy in metastatic melanoma, and there are some pre-clinical data, both in melanoma and in other histologies, to suggest that there may be synergy between the two modalities. There are two broad categories of mechanisms for potential synergy between immunotherapy and radiation therapy: [1] immunotherapy may sensitize cancer cells in the radiation field to the radiation therapy; and [2] radiation therapy may activate an immune response and thereby potentiate the effects of immunotherapy on cancer cells outside the radiation treatment field [73].

The latter mechanism describes the abscopal effects, a much lauded, but rarely observed, phenomenon. In 1953, Robin H. Mole first coined the *abscopal effect* term, defining it as "an action at a distance from the irradiated volume but within the same organism" [74]. From case reports to clinical trials, great efforts have been made to describe and understand the abscopal effect. In a well-known case report, Postow et al. described the abscopal effect in a female patient who was 33 years old at the time of melanoma diagnosis [75]. When she experienced recurrent disease 6 years later, she was initially treated with ipilimumab. Then in the following year, while she continued ipilimumab on a maintenance schedule, she experienced the progression of the disease. At this point, radiation was delivered; 10 months later, her right hilar lymphadenopathy and spleen mass regressed even though radiation was targeted to her paraspinal mass. A large single institution retrospective analysis also reported the abscopal effect in 68% of the 47 patient cohort treated with radiation and ipilimumab ($p = 0.006$) [76]. It is believed that immune-mediated changes from both radiation and immunotherapies are working synergistically to elicit the abscopal effect [77]. Ongoing clinical trials seek to better describe this effect in prospective studies. In a single-arm study, SBRT is being tested as a vaccination for extracranial metastatic melanoma. A secondary endpoint for this study is the rate of abscopal effect, and the study hypothesizes the rate to exceed 14% (NCT04042506). In phase I/II combination trial (pembrolizumab + intralesional IL-2 + hypofractionated radiotherapy), treatment efficacy will be determined in part by the abscopal response rate (NCT03474497). More than half a century has passed since the term *abscopal* was first used. While the effect is intriguing, its clinical reality and application remain unproven. Further data is necessary.

Pre-clinical data suggest that an immune response is activated by RT, which could act synergistically to improve clinical outcomes. Animal data suggest that immunotherapy and radiation therapy may act synergistically to improve local control [78]. What about the clinical data? In one retrospective study, Knisely et al. analyzed the outcomes of 77 patients who underwent definitive stereotactic radiosurgery with or without ipilimumab [79]. For the 35% of 77 patients who received ipilimumab with SRS, a substantially higher median survival was achieved compared to those who did not receive ipilimumab (21.3 months vs. 4.9 months), though this was not statistically significant on multivariate analysis, suggesting the finding may have been due to selection bias—a common problem in retrospective studies. Also in the realm of SRS and immunotherapy, some data suggest that immunotherapy may increase the risk of radionecrosis after SRS [80].

In a prospective phase I trial, 22 metastatic melanoma patients tolerated palliative radiotherapy with 4 cycles of ipilimumab [81]. Higher response rates were achieved in the radiotherapy and ipilimumab group when compared to the ipi-

limumab alone group. While the sample size was small, this study was the first prospective trial to support the feasibility of administering both immunotherapy and radiation to metastatic melanoma patients. To test whether radiation could improve anti-PD-1 utility, Maity et al. enrolled melanoma metastasis patients who had progressed with prior PD-1 or PD-L1 therapy [82]. Hypofractionated radiation (8 Gy × 3 fractions or 17 Gy × 1 fraction) with 6 cycles of anti-PD-1 (pembrolizumab) was then administered. Interestingly, 2 of the 4 patients with metastatic melanoma exhibited lasting partial response and overall survival greater than 20 months. This finding suggests that a subset of melanoma metastases patients could experience benefits from radiation synergistically working to improve immune response from PD-1 therapy, even after evidence of prior progression.

In one very intriguing retrospective study by Klemen et al., 52 patients with metastatic melanoma with oligoprogression in 1–3 sites while on immune checkpoint inhibitors received local therapy (surgery, SBRT, or ablation), which resulted in a 3-year progression-free survival of 31% and 5-year disease-specific survival of 60% [83]. They further stratified the cohort based on whether oligoprogression on checkpoint inhibitors was in pre-existing lesions or in new metastatic sites. Those with progression in pre-existing metastases had 3-year progression-free survival of 70% and 5-year disease-specific survival of 93% after local therapy for oligoprogression, whereas those with new metastases on checkpoint inhibitors had 3-year progression-free survival of 6% and 5-year disease-specific survival of 31% after local therapy for oligoprogression. Therefore, patients with oligoprogression in existing sites of disease on immunotherapy may be more appropriate candidates for SBRT and other local therapies than those with progression to new sites of disease on immunotherapy.

Combining immunotherapy and radiation therapy is relatively common now, but not for synergistic benefit. If a patient has an indication for palliative RT, SRS/SRT, or SBRT and is already on immunotherapy, we would typically not hold immunotherapy during radiation. Whether there is synergistic benefit is yet unproven.

14.11.3 Ongoing Trials

Prospective clinical data supporting the role of RT in the setting of immunotherapy specific to metastatic melanoma are lacking. Thus, it is important to note how ongoing clinical trials for radiation in metastatic melanoma tailor the growing interest to elucidate safe and efficacious combination therapies (Table 14.3). The University of Michigan Rogel Cancer Center is investigating how immunotherapy induction (2 doses of ipilimumab) may affect the efficacy of SRS and ipilimumab treatment for MBM patients (NCT02097732). Another ongoing study is evaluating the effects of SRS with PD-1 therapy and includes metastases with melanoma histology. This three-arm phase I study will test the efficacy of three SRS treatment schedules administered in conjunction with pembrolizumab (NCT02858869). For a complete list of clinical trials, visit http://clinicaltrials.gov/.

Table 14.1 Important studies on radiation therapy in the treatment of melanoma brain metastases

Institution/ Author/Year/ PMID	Study type	Total patient # (# with melanoma)	# of brain metastases	Median follow-up	Standard Arm vs. experimental Arm	Outcome(s)
Steroids ± WBRT						
Eastern Cooperative Oncology Group [10] Horton et al. 1971 PMID: 5541678	Randomized controlled	48 (not specified)	–	–	Arm 1: Prednisone 40 mg QD × 4 weeks, then 30 mg QD until disease progression vs. Arm 2: Prednisone 40 mg QD + whole brain RT	Clinical "remission" prednisone 63% vs. prednisone + RT 61%; duration of remission 5 weeks vs. 11 weeks (wide range) Median overall survival (OS): 10 weeks vs. 14 weeks
Outcomes of WBRT for melanoma						
New York University [84] Ziegler et al. 1986 PMID: 3759534	Single institution retrospective	72 (all)	Single or multiple (did not specify number of lesions)	–	Conventional fractionation (30 Gy in 10 fractions (52 patients)) Or High dose per fraction (30 Gy in increments of 5 Gy or 6 Gy per fraction, twice weekly)	No difference in outcomes Median survival: 4.5 vs 5.0 months *Toxicity incidence in:* Solitary metastasis: 14 vs 42% Multiple metastasis: 11 vs 27%
Helsinki University (Finland) [85] Isokangas et al. 1996 PMID: 8966226	Single institution retrospective	60 (all)	Single or multiple	–	40 Gy vs. normalized total dose (NTD) at 3 Gy (cutpoint at 30 Gy)	Median survival: 4.1 months Higher dose to tumor area had better survival ($p < 0.0006$) Improved survival in NTD 3 Gy > 30 Gy group vs. NTD 3 Gy ≤ 30 Gy group
Duke University [86] Sampson et al. 1998 PMID: 9420067	Single institution retrospective	702 (all)	Single or multiple	–	30 Gy (range 15–60 Gy) over 10 fractions	Median survival: 4 months Patients with longer survival (3+ years) had surgically treated single metastasis limited to the brain
Daniel den Hoed Cancer Center (Netherlands) [87] Lagerwaard et al. 1998 PMID: 10098435	Single institution retrospective	1292 (208)	Single or multiple	–	Steroids and WBRT (30 Gy in 10 fractions or 20 Gy in 5 fractions)	Median OS: 3.4 months *Survival based on treatment:* Steroids only: 1.3 months Radiotherapy: 3.6 months Neurosurgery followed by radiotherapy: 8.9 months ($p < 0.0001$)

MD Anderson [88] Ellerhorst et al. 2001 PMID: 11163501	Retrospective	87 (all)	Single or multiple	–	WBRT 30 Gy in 10 fractions	Median survival: 19 weeks 2% of all patients and 48% of symptomatic patients discontinue corticosteroid therapy at end of RT Improved survival in those who underwent resection of all brain metastases (45 weeks) and with no extracranial disease (54 weeks)
University of Sydney [89] Fife et al. 2004 PMID: 15051777	Single institution retrospective	686 (all)	Single or multiple	–	Common WBRT schedules: 20 Gy in 5 fractions or 30 Gy in 10 fractions	Median survival: 4.1 months *Survival based on treatment:* Surgery and post-operative radiotherapy: 8.9 months Surgery: 8.7 months Radiotherapy: 3.4 months Supportive care: 2.1 months No significant survival differences between surgery and radiotherapy vs surgery alone ($p = 0.21$). Improved survival with surgical treatment and metastases limited to brain.
University Hospital Schleswig-Holstein (Germany) [90] Rades et al. 2010 PMID: 19733017	Double institution retrospective	51 (all)	Single or multiple	–	30 Gy in 10 fractions vs higher doses (40 Gy in 20 fractions or 45 Gy in 15 fractions)	Improved overall survival with higher WBRT doses ($p = 0.010$), fewer than 4 brain metastases ($p = 0.012$), no extracerebral metastases ($p = 0.006$), and RPA class 1 ($p = 0.005$). Better intracranial control with higher WBRT doses and fewer than 4 brain metastases.
WBRT ± surgery						
University of Kentucky [12] Patchell et al. 1990[a] PMID: 2405271	Single institution Prospective Randomized	48 (3)	Single	Surgery group: 40 weeks Radiation group: 15 weeks	Arm 1: Surgery + WBRT (36 Gy in 12 fractions) Arm 2: WBRT only (36 Gy in 12 fractions)	Median OS: 40 vs. 15 weeks ($p = 0.01$) Median duration of functional independence: 38 vs. 8 weeks ($p = 0.005$)

(continued)

Table 14.1 (continued)

Institution/ Author/Year/ PMID	Study type	Total Patient # (# with melanoma)	# of brain metastases	Median follow-up	Standard Arm vs. experimental Arm	Outcome(s)
Daniel den Hoed Cancer Center (Netherlands) [13] Vecht et al. 1993 PMID: 8498838 University Hospital Leiden (Netherlands) [91] Noordijk et al. 1994 PMID: 8040016	Multi-center Prospective Randomized	63 (not specified)	Single	–	Arm 1: Surgery + WBRT (40/20 BID) Arms 2: WBRT alone (40/20 BID)	Median OS: 12 vs. 7 months ($p = 0.04$) Functional independence: 9 vs. 4 months ($p = 0.06$) Longer survival and functional independence for single brain metastasis treated with WBRT and surgery vs WBRT alone.
McMaster University (Canada) [14] Mintz et al. 1996 PMID: 8839553	Multi-center Prospective Randomized	84 (4) Note: Study included patients with KPS 50 or greater	Single	–	Arm 1: WBRT (30 Gy in 10 fractions) Arm 2: Surgery + WBRT (30 Gy in 10 fractions)	Median survival: 6.3 vs. 5.6 months ($p = 0.24$) No benefit from adding surgery to WBRT for patients with single brain metastasis
Surgery ± WBRT						
University of Kentucky [15] Patchell 1998[b] PMID: 9809728	Multi-center Prospective Randomized	95 (2)	Single	43–48 weeks	Arm 1: Surgery + post-operative WBRT (50.4 Gy over 5.5 weeks) Arm 2: Surgery only	Intracranial recurrence: 18% vs. 70% ($p < 0.001$) Neurologic death: 14% vs. 44% ($p = 0.003$) Lower intracranial recurrence and neurological death in WBRT arm. No difference in overall survival
WBRT ± SRS						
University of Pittsburgh [17] Kondziolka et al. 1999 PMID: 10487566	Single institution Prospective Randomized	27 (5)	2–4	–	Arm 1: WBRT (30 Gy in 12 fractions) Arm 2: WBRT + SRS boost	Median OS: 7.5 vs. 11 months ($p = 0.22$) 1 year local failure rate: 100% vs. 8% Median time to local failure: 6 vs. 36 months ($p = 0.0005$)

Radiation Therapy Oncology Group (95-08) [16] Andrews et al. 2004 PMID: 15158627	Multi-center Prospective Phase III trial	333 (14)	1–3	–	Arm 1: WBRT Arm 2: WBRT + SRS boost	Overall survival: 4.9 vs. 6.5 ($p = 0.039$) WBRT + SRS improved KPS score for patients with single unresectable brain metastasis
SRS ± WBRT						
Japanese Radiation Oncology Study Group (99-1) [19] Aoyama et al. 2006 PMID 16757720	Multi-center Prospective Randomized	132 (not specified)	1–4	7.8 months	Arm 1: WBRT + SRS Arm 2: SRS alone	Overall survival: 7.5 vs. 8 months ($p = 0.42$) Locoregional control at 12 months: 88.7% vs. 72.5% ($p = 0.002$)
MD Anderson [18] Chang et al. 2009 PMID 19801201	Single institution Prospective Randomized	58 (7)	1–3	9.5 months	Arm 1: SRS alone Arm 2: SRS + WBRT	Neurocognitive decline at 4 months: 24% vs. 52% Study was stopped prematurely due to detrimental neurocognitive effects in SRS + WBRT group
Surgery or SRS ± WBRT						
European Platform of Cancer Research [21] Kocher et al. 2011 PMID: 21041710	Multi-center Prospective Phase III trial	359 (18)	1–3	–	Arm 1: WBRT after surgery and/or SRS Arm 2: Observation after surgery and/or SRS	Overall survival: 10.9 vs 10.7 months ($p = 0.86$) Intracranial progression: 48 vs 78 months ($p = 0.001$)
Melanoma Institute of Australia ANZMTG [92] Fogarty et al. (interim analysis) 2015 PMID: 25952979 Hong et al. 2019 PMID: 31553661	Multicenter, prospective, open-label, phase III Randomized	215 (all)	1 or 2–3	48.1 months	Arm 1: Observation Arm 2: WBRT after surgery and/or SRS	Local failure: 33.6 vs. 20.0 ($p = 0.03$) Distant intracranial failure at 12 months: 50.5 vs. 42.0 ($p = 0.22$) Overall survival: 13 vs. 16.5 ($p = 0.86$)

(continued)

Table 14.1 (continued)

Institution/ Author/Year/ PMID	Study type	Total Patient # (# with melanoma)	# of brain metastases	Median follow-up	Standard Arm vs. experimental Arm	Outcome(s)
Surgery ± SRS to the surgical cavity						
MD Anderson Cancer Center [24] Mahajan et al. 2017 PMID: 28687375	Single tertiary institution Prospective Randomized	132 patients, 128 eligible for analysis [42]	1–3	11.1 months	Arm 1: Surgery + SRS Arm 2: Observation after surgery alone	12-month local tumor recurrence-free rate: 72% vs. 43% ($p = 0.015$) Overall survival: 17 vs. 18 months ($p = 0.24$) Patients with smaller tumors (0–2.5 cm) achieved lower local tumor-free recurrence rates
Multicenter 48 institutions, USA [25] Brown et al. 2017 PMID: 28687377	Multicenter, prospective Phase III Randomized	194 (not specified) Note: 21 patients categorized with radioresistant tumors defined as sarcoma, melanoma, or renal cell carcinoma)	1 or 2–4	11.1 months	Arm 1: Surgery + SRS (12–20 Gy in single fraction) Arm 2: Surgery +WBRT (30 Gy in 10 fractions or 37.5 Gy in 15 daily fractions of 2.5 Gy)	Cognitive-deterioration-free survival: 3.7 vs. 3 months ($p < 0.0001$) Overall survival: 12.2 vs. 11.6 months ($p = 0.70$)
Japan Clinical Oncology Group (JCOG) [26] Kayama et al. 2018 PMID: 29924704	Multi-center Prospective phase III Non-inferiority, randomized	271 (not specified)	1–4	–	Arm 1: Surgery + WBRT 37.5Gy in 15 fractions Arms 2: Surgery + SRS	Median survival: 15.6 months both arms Intracranial progression-free survival: 10.4 vs. 4.0 months KPS similar both arms Grade 2 to 4 cognitive dysfunction incidence: 16.4% vs 7.7%

Table 14.2 Studies on stereotactic body radiation therapy for extracranial metastatic melanoma

Author (Year)	Institution	Study design	Patient # (and # with Melanoma)	Site treated	Dosing regimens[a]	Local control and pain	Additional outcomes
Gerszten et al. [58] 2007 PMID: 17224814	University of Pittsburgh Medical Center	Single institution prospective cohort	500 (38)	Spine	Maximum intratumoral dose: 12.5 to 25 Gy (mean 20) in 1 fraction	90% Long-term radiographic tumor control (75% for melanoma pts) 86% long-term pain improvement (96% for melanoma pts)	21 months median follow-up
Amdur et al. [93] 2009 PMID: 19528790	University of Florida	Single institution prospective phase II	25 (not specified)	Spine	15 Gy in 1 fraction	95% local control 43% pain relief	5% 1-year progression-free survival 40% 1-year overall survival 12% vertebral compression fractures on imaging
Stinauer et al. [61] 2011 PMID: 21477295	University of Colorado Denver	Single institution retrospective	35 (17)	Lung Liver Bone	40–50 Gy in 5 fractions 42–60 Gy in 3 fractions	88% local control at 18 months	48 Gy in 3 fractions would result in >90% 2-year local control based on results and modeling 24.3 months median overall survival all patients Median overall survival not reached for those with oligometastatic disease
Garg et al. [94] 2012 PMID: 22511344	M. D. Anderson Cancer Center	Single institution prospective phase I/II	61 (not specified)	Spine	16–24 Gy in 1 fraction	88% 18-month local control	64% 18-month overall survival 21% vertebral fracture on imaging

(continued)

Table 14.2 (continued)

Author (Year)	Institution	Study design	Patient # (and # with Melanoma)	Site treated	Dosing regimens[a]	Local control and pain	Additional outcomes
Wang et al. [95] 2012 PMID: 22285199	M. D. Anderson Cancer Center	Single institution prospective phase I/II	149 (4)	Spine	27–30 Gy in 3 fractions	72% 2-year freedom from radiographic progression "No bone pain" increased from 26% pre-SBRT to 54% 6 months post-SBRT	72% 1-year overall survival; 49% 2-year overall survival
Patel et al. [96] 2014 PMID: 29296393	Duke University Medical Center	Single institution retrospective	83 (5) [a]52 patients with spine metastases	[a]Spine Lung Liver Other	[a]Primary spine SBRT: 1–5 fractions (median 1 fractions), mean dose 18.5 Gy [a]Salvage spine SBRT: 1–5 fractions (median 3 fractions), mean dose 18.9 Gy	83% local control at 12 months 88% symptomatic improvement	50% 1-year overall survival
Youland et al. [66] 2017 PMID: 29594220	Mayo Clinic	Single institution retrospective comparing conventional radiotherapy to SBRT	75 (all)	MSK[b] Spine Lung Abdomen Liver Other	Conventional radiation: 8–50 Gy in 1–20 fractions (median 30 Gy)	69% 1-year local control 29% 1-year regional progression	89% 1-year distant progression 7 months median overall survival
					SBRT: 18–60 Gy in 1–5 fractions (median 50 Gy)	95% 1-year local control ($p < 0.01$) 5% 1-year regional progression ($p < 0.01$)	75% 1-year distant progression ($p < 0.01$) 23 months median overall survival ($p < 0.01$)
Youland et al. [97] 2017 PMID: 28740933	Mayo Clinic	Single institution retrospective study assessing PET response with pre- and post-SBRT	48 (all) (59% received immunotherapy)	MSK[b] Spine Lung Abdomen Liver Other	24 Gy in 1 fraction 54 Gy in 3 fractions 60 Gy in 3 fractions 50 Gy in 5 fractions 60 Gy in 5 fractions	90% PET complete response at median 2.8 months from SBRT 94% 1-year local control 90% 3-year local control	74% 1-year overall survival 27% 3-year overall survival >24 Gy associated with improved local control (93% vs 75%, $p < 0.01$)

Franceschini et al. [98] 2017 PMID: 28707533	Humanitas Clinical and Research Center (Rozzano-Milan, Italy)	Single institution retrospective	31 (all)	Lung Liver Nodal	Varied by site, number, and volume of lesions, and proximity to organs at risk	97% 1-year local control 83% 2-year local control	41% 1-year overall survival 18.5% 1-year progression-free survival
Scorsetti et al. [99] 2018 PMID: 30477560	Humanitas Clinical and Research Center (Rozzano-Milan, Italy)	Single institution, phase II trial of SBRT for unresectable liver metastases	61 (2)	Liver	75 Gy in 3 fractions (to 82% of treated lesions)	94% 1-year local control 78% 5-year local control	85% 1-year overall survival 18% 5-year overall survival
Palma et al. [67] 2019 PMID: 30982687	Multi-institutional	Randomize open-label, phase II study of standard palliative therapy vs. SBRT for 1–5 metastases (patients had to have controlled primary)	99 (not specified)	Lung Bone Liver Adrenal Other	Control group	4.5% of the 66 patients in the SBRT group experienced treatment-related deaths	28 months median overall survival
					SBRT group		44 months median overall survival ($p = 0.09$; not powered for 0.05 level of significance)

[a]Mean dose, unless otherwise specified
[b]MSK: musculoskeletal
[c]SFED = single-fraction equivalent dose

Table 14.3 List of select ongoing clinical trials for metastatic melanoma

Institution *Clinical Trials ID*	Patient population	Study details	Anticipated completion
Melanoma and Skin Cancer Trials Limited *NCT02392871*	Patients with unresectable or metastatic BRAF positive melanoma[a]	Single-arm, open-label study, phase I/II trial evaluating toxicity and efficacy of combination therapy: Dabrafenib and trametinib plus palliative radiotherapy	November 2020
Abramson Cancer Center of the University of Pennsylvania *NCT02639026*	Patients with metastatic melanoma, lung, breast, and pancreatic cancer (did not exclude MBM)	Phase I trial to determine best hypofractionated radiotherapy dosing regimen in combination therapy: Durvalumab + tremelimumab + one of two dosing regimens: 1. 8 Gy × 3 fractions 2. 17 Gy × 1 fraction	December 2020
University of Michigan Rogel Cancer Center *NCT02097732*	Patients with MBM	Phase II randomized trial evaluating SRS + ipilimumab with or without ipilimumab induction	January 2021
M.D. Anderson Cancer Center *NCT01644591*	Patients with 3+ MBM lesions	Phase II trial investigating efficacy of SRS to 3+ brain lesions as measured by local control and level of neurocognitive function	June 2021
Canadian Cancer Trials Group[b] *NCT02974803*	Patients with BRAF positive MBM (1–10 lesions)	Phase II trial evaluating efficacy of dabrafenib and trametinib + SRS to manage patients with 1–4 or 5–10 brain lesions	June 2021
Emory University[c] *NCT02858869*	Patients with melanoma or NSCLC brain metastasis	Phase I pilot trial testing pembrolizumab + one of three SRS dosing regimens: 1. 6 Gy × 5 fractions 2. 9 Gy × 3 fractions 3. 18–21 Gy × 1 fraction	October 2021
Melanoma and Skin Cancer Trials Limited[e] *NCT01503827*	Patients who received local treatment for MBM	Phase III randomized trial, measuring efficacy of adjuvant WBRT on MBM patients after surgery or SRS	June 2022
Abramson Cancer Center of the University of Pennsylvania *NCT03646617*	Patients with metastatic melanoma[a]	Phase II randomized trial comparing: Ipilumumab and nivolumab alone vs. Ipilumumab and nivolumab with hypofractionated radiotherapy (8 Gy × 3 fractions)	February 2023
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins[d] *NCT02716948*	Patients with untreated MBM or melanoma metastases to the spine	Phase 1 pilot trial testing safety and efficacy of nivolumab with SRS	March 2023
Melanoma Institute Australia[f] *NCT03340129*	Patients with asymptomatic and untreated MBM	Phase II, open-label, randomized trial, comparing: Ipilimumab and nivolumab alone vs. Ipilimumab and nivolumab + SRS (16–22 Gy × 1 fraction) or SRT (24–30 Gy hypofractionated) for larger lesions	August 2025
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins[f] *NCT04042506*	Patients with metastatic melanoma[a]	Single-arm, phase II study, measuring efficacy of SBRT (8–10 Gy × 3 fractions) to a single extracranial metastatic site to overcome resistance to nivolumab	April 2028

Trial Description by NCT number may be found on https://clinicaltrials.gov/

[a]Study excludes patients with brain metastases, or, in the case of NCT03646617, the study excludes patients with leptomeningeal disease or brain metastases requiring urgent intervention

[b]Collaborator: Novartis

[c]Collaborator: Merck Sharp and Dohme Corp

[d]Collaborator: Accuray Incorporated

[e]Collaborator: Trans-Tasman Radiation Oncology Group (TROG) and University of Oxford

[f]Collaborator: Bristol-Myers Squibb

14.12 Conclusion

RT plays an important role in metastatic melanoma. Its role in the setting of immunotherapy continues to evolve, but at its core, RT continues to function as an important palliative therapy modality, and as an ablative therapy in patients with limited oligometastatic disease. With the growing attention on combination therapies, it is evident that management for each patient case will increasingly require collaboration across multiple disciplines.

Appendix

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Part VI

Melanoma Management: Future of Melanoma Management

Novel Therapies in Melanoma

15

Bilal Fawaz, Debjani Sahni, and Adam Lerner

15.1 Introduction

The treatment of unresectable or metastatic melanoma was revolutionized by the advent of immunotherapy and targeted inhibitors of the Mitogen Activated Protein Kinase (MAPK) pathway. However, a high rate of resistance to the BRAF/MEK inhibitor combination has resulted in limited long-term benefit in the majority of patients receiving targeted therapy [1]. Additionally, while immunotherapy has unequivocally improved the outcome of advanced melanoma patients, overall survival at 5 years in patients treated with combined ipilimumab and nivolumab was 52%, leaving considerable room for improvement [1, 2]. Clinical trials are now focused on new therapeutics that may augment the effect of immune checkpoint and targeted inhibitors, with the ultimate goal of achieving more durable responses in a greater number of patients. This chapter aims to touch on some of the approaches that are currently being pursued to accomplish this goal.

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15.1.1 Updates on the Targeted Therapy Approach

15.1.2 Novel Combinations of Therapies

Early attempts to combine BRAF inhibitors with immunotherapy were hindered by dose-limiting toxicities and limited efficacy [3–5]. The combination of vemurafenib (BRAF inhibitor) and ipilimumab (CTLA-4 inhibitor) led to dose-limiting hepatotoxicity, necessitating trial discontinuation [3]. The inclusion of MEK inhibitors in the combination was better tolerated and appeared to potentiate anti-tumoral activity. Therefore, triple combination therapy with BRAF/MEK inhibitors and anti-PD-1 therapy has garnered considerable attention recently [4, 5]. A phase I study of 15 patients receiving dabrafenib (BRAF inhibitor), trametinib (MEK inhibitor), and pembrolizumab (PD-1 inhibitor) demonstrated an objective response rate of 73%, with 40% of patients having continued response after a median of 27 months [4]. However, 14/15 patients experienced toxicities necessitating dose modifications, and 10/15 patients experienced grade 3–4 adverse events (AEs), most notably transaminitis and pyrexia [4].

A phase II randomized trial comparing dabrafenib, trametinib, and pembrolizumab (triplet therapy) to placebo (doublet therapy: dabrafenib/

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trametinib) resulted in a numerically significant prolongation of progression-free survival (PFS; 16.0 vs. 10.3 months, $p = 0.043$) [5]. However, given the small sample size, the study did not reach its primary statistical end point. Interestingly, the overall response rate (ORR) was higher in the placebo vs. the experimental group (72% vs. 63%). Additionally, grade 3–5 AEs occurred in a greater proportion in the triplet group compared to doublet arm (70% vs. 45%, respectively), including one death in the triplet arm due to pneumonitis [5].

Following the results of a recent phase III randomized controlled trial (RCT), the triplet combination of vemurafenib, cobimetinib (MEK inhibitor) and atezolizumab (PD-L1 inhibitor) has been approved for unresectable, advanced melanoma that is BRAF-mutant. This is discussed in more detail in the "Systemic Therapy in Melanoma" chapter. Another similar phase III trial is currently underway evaluating dabrafenib plus trametinib with and without a novel PD-1 inhibitor (Spartalizumab, PDR001) for metastatic BRAF-mutant melanoma (NCT02967692) [6]. The early phase data from this combination demonstrated a CRR of 42% and an ORR of 75% [6]. Seventy-eight percent of patients experienced grade 3 or higher AEs, with 17% resulting in treatment discontinuation. Common AEs included pyrexia, chills, and fatigue [6].

The main criticism of the aforementioned triplet studies revolves around the choice of the control group. The trials do not address whether triplet therapy provides clinical benefit over immunotherapy alone (i.e., PD-1/CTLA-4 inhibitor combination or anti-PD-1 monotherapy). As addressed in the prior chapter, given its greater likelihood of durable effects, checkpoint inhibitor therapy is usually considered the preferred initial treatment choice in metastatic melanoma. This important question of whether combined BRAF/MEK and checkpoint inhibitor therapy is superior to checkpoint inhibition alone, unfortunately, remains unanswered. It is notable that triplet therapy has significant, high-grade toxicities, and more studies are warranted to determine whether the addition of BRAF/MEK inhibitors to immunotherapy yields further clinical benefit.

15.1.3 NRAS-Targeted Therapies

Identification of driver mutations within overactive signaling pathways is crucial to the development of targeted therapies. The three RAS genes (KRAS, HRAS, and NRAS) are known to be involved in a wide array of malignancies, with NRAS mutations being the second most common mutation in melanoma after BRAF, occurring in approximately 20–30% of all melanomas [7]. While some have argued that the presence of NRAS mutations in T2b primary melanomas portends a more aggressive clinical course, the prognostic significance of an NRAS mutation in stage 4 disease is controversial [8–11]. Some authors believe that NRAS mutated stage 4 melanomas have a particularly high response rate to checkpoint inhibitor therapy [12]. While targeting the downstream effectors of RAS, BRAF, and MEK, dramatically improved melanoma outcomes, the development of NRAS-selective inhibitors has thus far been unsuccessful [7, 13].

Early attempts to target the RAS pathway by farnesyltransferase inhibitors (FTI) demonstrated no efficacy in clinical trials, despite promising preclinical studies [13]. Farnesyltransferase plays a critical role in the posttranslational modification of RAS, allowing its activation and membrane translocation. FTIs target this key regulatory step, inhibiting RAS' ability to mediate the stimulation of downstream effectors [13]. NRAS bypassed FTI inhibition effectively by utilizing substrates within a related group of enzymes. The lack of success of FTI inhibitors in clinical practice has unfortunately dissuaded the aggressive pursuit of other RAS-specific inhibitors for some time [1, 7, 13].

The difficulty of targeting RAS molecules has been attributed in part to the high affinity of GTP binding to RAS proteins, as well as the lack of deep hydrophobic pockets that allow tight binding of small molecules [7]. Nonetheless, recent progress has been made in targeting KRAS

G12C in patients with non-small cell lung cancer. Studies of the FDA-approved drug sotorasib have provided "proof of principle" that inhibition of RAS family members can in fact lead to important clinical responses (32% response rate) in tumors addicted to this oncogene [14]. The critical insight in this work was that the novel cysteine residue present in the G12C mutant KRAS molecule could serve as a reactive site for a drug that binds covalently at this site, thereby inhibiting KRAS by altering its conformation and ability to activate downstream effector molecules. Of some note, while certainly not the most common type of NRAS mutation, both G12C and G13C mutations have been reported in cutaneous melanomas, raising the possibility that this novel class of cysteine-targeted Ras oncogene-directed therapy may someday prove useful in a subset of patients with NRAS mutated melanomas as well [15].

As an alternate approach, a serine-threonine kinase (STK19) has been identified as a novel NRAS activator and a potential target in the treatment of NRAS-mutant melanoma [16]. In genetically engineered human melanocytes, STK19 was shown to activate NRAS via the MEK-ERK and PI3K-Akt pathways, contributing to its oncogenic potential [16]. Following STK19 inhibition in vitro and in vivo, NRAS-driven malignant transformation and melanoma growth were substantially inhibited [16]. The study offers preclinical proof of concept regarding the targeting of STK19 in melanomas with NRAS melanoma [16]. Validation of these results in clinical trials is the next step.

15.1.4 BET Inhibitors

In the first weeks of BRAF/MEK inhibitor therapy, the remaining tumor population undergoes an epigenetic-mediated change, resulting in increased expression of transcription factors and upregulation of various receptor tyrosine kinases (RTKs) critical to their survival [17, 18]. RTKs stimulate the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathway, thereby bypassing BRAF/MEK inhibition [17]. Epigenetic regulators, such as the Bromodomain and Extraterminal Domain (BET) proteins BRD2, BRD3, and BRD4, were found to regulate cellular proliferation, and their inhibition reduced expression of RTKs, leading to decreased tumor cell survival [18]. In preclinical studies, NRAS-mutant melanomas, in particular, were found to be dependent on overexpression of BET proteins for survival, particularly BRD2/4 [18].

The addition of BET inhibitors (BETi) to BRAF/MEK inhibitors was also shown to offset treatment resistance and prolong survival in preclinical melanoma studies [18]. Unfortunately, early phase clinical studies have so far revealed the limited clinical benefit of BETi as monotherapy in patients with advanced solid tumors [19]. In one trial, no partial or complete responses were noted, and AEs were common (89% patients) [19]. Grade 3 or higher AEs were reported in 54% of patients, and 26% required dose discontinuation, most commonly due to thrombocytopenia, nausea, and fatigue [19]. The authors concluded that BETi is safe at doses up to 2 mg/kg but admitted that the clinical efficacy was limited with a narrow therapeutic window [19].

One important caveat of the BETi clinical trials described above is that the BETi used thus far do not have significant isoform specificity, yet each of the BET isoforms has important and non-redundant functions in human physiology [20]. There is thus concern that BET inhibition may be prematurely dismissed as an attractive approach to the treatment of human malignancies such as melanoma due to off-target effects of relatively non-isoform specific agents. Once more selective BET inhibitors are developed, their activity in melanoma will need to be re-examined, and such studies are eagerly awaited.

15.1.5 CDK4/6 Inhibitors

The cyclin-dependent kinases, CDK4 and CDK6, regulate progression through the G1 phase of the cell cycle. When activated, CDK4/6 hyperphosphorylates retinoblastoma (Rb) protein, releasing it from the E2F transcription fac-

tor, thereby enabling cell cycle progression [21]. CDK4/6 activating mutations are frequently present in various malignancies, including melanoma, and inhibition of these mutant hyperactive kinases impedes the release of E2F, resulting in cell cycle arrest. CDK4/6 inhibitors such as ribociclib have emerged as an effective new class of anticancer drugs when combined with other agents that target the G0/G1 transition such as anti-estrogens in hormone receptor-positive breast cancer [21–24].

After preclinical studies demonstrated improved antitumoral activity, several early phase trials in melanoma have reported positive findings [23, 24]. A phase IB/II multicenter study recently evaluated the CDK4/6 inhibitor ribociclib in combination with the MEK inhibitor binimetinib for the treatment of 16 patients with NRAS-mutant melanoma [23]. Four patients (25%) developed a partial response, and seven patients (44%) had stable disease. Common grade 3–4 AEs included transaminitis (6–19%), nausea (19%), rash, and neutropenia [23]. A phase II trial is currently underway to further assess the antitumor activity of this combination [23].

Another phase Ib/II trial compared triple combination therapy with ribociclib, encorafenib (a BRAF inhibitor), and binimetinib to BRAF/MEK inhibition alone in patients with advanced BRAF-mutant melanoma [24]. The ORR was 52.4% (4 CR; 18 PR; 15 SD), and the median PFS was 9.0 months [24]. Ten patients (23.8%) discontinued treatment due to AEs, most commonly transaminitis in four patients. Other AEs included neutropenia and anemia [24]. The authors concluded that CDK4/6 inhibition is overall well-tolerated and may improve clinical response rates when used in combination with BRAF/MEK inhibitors [24].

15.1.6 ERK Inhibitors

Extracellular signal-regulated kinase (ERK) has been shown to play a pivotal role in acquired resistance to BRAF/MEK inhibitors [25]. The intracellular protein is the most distal kinase of the MAPK pathway, and its stimulation enables reactivation of the signaling pathway, resulting in continued gene expression and treatment evasion [25]. As a result, ERK inhibitors were developed as a potential strategy to overcome the high rates of resistance to targeted therapy, and they have demonstrated favorable results in early studies [25, 26].

Ulixertinib, a selective ERK1/2 inhibitor, was found to inhibit tumor growth in human xenograft models that were resistant to BRAF and MEK inhibitors [25]. The first-in-class phase I study evaluated ulixertinib in 135 patients with advanced solid tumors, including 53 with melanoma [26]. Out of 17 evaluable patients with NRAS-mutant melanoma, 3 (18%) achieved a PR, 6 had SD, and 8 had progressive disease (PD). In BRAF/MEK inhibitor-refractory BRAF-mutant melanoma, 3/19 patients (15%) had a PR [26]. Treatment discontinuation due to AEs were noted in 19% of patients. Acneiform eruptions, diarrhea, and fatigue were the most common AEs, and no patients experienced a grade 4 or 5 treatment-related AE [26]. The authors concluded that ulixertinib was safe and effective in the treatment of NRAS- and BRAF-mutant solid tumor malignancies. They recommended further evaluation of ERK inhibitors both as a single agent and in combination therapies [26].

15.1.7 KIT Inhibitors (Imatinib, Sunitinib, Dasatinib, Nilotinib)

Mutations in KIT, a transmembrane receptor tyrosine kinase (RTK), have been detected in numerous melanoma subtypes, most notably acral, mucosal, and chronically sun-damaged skin melanoma [27]. Aberrations in KIT result in constitutive activation of several pathways, including MAPK, PI3K/AKT, and the Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathway, thereby promoting melanocytic oncogenesis [27]. Imatinib

has received the most attention in its class for the treatment of KIT-mutant melanoma, as discussed in the previous chapter "Systemic Therapies in Melanoma." However, various other KIT inhibitors are also being evaluated in this setting, with mixed results thus far [28–30].

Sunitinib was the first to be studied in ten evaluable patients with KIT aberrations [28]. One patient achieved a CR, three achieved PRs, and one SD [28]. The authors did note that KIT mutations were only present in 4/10 patients, whereas the rest had KIT amplification or overexpression. Among the four patients with KIT mutations, one achieved a CR and three achieved a PR, indicating that sunitinib may be efficacious in KIT-mutant melanomas [28]. The medication was not well-tolerated, however, as five patients required a dose reduction, and one patient required therapy discontinuation due to new-onset congestive heart failure [28].

Dasatinib has been investigated in advanced mucosal, acral, or vulvovaginal melanomas [29]. The medication demonstrated a low response rate (18%), with a median OS of 7.5 months, PFS of 2.1 months, and no CRs. Forty-four percent of patients experienced grade 3 AEs, including myocardial infarction in two patients and pleural effusions in four patients. Dasatinib was discontinued in 12% of patients due to AEs [29].

Lastly, nilotinib was investigated in a phase II study of 42 patients with KIT-mutated melanoma [30]. 400 mg twice daily was used, and the primary endpoint of ORR was 26.2% ($n = 11/42$; all 11 cases achieved PRs). Twenty patients had SD (47.6%) and ten patients had PD (23.8%). The median PFS was 4.2, and OSS was 18 months [30].

Overall, KIT inhibitors as a class achieved moderate clinical efficacy, and they should be considered for the treatment of KIT-mutant melanomas in the appropriate clinical setting. Clinicians and patients should be aware of the significant rate of high-grade AEs however, and close clinical monitoring of patients is recommended to identify and address any serious AEs that may arise while on treatment.

15.1.8 Angiogenesis Inhibitors

One promising strategy to enhance immune responses to cancers is to combine immune checkpoint inhibitors with inhibitors of angiogenesis [31]. Vascular endothelial growth factor (VEGF-A) has been shown to play a key role in promoting malignant cell growth and immunosuppression. Specifically, VEGF augments tumor angiogenesis and inhibits dendritic cell function and lymphocyte migration into the tumor microenvironment [32]. Levels of this growth factor have also been found to predict outcomes to ipilimumab therapy, with high VEGF levels correlating with less favorable outcomes [32]. VEGF inhibitors, such as bevacizumab, levatinib, and axitinib, were therefore developed to mitigate the tumor-promoting activities of VEGF [32–34].

A phase I study in metastatic melanoma patients combining bevacizumab and ipilimumab demonstrated an overall disease control rate (DCR) of 67.8% (8/46 PRs and 22/46 SDs) [32]. 13 patients experienced high-grade AEs, including giant cell arteritis, palpable purpura, and eosinophilic hepatitis. No treatment-related deaths were reported [32]. Tyrosine kinase inhibitors with various anti-angiogenic activities are also undergoing early phase studies for melanoma. Levatinib and axitinib both inhibit VEGF, in addition to various other receptors, such as KIT, platelet-derived growth factor (PDGF) and fibroblast growth factor receptor (FGFR1–4) [33, 34]. Levatinib demonstrated an overall DCR of 40.3%, with 5/29 patients experiencing PR [33]. The most common AEs were dose-limiting hypertension, fatigue, and proteinuria. Axitinib in combination with PD-1 inhibitor toripalimab achieved a 48.3% ORR with a median PFS of 7.5 months [34]. Grade 3 or greater AEs occurred in 39.4% of patients, including diarrhea, proteinuria, hand-foot syndrome, and fatigue [34].

The authors believe the aforementioned studies provide enough evidence to support further investigation of VEGF inhibitors in the treatment of melanoma, especially in combination with

immune checkpoint blockade [32–34]. RCTs are currently underway to confirm the clinical efficacy noted in early phase studies.

15.2 Novel Immune Therapy

15.2.1 Indoleamine 2,3-Dioxygenase 1 (IDO1) Inhibitors

The impressive efficacy of anti-PD-1 and anti-CTLA-4 therapies has led to efforts to discover other immune-based therapies. Indoleamine 2,3 dioxygenase (IDO) is an intracellular enzyme that converts tryptophan to its metabolites, depleting local stores of tryptophan [35]. Decreased tryptophan induces T-cell apoptosis and cell cycle arrest, leading to local immunosuppression in the tumor microenvironment [35]. As a result, IDO inhibitors, such as epacadostat, were developed to potentially circumvent this method of immunosuppression [36, 37].

After promising preclinical studies, clinical trials have yielded mixed results for IDO1 plus PD-1 inhibitor combination therapy [36, 37]. A phase III RCT comparing epacadostat plus pembrolizumab to monotherapy with pembrolizumab demonstrated no significant difference in PFS or OS [36]. The trial was therefore terminated after a median follow-up 12.4 months [36]. The rate of AEs and treatment modification was also similar between both groups, except for hepatitis, which was more frequent in the combination group [36].

Epacadostat was also investigated in combination with nivolumab in 50 patients with advanced melanoma [37]. The ORR was 62% (9 CR, 22 PR) and DCR of 80% (32/40). The rate of grade 3 or more AEs was 48% with 300 mg BID of epacadostat and 13% with 100 mg BID. Pneumonitis was the only grade 3 or higher AE, and no treatment-related deaths were reported [37]. Phase III studies are underway.

A phase I study of epacadostat + ipilimumab demonstrated poor tolerability overall, with five treatment-related deaths, 28% high-grade AE, and a 40% treatment discontinuation rate [38]. 10/39 immunotherapy-naive patients had an objective response rate (3 CR, 7 PR, 15 SD), whereas none of the 11 patients previously treated with immunotherapy experienced an objective response (4 SD, 5 PD, and 2 missing) [38]. Phase II studies were suspended due to the emerging success of PD-1 inhibitors [38].

15.2.2 Histone Deacetylase Inhibitors

A delicate balance of acetylation and/or phosphorylation of histones and other proteins within normal cells is integral to the process of regulating gene transcription. Tumors can exploit this equilibrium resulting in imbalanced gene transcription that favors repression of tumor suppressor genes. Histone deacetylase (HDAC) is known to play a critical role in this process and shows increased expression in many cancers [39]. In accordance with this, inhibitors of HDAC are being developed as potential anticancer therapies [39–42].

Panabinostat is a pan-deacetylase inhibitor that demonstrated promising results in preclinical studies in melanoma patients. Based on this data, the drug was utilized in a phase I trial in unresectable stage III and stage IV melanoma [40]. However, monotherapy with panobinostat did not corroborate the early results and was unable to demonstrate any clinical activity as a single agent in the treatment of metastatic melanoma [40].

A subset of patients in the trial showed increased MHCI staining and CD8+ T-cell tumor infiltration, suggesting a role for the combination of panabinostat with immune checkpoint inhibitors [40]. Subsequently, 17 patients with advanced melanoma were treated with panobinostat and ipilimumab combination, yielding a 12% ORR and 35% SD rate [41]. PFS and OS were 2.2 months and 21.0 months, respectively. 1/6 patients on the 5 mg and 3/9 patients on the 10 mg dose developed a dose-limiting toxicity (hydronephrosis, rash, diarrhea, and thrombocytopenia) [41].

Entinostat is a class I selective HDAC inhibitor. In an early phase trial, 53 patients with advanced melanoma resistant to PD-1 inhibitors

were treated with entinostat in combination with pembrolizumab [42]. The confirmed ORR and DCR were 19% and 32%, respectively, with 1 CR, 9 PRs, and 7 SDs. PFS was 4.2 months, and the median duration of response was 12.5 months. Five patients (9%) experienced grade 3/4 iRAE, including rash, colitis, pneumonitis, and hepatitis [42]. The study showed significant clinical activity with tolerable toxicity of entinostat with pembrolizumab in patients who had previously progressed on immune checkpoint inhibitor therapy, demonstrating promising results that need further corroboration in larger trials.

15.2.3 Other

A variety of other immunomodulatory agents have been identified as potential drug therapies that may enhance the efficacy of checkpoint inhibition. Factors associated with a reduced response to ICI include low tumor PD-L1 expression, low tumor-infiltrating lymphocytes (TILs) and a tumor microenvironment that does not favor T-cell activation [43–45]. Thus, agents that can stimulate T-cells and circumvent T-cell exhaustion could act synergistically with ICI. Bempegaldesleukin (BEMPEG) is a first-in-class interleukin-2 (IL-2) pro-drug that results in CD8+ T-cell stimulation, increasing TILs and PD-1 expression on CD4+, CD8+ T-cells and NK cells [46]. BEMPEG preferentially targets the CD122/CD132 intermediate-affinity IL-2 receptor over the CD122/CD132/CD25 high-affinity IL-2 receptor and expands effector T-cells over Tregs [46]. In phase I/II studies, 38 patients with treatment-naive metastatic melanoma were treated with BEMPEG and nivolumab combination [47]. A durable response was noted after a median duration of 12.7 months, with a 53% ORR, 34% CR, and 74% DCR [47]. Treatment was generally well-tolerated, although 9.8% of patients necessitated treatment discontinuation due to AEs [47]. This led to the design of a currently underway randomized phase III trial of BEMPEG and nivolumab vs. nivolumab monotherapy [48].

Lymphocyte activation gene-3 (LAG-3) is another immune checkpoint regulator that has garnered attention recently. Similar to PD-1, LAG-3 activation by cancer cells results in T-cell inhibition and immune evasion [49]. An anti-LAG-3 antibody (BMS-986016) combined with nivolumab was investigated in a phase I/IIa study involving 43 patients with advanced melanoma previously resistant to anti-PD-1 therapy [49]. Out of 31 evaluable patients, preliminary data suggests an ORR of 16% and DCR of 45%, with a tolerable side effect profile [49]. The authors concluded that the addition of LAG-3 inhibitor to nivolumab displayed encouraging clinical efficacy and a comparable side effect profile to PD-1 monotherapy [49].

15.2.4 Adoptive Cell Transfer

Adoptive Cell Transfer (ACT) is a specialized oncologic therapy that involves the isolation and expansion of tumor-infiltrating lymphocytes (TILs) in vitro, followed by their re-introduction into the patient to improve antitumor immunity [50]. The addition of high-dose IL-2 to the TIL isolate in vitro yields a 1000-fold expansion of the T-cell population, resulting in potent antitumor activity [50]. Shortcomings in the treatment protocol in earlier studies led to lower objective response rates of ~35%. This was largely attributed to the failure of persistence of the transferred TILs in vivo, leading to therapy modification, most importantly, the inclusion of nonmyeloablative depletion of lymphocytes prior to the reintroduction of TILs [51–53]. Lymphodepletion in the host prior to the transfer of lymphocytes is critical as it depletes regulatory T-cells. It also diminishes other T lymphocytes that would normally compete with the transferred TILs for key regulatory cytokines such as IL-7 and IL-15. Host lymphodepletion is achieved using chemotherapy (cyclophosphamide/fludarabine) with or without total body irradiation (TBI). Following the infusion of the TILs, patients are treated with high-dose IL-2 to improve the survival and expansion of the transfused TILs. These altera-

tions to the protocol have led to improved objective response rates of 38–50% [51–53].

In one of the largest studies to date, 93 patients undergoing ACT with chemotherapeutic lymphodepletion were subdivided into three cohorts: 43 patients only received chemotherapy as their method for lymphodepletion, whereas 25 patients received additional low-dose TBI (2 Gy), and 25 patients received high-dose TBI (12 Gy) [51]. 20/93 patients (22%) achieved CR, and 32/93 patients (34%) achieved a PR [51]. The responses were noted to be durable, as 19 of the patients with CR (95%) remained free of disease beyond 3 years [51]. The overall 3- and 5-year survival was 36% and 29% (100% and 93% for CR; 31% and 21% for PRs, and 7% and 5% for the non-responders, respectively). The majority of patients tolerated the therapy well [51]. However, one treatment-related death was reported, secondary to sepsis. One patient developed chronic pulmonary hypertension, and five patients developed microangiopathic nephropathy [51]. It is also worth noting that patients receiving high-dose TBI had an increased rate of CR, however, given this was a non-randomized study, the authors advised caution on this final point [51].

To further evaluate the effect of TBI on rates of CR and OS, 101 patients with metastatic melanoma were randomized to receive either chemotherapy or chemotherapy plus TBI (12Gy) for their lymphodepleting regimen [52]. This study found no significant difference in outcomes between the two groups, with a CR rate of 24% in both groups and OS rates of 38.2% and 36.6% in the experimental and control group, respectively. The authors attributed the better results of TBI in the previous studies to patient selection bias in a non-randomized study [52]. The responses were similarly durable, as only 1/24 patients with CR recurred after a median follow-up of 40.9 months. The TBI arm had slightly longer neutropenic periods, in addition to the unique complication of thrombotic microangiopathy in 13 patients (27%), resulting in one death [52].

Despite showing significant clinical benefit, ACT is associated with severe grade 3 and 4 toxicities. Some are attributable to the lymphodepleting chemotherapy regimen, while others are related to the use of the post-transfusion high-dose IL-2. A phase II trial involving 12 patients with melanoma utilized a low-dose, subcutaneous IL-2 instead of the standard high-dose intravenous IL-2 to investigate the feasibility and clinical activity of this modified protocol [53]. In contrast to high-dose IL-2, the majority of adverse events were grade 1 and 2 and could be managed outside an ICU setting. The study reported two confirmed PR and one unconfirmed PR, as well as six patients with stable disease. This met the pre-determined criteria of treatment efficacy, however, no patient achieved a CR, and the PRs were not durable. The authors hypothesized the low objective response might be related to the low dose of IL-2 utilized in this study, or the inclusion of non-cutaneous melanomas (3/12 mucosal or ocular), which are known to have a lower response rate to immunotherapy. The study results demonstrated persistence of the transfused TILs for greater than 2 years in one of the patients. Altogether, the study supported the further investigation into modified dosing of IL-2 to enable better tolerability of ACT [53].

ACT is a highly personalized and complex oncological treatment modality. While this may contribute to its efficacy, the attributes will make it difficult to be readily applied in current oncological practice. The treatment requires specialized personnel and equipment that is labor-intensive, making it difficult to mass produce, commercialize, and administer. At present, this treatment is only available in a few academic centers for metastatic melanoma. ACT is proof of concept that the introduction of highly avid T lymphocytes against metastatic melanoma can successfully lead to tumor regression and complete responses in a durable manner with potential for cure in some cases. Further studies are needed to augment the antitumor response and better optimize the tumor microenvironment. Following the success of immune checkpoint blockade, a natural next step forward is to combine this with ACT with studies already underway [54].

15.2.5 Vaccines

Extensive resources have been dedicated to the development of cancer vaccines due to their theoretical appeal [55]. Such vaccines have the potential to induce targeted, tumor-specific immune responses with limited toxicity and extended durability. Early attempts utilizing non-mutated, tumor-associated self-antigens were largely unsuccessful in eliciting an adequate immune response [55, 56]. This failure is thought to be a result of central T-cell tolerance to self-antigens, and the focus has now shifted to novel vaccine components, based on whole tumor cells, specific peptides, and DNA/RNA-based vaccines [55–62]. In addition, oncolytic viral vaccines and intratumoral immunotherapies have also garnered significant attention recently [62–67].

15.2.5.1 Immunotherapeutic Vaccines

Several highly immunogenic peptides are being investigated for the treatment of advanced melanoma, given their ability to induce an epitope-specific T-cell response against malignant melanocytes [57–59]. A short peptide vaccine using a modified gp100 peptide was investigated in a phase III RCT after preclinical studies demonstrated impressive T-cell-stimulating capabilities [57, 58]. Its addition to IL-2 resulted in a modest but significant improvement in ORR (16% vs. 6%, $p = 0.03$) and PFS (2.2 months vs. 1.6 months, $p = 0.008$) [58]. Another peptide vaccine composed of a mixture of 6 melanoma helper peptides (6MHP) was found to significantly improve OS (95% and 57% at 1 and 5 years vs. 57% and 16% in the control group, $p < 0.001$) [59].

More recently, an RNA-based nanoparticulate intravenous vaccine, Melanoma FixVac, was investigated in its first human trial [60]. The vaccine contains four tumor-associated, highly-immunogenic antigens, including squamous cell carcinoma 1 (NY-ESO-1), melanoma-associated antigen A3 (MAGE-A3), tyrosinase, and transmembrane phosphatase with tensin homology (TPTE) [60]. The antigen combination activates type I interferon pathways via TLR-7, resulting in tumor-specific T-cell expansion. A total of 56 patients received either FixVac monotherapy or a combination of FixVac + anti-PD1 therapy. Out of 25 evaluable patients in the FixVac monotherapy group, 1 patient had CR, 3 patients had PRs, and 7 had SD. In the combination FixVac/anti-PD-1 inhibitor group ($n = 17$ evaluable patients), six patients developed a PR, and two had SD. Most patients had a durable response over an observation period of over 2 years [60]. The authors also demonstrated that most patients developed either an antigen-specific CD4+ T-cell response or a mixed CD4+ and CD8+ response. In some patients who had failed immunotherapy, the addition of FixVac to the treatment regimen resulted in a subsequent clinical response to another round of PD-1 inhibition [60]. In contrast, a DNA-based vaccine containing gp100 and TRP-2 showed limited clinical efficacy in phase I/II trial, with only 1/15 patients displaying an objective response [61].

Lastly, an autologous melanoma vaccine is currently under investigation as adjuvant therapy in stage IIIB and IIIC disease [62]. After the isolation of melanoma cell lines from each patient's resected specimens, the BCG vaccine is added to potentiate the immune response, and eight vaccine doses at three-week intervals are typically given [62]. The use of patients' own resected tumors to develop the vaccine has the advantage of overcoming tumor antigen variability amongst individuals, and the inclusion of each patient's own major histocompatibility complex molecules is believed to be crucial in producing an antigen-specific lymphocytic response [62]. A phase II trial in 35 patients with stage IIB or III disease displayed an overall 5-year OS of 54% and DFS of 34%. A delayed-type hypersensitivity (DTH) reaction to an intradermal injection of the melanoma isolate was found to strongly correlate with OS and DFS [62]. Patients with a strong DTH had significantly improved outcomes when compared to patients with a weak DTH response (OS of 75% vs. 44% [$p < 0.0001$] and DFS of 47% vs. 26% [$p = 0.27$], respectively) [62]. The trial also demonstrated significantly improved 3-year OS in combination with ipilimumab when compared

to nonvaccinated patients treated with ipilimumab alone (46% vs. 19%, $p = 0.007$) [62].

Contrary to most other treatments discussed in this chapter, vaccines have demonstrated an excellent tolerability profile. AEs overall were mild and transient when used as monotherapy, most commonly including transient flu-like symptoms [56–62]. The clinical efficacy as a monotherapy leaves more to be desired. However, their addition to immunotherapy has the potential to augment the already impressive efficacy of PD-1/CTLA-4 inhibitors. Therefore, the combination of both treatment modalities is a promising therapeutic avenue that requires further investigation.

15.2.5.2 Intratumoral Immunotherapy

Intratumoral immunotherapies cause direct neoplastic cell lysis, releasing tumor-specific antigens and resulting in targeted T-cell activation [63]. The end result is enhanced locoregional anti-neoplastic response with reduction of systemic toxicity [63]. Intratumoral agents are subdivided into oncolytic viral (OV) therapies, such as talimogene laherparepvec (T-VEC) and non-oncolytic viral therapies, including PV-10 and toll-like receptor 9 agonists [63].

T-VEC is the first FDA-approved therapy in this class and is discussed in more detail in the Systemic Therapy in Melanoma chapter. Various other intratumoral agents have shown promise in early studies [64–67]. Most notably, Coxsackievirus A21 (i.e., CAVATAK) is an OV that preferentially causes tumor cell lysis by recognizing increased levels of intercellular adhesion molecule 1 (ICAM-1) on cell surfaces [64]. A phase II, open-label study involving 57 patients with stage IIIC-IV M1c melanoma was considered successful after the primary end point was reached, with 36.8% of patients having PFS at 6 months [64]. The treatment also resulted in increased CD-8+ T-cell infiltration and increased expression of PD-L1+ cells in 4/4 patients who previously failed immunotherapy [64]. The authors, therefore, concluded that CAVATAK showed promising clinical efficacy and may improve response rates in combination with immunotherapy, which is currently being investigated in numerous studies [64]. A phase Ib study combining CAVATAK with ipilimumab demonstrated an ORR of 50% (9/18 patients) with minimal toxicity [65]. The treatment was considered to be well-tolerated in both studies [64, 65].

HF-10 is an OV containing herpes simplex virus-1, which replicates efficiently within tumor cells, resulting in impressive cytolytic activity and subsequent tumor-specific immune activation [66]. A phase II trial combining HF-10 with ipilimumab displayed a CRR of 16% (7/44 patients) and an ORR of 41% (18/44 patients) [67]. The treatment was well-tolerated with minimal side effects [67]. Both CAVATAK and HF10 are under further investigation in combination with PD-1 inhibitors (NCT03259425 and NCT02565992, respectively) [63].

15.3 Conclusion

The introduction of targeted inhibitors and immune-based therapies in the armamentarium against metastatic melanoma has dramatically improved survival outcomes. Over the past decade, clinicians and scientists have sought to build upon the early success of MAPK pathway inhibitors and immunotherapies in an attempt to improve the efficacy and durability of responses. While no individual treatment modality has matched the efficacy of our current first-line treatments, numerous systemic and intratumoral agents have the potential to augment their responses. The future of melanoma treatment underscores the use of combination therapy as the way forward. The challenge will be to choose the right combination of agents for the right patient. The ultimate goal lies in personalizing oncologic therapy for each individual that is specific to the characteristics of their own tumor and immune system. In contrast to the limited treatment options for metastatic melanoma prior to 2011, the currently approved therapies discovered over the past decade have been a truly astounding explosion of science. The next decade promises further advances in this very exciting field.

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16 Predictive Biomarkers of Melanoma

Ailish Hanly, Frederick Gibson, and Rhoda M. Alani

16.1 Diagnostic Biomarkers

16.1.1 S100

The S100 protein family was first identified in glial cells and has since been used as a marker for several tumors, including melanoma [2, 3]. These dimeric calcium sensors play a role in numerous cellular processes, including cell cycle, apoptosis, cell motility, and differentiation [4]. S100 is among the most commonly used IHC markers for melanoma, having first been identified in melanoma in 1980 [3]. The utility of S100 in the diagnosis of melanoma is a function of its high sensitivity, with over 90% of melanoma tumors staining positive for S100 [5, 6]. However, its specificity is low, estimated to be between 70–87% [7–9], given its expression in a number of different tissues.

16.1.2 HMB-45

HMB-45, a monoclonal antibody that recognizes gp100, has been shown to be highly specific for melanoma. Several studies, in fact, have demonstrated 100% specificity for melanoma [10–12]. Its sensitivity, however, ranges from 69–93%, with higher sensitivity observed in primary compared to metastatic melanomas [7]. In addition, it has been shown to be unreliable in the detection of nodal disease [13], suggesting that the most useful application of HMB-45 is in conjunction with other markers.

16.1.3 Melan A

Melan A, also known as MART-1, is a cell surface protein expressed in primary human melanocytes and melanomas recognized by autologous T-cells [14]. It is expressed in melanomas, benign nevi, and normal melanocytes as well as perivascular epithelioid cell tumors (PEComas), clear cell sarcomas, adrenal cortical tumors, and some sex cord stromal tumors. While it has lower sensitivity than S100, it is superior in terms of specificity, with many studies reporting >95% specificity for melanoma versus other malignancies [7, 15]. Melan A has higher sensitivity in primary melanomas (~85–97%) compared to metastatic (57–92%) [6]. Because it is not expressed in the dendritic cells in the lymph

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nodes, it is superior to S-100 and HMB-45 in detecting microsatellites in sentinel lymph nodes [7, 13]. In addition, it is one of the recommended stains during Mohs micrographic surgery given its high sensitivity in frozen sections [16, 17].

16.1.4 Chondroitin Sulfate Proteoglycan 4 (CSPG4)

Chondroitin sulfate proteoglycan 4 (CSPG4), also known as high molecular weight melanoma-associated antigen or melanoma chondroitin sulfate proteoglycan, is involved in tissue development, cell adhesion and motility, and possibly metastasis [18]. It is expressed in >85% of primary and metastatic melanomas [19, 20]. It has shown superiority to Melan A, S-100, and HMB-45 in staining metastatic lesions, with >90% sensitivity [21]. Moreover, it is particularly useful for diagnosing desmoplastic melanoma, showing greater sensitivity compared to HMB-45 and Melan A [22].

16.2 Prognostic Biomarkers

16.2.1 Immunohistochemical Markers

16.2.1.1 Mitotic Rate

Mitotic rate, while no longer included in the American Joint Commission on Cancer (AJCC) melanoma staging system, is nonetheless a significant predictor of patient survival. Higher mitotic rate in a primary melanoma correlates with lower survival probability, and is the second most significant predictor of melanoma-specific survival after tumor thickness [23].

16.2.1.2 Ki-67

Ki-67 is a commonly used marker of cell proliferation that is expressed during all active stages of the cell cycle (late G_1, S, G_2, and M) [24] and is therefore sometimes used as an alternative to mitotic count [25]. The utility of Ki-67 in determining prognosis in melanoma is somewhat controversial. While Ostmeier et al. reported Ki-67 to be an independent prognostic factor in primary melanomas [26], other studies suggest that the relationship between Ki-67 and poorer clinical outcomes is mediated by other clinicopathologic features, such as ulceration [27, 28]. Additionally, there is conflicting evidence regarding the correlation between Ki-67 and tumor thickness. Moretti et al. found a positive correlation between Ki-67 staining and metastatic activity in melanomas <1.5 mm thick, while there was a negative correlation in primary melanomas >1.5 mm thick [29]. However, other studies have reported an opposite trend, finding the association only in thick melanomas [30–32].

16.2.1.3 Melanoma Cell Adhesion Molecule (MCAM)

Melanoma cell adhesion molecule (MCAM or Mel-CAM), also known as MUC18 or CD146, is a cell adhesion molecule that plays a role in the invasiveness and motility of melanoma. It is highly expressed in both primary and metastatic melanoma [33]. Non-metastatic melanoma cells transfected with MCAM showed increased metastatic potential and tumorigenicity compared to controls [34]. Prospective studies investigating the relationship between MCAM expression and patient outcomes found that increase in MCAM staining intensity was associated with decreased survival [35]. Furthermore, MCAM expression was independently predictive of survival and development of metastases in patients meeting criteria for sentinel lymph node biopsy (SLNB), suggesting that MCAM expression may have utility in stratifying SNLB based on risk [36].

16.2.1.4 Multiple Marker Arrays

Although the biomarkers discussed above have each shown diagnostic and prognostic value, they are all limited by either their sensitivity or specificity. More recently, Alonso et al. used a tissue microarray (TMA) study to analyze 165 malignant melanoma tumors. They identified a predictor model with four antibodies (Ki67, $p16^{INK4a}$, $p21^{CIP1}$, and Bcl-6) that was associated with shorter overall survival (OS) in patients with ver-

tical growth phase melanoma [37]. Kashani-Sabet and colleagues have developed two multi-marker assays for use in melanoma diagnosis and prognosis. The first, a five marker diagnostic assay consisting of ARPC2, FN1, RGS1, SPP1, and WNT2, was 95% specific and 91% sensitive in distinguishing melanoma from benign and dysplastic nevi [38]. The second study identified an array of three biomarkers (NCOA3, SPP1, and RGS1) that was found to be an independent prognostic predictor of disease-specific survival [39]. Gould-Rothberg et al. used the Automated Quantitative Analysis (AQUA) method for immunofluorescence staining and identified five key markers (ATF2, $p21^{WAF1}$, $p16^{INK4A}$, β-catenin, and fibronectin) that distinguished high- and low-risk groups for melanoma-specific mortality [40]. A more recent study included seven biomarkers (Bax, Bcl-X, PTEN, COX-2, loss of β-catenin, loss of MTAP, and presence of CD-20 positive B-lymphocytes) in their model, which was an independent negative predictor for OS and recurrence-free survival (RFS) [41]. While these IHC panels are likely to be more useful at determining prognosis in melanoma than individual biomarkers, their clinical utility remains to be determined.

16.2.2 Genetic Biomarkers

16.2.2.1 KIT

KIT is a receptor tyrosine kinase (RTK) that plays a role in the development of numerous cell lineages including melanocytes, mast cells, and hematopoietic progenitor cells [42]. Amplifications and activating mutations of KIT have been observed at increased frequency in melanomas of mucosal, acral, and chronically sun damaged skin [43]. While early studies treating melanoma patients with imatinib showed limited clinical efficacy and significant toxicity; these studies did not select for patients with KIT mutations or amplifications [1, 44–46]. More recent studies in melanoma patients harboring activating KIT alterations have demonstrated significant efficacy of RTK inhibitors [47–51].

16.2.2.2 Cdkn2a/b

While UV radiation is a known environmental risk factor for melanoma, large pedigrees of familial melanomas have allowed for the identification of heritable genetic mutations associated with a predisposition to melanoma [52]. Two genes associated with a predisposition to melanoma, CDKN2A and CDKN2B, are located in the INK4 locus on chromosome 9p21 and encode tumor suppressor proteins [53]. Germline CDKN2A mutations have been observed in an estimated 20% of tested melanoma families [52, 54–56]. CDKN2A encodes p16 and $p14^{ARF}$. The p16 protein inhibits CDK4 and CDK6, thereby preventing the formation of CDK/Cyclin D complexes that phosphorylate and activate the retinoblastoma protein. Loss of p16 results in uninhibited cell cycle progression and contributes to tumorigenesis [56, 57]. The $p14^{ARF}$ protein acts through the p53 pathway to allow cell cycle arrest and apoptosis [58, 59]. Partial or complete deletion of the INK4 gene cluster has been observed in most melanoma cell lines and in almost half of melanoma metastases [60–62]. Conway et al. found that reduced gene dosage of the regions of 9p21 encoding CDKN2A, CDKN2B, and P14ARF was associated with increased tumor thickness, mitotic rate, and ulceration [59]. Similarly, Grafström et al. reported that monoallelic or biallelic deletions in the INK4 region were associated with reduced median survival [62].

16.2.2.3 Expression Profiling

Gene expression profiling (GEP), which involves measuring the expression of a panel of genes using mRNA, has been used to predict prognosis and response to therapy for a number of different cancers [63]. While there are commercially available GEP tests marketed as being able to classify cutaneous melanoma based on the risk of metastasis, it remains unclear whether the use of GEP tests provide any additional prognostic information in comparison with or in addition to known clinicopathologic factors (patient age, sex, tumor location, thickness, ulceration, SLNB status, lymphovascular invasion, microsatellites, and

mitotic rate), according to the 2020 National Comprehensive Cancer Network (NCCN) guidelines [64]. Winnepenninckx et al. performed the first study linking gene expression profiling of melanoma to clinical outcome and identified 254 genes that were associated with distant metastasis-free survival of patients with primary melanoma [65]. In stage III melanoma, a set of 21 genes was identified that accurately predicted clinical outcome in 85–90% of patients [63]. Jönsson et al. performed hierarchical clustering of 3000 genes from stage IV melanomas and found four tumor subtypes characterized by expression of immune response, pigmentation, proliferation, or stromal composition [66]. They observed a different prognosis between subtypes, with the proliferative subtype associated with the worst survival [66]. Several other studies have identified gene profiles in subsets of melanoma patients that predict clinical outcomes [67–69]. In 2015, Gerami et al. identified a 28-gene signature that classifies tumors as either low risk (class 1) or high risk (class 2) of metastasis [70]. A diagnostic test comprised of these 28 genes, along with 3 control genes, has since been developed, called DecisionDx-Melanoma. Its prognostic utility in predicting recurrence and metastasis has been validated in three prospective studies [71, 72], and the test is now covered by Medicare and Medicaid for patients over 65 years old with T1a, T1b, and T2 tumors [73]; however, its ability to provide clinically actionable prognostic information remains to be determined.

16.2.2.4 MicroRNA (miRNA)

miRNAs are short non-coding RNAs that act post-transcriptionally to modify gene expression and have been shown to be differentially expressed in melanoma compared to healthy controls [74]. Circulating miRNA expression has been found to have the potential to improve the diagnosis, prognosis, and monitoring of response to treatment in melanoma patients [75, 76]. While several studies have found single miRNA expression (miR-16, miR-206, miR-210, miR-15b, miR-205, miR-29c, miR-221, miR-21) to correlate with melanoma disease stage, survival, tumor burden, and recurrence [77–85]; others have focused on developing miRNA expression panels to improve diagnostic and prognostic accuracy. A miRNA array from 59 melanoma metastases identified a signature of 18 miRNAs whose overexpression was significantly associated with survival [86]. Stark et al. developed an miRNA panel of seven miRNAs that was able to detect melanoma with high sensitivity (93%) and specificity (82%) and was reported to be superior to LDH and S100B for melanoma progression, recurrence, and survival [87]. Analysis of 355 miRNAs in the sera of 80 melanoma patients at primary diagnosis revealed a signature of 5 miRNAs classifying melanoma patients into high and low recurrence risk groups and 4 miRNAs that varied dynamically with tumor burden [88], while analysis of serum levels of 12 miRNAs from 283 melanoma patients at diagnosis found a panel of four miRNAs to be predictive of RFS, OS, and recurrence in combination with stage [89]. To date, no single miRNA or miRNA panel has been proven to be an actionable clinical biomarker.

16.2.2.5 Circulating Tumor DNA (ctDNA)

Levels of circulating tumor DNA (ctDNA) in cancer patients are associated with tumor burden, cell turnover, and location of metastasis [90]. BRAF and NRAS mutations occur in approximately 50–70% and 20% of melanomas, respectively [91, 92], and may be detected in peripheral blood of melanoma patients arising from necrotic or apoptotic circulating tumor cells. In melanoma patients with early stage disease, ctDNA levels are often undetectable [93]; however, in patients with late stage metastatic disease, levels of ctDNA have been shown to be significantly associated with progression free survival (PFS) and response to treatment [94, 95]. In a longitudinal assessment of ctDNA in patients treated with PD-1 inhibitors, a favorable ctDNA profile (undetectable ctDNA at baseline and during treatment) predicted OS, PFS, and tumor response to treatment compared to an unfavorable ctDNA profile (detectable ctDNA at baseline and during treatment) [96]. ctDNA may also be useful for monitoring development of resis-

tance to treatment, particularly targeted therapy, by detecting resistance mutations along with monitoring disease progression [94, 97].

16.2.2.6 DNA Methylation

Epigenetic changes of ctDNA, such as DNA methylation, are detectable in peripheral blood and are actively being investigated for their use as biomarkers in a number of cancers [98]. In melanoma, hypermethylation of a number of genes (RAR-beta2, RASSF1A, IDH1, CDKN2A) has been identified and shown to have prognostic and therapeutic significance [99, 100]. Hypermethylation of genes involved in tumor suppression and DNA repair such as RASSF1A, MGMT, and RAR-beta2 have been associated with poorer survival and treatment response [100–104]. A comprehensive DNA methylation analysis of all stages of melanoma revealed a prognostic signature of three genes (MEOX2, OLIG3, and PON3) for which the degree of DNA methylation may predict the prognosis of melanoma patients [105]. More recently, Guo et al. identified a prognostic four-DNA methylation signature independent of all clinical factors with high predictive performance for patients in early stages and with tumor thickness less than 2 mm [106]. In addition, DNA methylation profiles from melanoma tumors have been shown to be distinct from other tumors and methylation profiles of healthy controls [101].

16.3 Serologic Biomarkers

16.3.1 Lactate Dehydrogenase (LDH)

Lactate dehydrogenase (LDH) is essential for anaerobic glycolysis and is frequently upregulated in tumor cells, providing a survival advantage in a hypoxic environment. While LDH is not specific to melanoma progression, it is the strongest independent prognostic factor for melanoma progression in late stage disease [107]. Serum LDH is the only marker so far that has been incorporated into the AJCC melanoma staging and classification system [108] and is recommended as part of the standard workup following identification of metastatic disease by the 2020 NCCN guidelines [64]. In a meta-analysis of 7972 patients with stage IV melanoma, elevated serum LDH was an independent and significant predictor of survival outcome with 1- and 2-year OS rates of 65% and 40%, respectively, for those with normal serum LDH compared to 32% and 18% for those with elevated serum LDH [108]. Serum LDH is commonly used in the management of patients with late stage melanoma; however, due to its low specificity, false positive results are common from other conditions involving hemolysis, necrosis, and apoptosis, and it has not been helpful in distinguishing patients with early stage melanoma from healthy controls [109].

16.3.2 S100

Serum S100 Beta (S100B) is an indicator of tumor burden and has been correlated with tumor stage, survival, and recurrence [110, 111]. S100B has also been shown to be more specific for melanoma metastases compared to LDH [112]. In a meta-analysis of 3393 patients with stage I to IV melanoma, S100B positivity was associated with significantly poorer survival in all stages of melanoma [113]. However, other studies have failed to find any prognostic significance in patients with microscopic disease or those who are clinically tumor-free after surgery [114–116]. Egberts et al. found baseline serum levels of S100B to be significantly associated with treatment response in stage IV melanoma patients along with a strong correlation between treatment response and unchanged or declining S100B levels over time [109]. Higher S100B levels at baseline and increases over time are associated with poorer RFS and OS [117]. Increasing S100B levels during treatment may indicate that another treatment strategy is needed [117].

Although S100B is a more specific serum marker for melanoma than LDH, it may also be elevated in CNS, liver, renal, and cardiovascular disease [118, 119]. In clinical practice, S100 is primarily used only in European countries to monitor treatment response in advanced meta-

static melanoma given its relative unreliability for screening and detection in stage I and II disease [113].

16.3.3 Melanoma-Inhibiting Activity (MIA)

Although numerous serum biomarkers have been studied for their prognostic significance in melanoma, none have shown a higher sensitivity-specificity profile than LDH or S100B. Serum melanoma-inhibiting activity (MIA) is a protein highly expressed and secreted from melanoma cells. In a study of 112 patients with melanoma, 13% of patients with stage I disease, 23% with stage II, and 100% in stage III and IV were found to have elevated serum MIA levels. Furthermore, of 350 patients with a history of stage I/II melanoma who had been declared tumor free after surgical resection, 32 patients developed positive MIA values of which 15 had developed metastases, suggesting serum MIA may be useful to identify metastatic disease progression [120].

16.3.4 Circulating Melanoma Cells (CMCs)

In order to metastasize, tumor cells must leave the primary tumor site and intravasate into the bloodstream or lymphatics. The detection of circulating melanoma cells (CMCs) in the peripheral blood of melanoma patients has demonstrated prognostic value [121–125]. In a meta-analysis of 5433 patients, CMC status correlated with disease stage and OS [124]. In a retrospective analysis of 44 patients with melanoma, patients with two or more CMCs detected in peripheral blood were found to have an OS of 2.0 months versus 12.1 months for those with less than two CMCs detected [126]. The use of CMCs as a biomarker in the clinic is limited due to controversy surrounding the sensitivity, specificity, and reliability of CMCs as a biomarker given the high heterogeneity of CMCs along with differences in CMC collection and analysis [127]. To combat the heterogeneity of CMCs, Aya-Bonilla et al. used a multi-marker approach taking into account up to 19 genes. In these studies, CMC detection was associated with poorer OS and PFS while changes in plasma CMC concentration were found upon treatment initiation [128].

16.3.5 Exosomes

Exosomes are secreted cellular vesicles with a molecular profile characteristic of the cell of origin. Recent studies have identified unique mRNA, miRNA, and protein profiles in exosomes secreted by melanoma cells [129]. Lazar et al. identified a proteome signature present in exosomes from aggressive melanoma cell lines enriched in proteins involved in cell motility, immune response, and angiogenesis [130]. Analysis of exosomes from human melanoma tumors revealed a “melanoma signature” comprised of TYRP2, VLA-4, HSP70, and MET. Of patients with stage IV disease, those with protein-poor exosomes (<50 ug/mL) were found to have a survival advantage versus those with protein-rich exosomes (>50 ug/mL) [131]. Analysis of exosomal miRNAs from melanoma patients revealed significantly higher levels of miR-17, miR-19a, miR-21, miR-126, and miR-149 in patients with metastatic sporadic melanoma compared to familial melanoma patients and healthy controls [132].

16.4 Biomarkers of Treatment Response: Immunotherapy

The only biomarkers recognized by the 2020 NCCN guidelines with potential utility for immune therapy include programmed death-ligand 1 (PD-L1) expression and somatic mutation burden [64]. High PD-L1 expression (>5%) may be a marker for equivalent outcomes with nivolumab monotherapy compared to nivolumab and ipilimumab combination therapy in patients with metastatic melanoma [133]. Currently, PD-L1 is the only FDA-approved ICI biomarker which serves as a companion test for pembrolizumab treatment (PD-L1 IHC 22C3 pharmDx).

Tumor mutational load may also be predictive of response to ICIs. High mutational load in tumor tissue has been associated with OS in patients treated with CTLA-4 inhibitors and PD-1 inhibitors [134]. Further, exome analysis of tumor mutational load has revealed T-cell responses against patient-specific neoantigens [135]. A higher mutational burden may predict a more robust T-cell response. In a retrospective cohort of 173 patients with metastatic melanoma, Queirolo et al. identified two single nucleotide variants of the CTLA-4 gene that correlate with OS in those treated with anti-CTLA-4 therapy (3-year OS of ~30% versus ~13%), which may be used to predict patients with favorable outcomes to CTLA-4 therapy [136].

Many of the potential biomarkers being looked at for immune checkpoint inhibitor (ICI) response are involved in known immune response pathways. An effective response to ICIs is dependent on T-cell infiltration of the tumor microenvironment (TME) [137]. Early studies focused on serologic factors that may predict response to ICIs, including lymphocyte and eosinophil count, both of which are positively associated with improved survival [138–144]. In contrast, an elevated neutrophil count or high neutrophil/lymphocyte ratio (NLR) in patients treated with monotherapy ipilimumab (an anti-CTLA-4 antibody) or nivolumab (an anti-PD-1 antibody) was associated with poor OS or no response [141, 144–147].

Other serologic biomarkers such as LDH and C-reactive protein (CRP) have also been looked at in the context of immunotherapy. Elevated LDH and CRP at baseline and during treatment have been found to be significantly associated with poorer OS in patients treated with ICIs [141–143, 148]. Other proposed serum biomarkers include IL-8 and angiopoietin-2. IL-8, which may be secreted by melanoma tumor cells, has been found to be inversely correlated with OS in melanoma and non-small cell lung cancer (NSCLC) patients treated with PD-1 inhibitors [149]. High baseline and increasing angiopoietin-2 levels during treatment have been associated with reduced OS in PD-1 and CTLA-4 inhibitor-treated patients [150].

Cellular biomarkers are also being investigated to predict treatment response to ICIs. Subrahmanyam et al. found subsets of CD4+ and CD8+ T cells to vary between responders and non-responders to anti-CTLA-4 treatment, while subsets of natural killer (NK) cells were shown to correlate with clinical response to anti-PD-1 therapy [151]. Others have observed an increased response to PD-1 inhibitors in patients with greater tumoral CD8+ T-cell infiltration and PD-1/PD-L1 expression pre-treatment [152, 153]. In patients treated with anti-PD-1 therapy, the presence of PD-1+ CTLA-4+ cells within the tumor-infiltrating CD8+ T-cell population was found to significantly correlate with response to therapy and PFS, which was 31.6 months in those with tumors with more than 20% PD-1+ CTLA-4+ CD8+ T cells compared to 9.6 months for tumors with 20% or fewer [154].

Another marker of response to treatment with ICIs may be immune-related adverse events (irAEs) during treatment. Downey et al. observed increased efficacy of anti-CTLA-4 treatment in patients who experienced irAEs (26% objective responders) compared to those who did not (2% objective responders). The severity of irAE seemed to correlate with response as those with high grade irAEs (grade 3–4) showed an even greater objective response [155]. Blank et al. proposed using an "immunogram" looking at seven different parameters (mutational load, T-cell infiltration, expression of immune checkpoints, CRP/IL-6, lymphocyte count, and expression of MHC class I) to predict response to immunotherapy. This builds on the observation that (1) the outcome of cancer-immune interactions depends on many unrelated parameters such as T-cell inhibitory mechanisms and tumor "foreignness" and (2) the value of the parameters may vary significantly among patients [156].

16.5 Biomarkers of Treatment Response: Targeted Therapy

Screening for BRAF and NRAS mutations is currently routine in the management of cutaneous melanoma while KIT mutations are evaluated in

melanomas in sites of chronic sun exposure, acral sites, and mucosal melanomas. According to the 2020 NCCN guidelines, BRAF mutation testing and, in the appropriate clinical setting, KIT mutation testing is recommended upon initial presentation with stage III or IV disease or clinical recurrence [64]. Identification of a BRAF or KIT mutation/amplification in melanoma allows for the use of effective targeted therapies in patients harboring these tumors. Treatment of patients with tumors harboring V600E BRAF mutations with BRAF inhibitor (BRAFi) monotherapy or combined MEK inhibition (MEKi) has demonstrated complete or partial tumor regression in the majority of patients [157, 158]. On the other hand, BRAFi use is not recommended and available evidence suggests there is no benefit in treating patients without V600E BRAF mutations [64, 159]. KIT mutations are observed to occur in "hotspots" across the gene and demonstrate variable sensitivity to KIT inhibitors with observed disease control rates around 50% in patients with KIT mutations [47–49]. NRAS-mutant melanomas are generally unresponsive to targeted therapies and are therefore generally treated with ICIs in advanced disease.

BRAF-mutant ctDNA has been widely studied, and high baseline levels have been found to be associated with poor response to MAPK-inhibitor (MAPKi) therapy, alone or combination [160–163]. In a prospective analysis of 48 patients with advanced metastatic melanoma treated with targeted or immunotherapy, lower BRAF-mutant ctDNA levels pre-treatment were significantly associated with response to treatment and longer PFS, regardless of treatment type. However, levels of ctDNA decreased significantly corresponding to response to therapy in those treated with targeted therapy, unlike those receiving immunotherapy [94].

In a retrospective analysis of 617 patients with BRAF-mutant melanoma treated with dabrafenib plus trametinib; LDH level and number of metastatic disease sites (less than three) were significantly associated with PFS and OS [164]. Wang et al. identified cancer-specific extracellular vesicle (EV) phenotypes in melanoma patient plasma and identified specific EV profiles associated with resistance to targeted therapy [165]. Recently, an analysis of 90 patients with BRAF V600-mutant melanoma treated with either BRAFi alone or combined with a MEKi revealed PFS of 9.1 and 3.5 months, respectively, and OS of 17.2 and 5.5 months, respectively, for patients with NLR less than 5 and NLR greater than or equal to 5 [166].

Recent studies have explored gene signatures and genetic profiles associated with response to targeted therapy. In a retrospective study of 64 patient tumor samples treated with BRAFi monotherapy, pre-treatment overexpression of a subset of genes was significantly associated with PFS and OS [167]. In a retrospective analysis including patients with BRAF V600-mutant metastatic melanoma treated with vemurafenib with or without cobimetinib from BRIM-2, BRIM-3, BRIM-7, and coBRIM studies, whole exome sequencing revealed alterations in MITF and TP53 were more frequent in tumors from patients with rapid progression, while alterations in NF1 were more common in tumors from patients with complete response. In addition, RNA sequencing analysis revealed enrichment of genes associated with immune response in those patients with complete response, while genes related to keratinization were enriched in tumors from patients who experienced rapid progression [168]. Wongchenko et al. identified two gene signatures, immune and cell cycle, from patients in BRIM-2 and BRIM-3, of which, the cell-cycle gene signature was associated with shorter PFS in those treated with vemurafenib monotherapy [169]. Others have noticed a higher baseline PTEN expression to be associated with response to vemurafenib monotherapy [170]. Wagle et al. constructed a MAPK pathway activity score focusing on the expression of 10 MAPK target genes and found a higher score to be associated with improved PFS [171].

16.6 Summary

While investigators have been evaluating the potential utility of diagnostic and prognostic melanoma biomarkers for decades, more recent advances in the development of effective melanoma therapies targeting driver mutations in mel-

anoma have informed the development of biomarkers predictive of treatment effectiveness and the monitoring of treatment responses. Emerging molecular technologies are currently being developed to provide meaningful diagnostic and prognostic information for melanoma; however, insufficient data currently exists to make such technologies clinically useful. As additional data accumulate regarding resistance mechanisms to targeted therapies and immunotherapies, we expect new biomarkers will be developed to detect early treatment resistance in patients and support therapies to overcome treatment-specific resistance mechanisms in melanoma (Table 16.1).

Table 16.1 Biomarkers used for prognosis and treatment response in melanoma

Biomarker	Study Cohort	Correlation	Methodology	References
Molecular biomarkers				
Ki-67	688 patients with primary melanomas 202 patients with nodular melanoma 68 patients with melanoma ≥4 mm thick	PFS, OS OS PFS, OS	IHC IHC IHC	Ostmeier et al. 2001 [26] Ladstein et al. 2010 [30] Robinson et al. 2018 [31]
MCAM	76 patients with stage IA to III 78 patients with primary melanoma, 92 patients with metastatic melanoma	OS OS, nodal progression	IHC IHC	Pacifico et al. 2004 [35] Pearl et al. 2007 [36]
Genetic biomarkers				
CDKN2A/B	74 relapsed patients, 42 nonrelapsed patients 112 melanoma tumor samples from 86 patients	Tumor thickness, mitotic rate, ulceration, risk of relapse OS	MLPA, PCR, IHC PCR, RTPCR	Conway et al. 2010 [59] Grafstrom et al. 2005 [62]
ctDNA	48 patients stage IV 92 patients stage IV, BRAF-mutant	PFS, treatment response PFS, treatment response	ddPCR RTPCR	Gray et al. 2015 [94] Ascierto et al. 2013 [95]
Serologic biomarkers				
LDH	30,946 patients stage I-III and 7972 patients stage IV 50 patients stage I-II, 61 patients stage IV	OS Tumor stage	Meta-analysis Photometric assay	Balch et al. 2009 [108] Egberts et al. 2011 [109]
S100B	3393 patients stage I-IV 50 patients stage I-II, 61 patients stage IV. 20 patients stage III-IV 670 patients stage IV	OS Tumor stage, survival, treatment response Metastasis (75% sensitive, 92% specific) OS, RFS	Meta-analysis Photometric assay ELISA Chemiluminescence	Mocellin et al. 2008 [113] Egberts et al. 2011 [109] Oberholzer et al. 2008 [110] Tarhini et al. 2009 [117]
MIA	112 patients stage I-IV 350 patients stage I-II	Prognosis Metastasis, disease progression	ELISA	Bosserhoff et al. 1997 [120]
CMCs	5433 patients stage I-IV 44 patients stage III-IV 43 patients stage IV	Disease stage, OS, PFS OS OS, PFS	Meta-analysis Automated CTC assay IHC, RTPCR, ddPCR	Mocellin et al. 2006 [124] Rao et al. 2011 [126] Aya-Bonilla et al. 2020 [128]

PFS Progression free survival, *OS* Overall survival, *IHC* Immunohistochemistry, *MLPA* Multiplexed ligation-dependent probe amplification, *PCR* Polymerase chain reaction, *RTPCR* Real-time PCR, *ddPCR* Droplet digital PCR, *RFS* Relapse free survival, *CMCs* Circulating melanoma cells, *CTC* Circulating tumor cells

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Part VII

Melanoma Subtypes in Targeted Populations

Acral Melanoma

17

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17.1 Introduction

Acral melanoma (AM) is a rare variant of cutaneous malignant melanoma (CMM), accounting for approximately 2–3% of all cases [1]. Despite its rarity, AM is the most common subtype of melanoma in minorities, representing 36% of all CMM in blacks, 18% in Asian/Pacific Islanders, 9% in Hispanic whites, and only 1% in non-Hispanic whites [1]. Studies from East Asian countries have shown more dramatic results, with AM accounting for approximately 50–58% of CMM [2]. The age-adjusted incidence of AM is 1.8 per 1,000,000 person-years, with a comparable overall incidence amongst non-Hispanic whites and blacks [1]. A higher incidence was noted amongst Hispanics when compared to non-Hispanic whites, whereas a lower incidence was noted in Asian/Pacific Islanders [1].

The mean age at presentation is 62.8 years, compared to 58.5 years for CMM overall [1]. The incidence was noted to increase 6% with each year of advancing age, without variation amongst men and women [1]. It typically involves the palms, soles, and the nail apparatus, more commonly developing on the lower extremities than the upper extremities [1]. Histologically, the lentiginous pattern is the most common subtype reported. Therefore, AM and acral lentiginous melanoma are often used interchangeably [1]. Outcomes remain unfavorable, with a 5- and 10-year melanoma-specific survival rate of 80.3% and 67.5%, respectively [1].

17.2 Pathogenesis and Risk Factors

Our understanding of AM's etiology remains limited. AM has not been found to correlate with known risk factors for CMM, such as sun exposure, fair skin type, and a history of melanoma. Divergent molecular analyses between AM and CMM also suggest that different pathogenic processes may be involved in the development of melanoma on acral surfaces. AM is known to have a lower mutational burden than CMM, with a notable absence of UV signature mutations [3]. In addition, AM has a lower incidence of BRAF, NRAS, and NF-1 mutations, and a higher incidence of mutations in cyclin D1 (CCND1) and KIT proto-oncogenes [3].

No widely accepted theory currently exists that offers an alternative explanation to the pathogenesis behind AM. The main prevailing theory is related to mechanical stress and repeated trauma, given AM's propensity to develop on the soles of the feet, an area constantly exposed to pressure, friction, maceration, and irritation [4].

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A study from Japan involving 123 patients with plantar AM found that most melanomas developed on the heel or the forefoot, with relative sparing of the arch. The authors, therefore, concluded that mechanical stress is conducive to the development of AM [4]. Results from other studies have been mixed, however, with a recent US-based study demonstrating no significant differences between weight-bearing and non-weight-bearing areas of the feet [5].

17.3 Clinical Presentation

17.3.1 Palmoplantar

The lentiginous subtype represents the most common variant of melanoma arising on acral surfaces. It often arises as an asymmetric, irregularly bordered patch with variegated pigmentation. A brown-black nodularity with a keratotic surface may subsequently arise within the lesion [6]. The natural evolution of AM is slow and can occur over years before a diagnosis is made. Due to the delay in diagnosis, the size is often large at presentation, with a median diameter of 20 mm and a range of 7–80 mm [6]. In as high as 38% of cases, AM can completely lack pigment, and instead present as a friable papulonodule or verrucous plaque, mistaken for pyogenic granulomas or plantar warts [6]. Most cases of AM arise on the plantar feet (70–85%), with the heel representing the most common location. The heterogenous clinical presentation, low public awareness, and often concealed location contribute to the delay in diagnosis. Special site nevi also complicate the diagnosis, as they often have several atypical features, clinically and histologically [6]. Distinguishing between benign and malignant acral melanocytic lesions can be problematic, and the level of clinical suspicion needs to be weighed appropriately against the procedural morbidity.

Dermatoscopically, AM is characterized by a broad parallel ridge pattern (PRP), in contrast to the benign parallel furrow pattern in acral nevi [7]. Irregular blotches, asymmetry of structures, and multiple colors may also be seen. Several acronyms have been developed to aid with the diagnosis. The most clinically useful may be the BRAAFF scoring system, which incorporates both worrisome and reassuring features, including: irregular blotches (+1 point), parallel ridge pattern (3 points), asymmetry of structures (1 point), and asymmetry of colors, as well as parallel furrow pattern (−1 point) and fibrillar pattern (−1 point). Any lesion with a total score of 1 or higher should be biopsied, and the sensitivity/specificity were 93.1% and 86.7%, respectively [7].

17.3.2 Nail Apparatus

Up to 30% of AM cases involving the nail apparatus present as longitudinal melanonychia. The color may vary from light brown to black, and the size ranges from 1 mm to more than 5 mm [7]. Nail dystrophy may also be present in half the cases. Hutchinson's sign, defined as an extension of the pigment onto the periungual skin, is present in ~30% of cases, though it is not pathognomonic for subungual melanoma [8]. Similarly to palmoplantar AM, an amelanotic presentation is noted in up to 30% of cases, often presenting as a pink-red, enlarging papulonodule. In contrast to palmoplantar AM, ungual AM more frequently arises on the hands than the feet [9]. The thumb represents the most common digit involved (41%), followed by the great toe (30%) [9].

A modified ABCDE summarizes the clinical features for subungual melanoma, which includes the following: **A**ge in the fifth to seventh decade of life; **B**and (i.e., brown-black longitudinal streak 3 mm or more); **C**hange in the nail band (or a lack of change in the nail morphology in spite of presumed adequate treatment); **D**igit most commonly involved, which is the thumb; and **E**xtension of the pigment onto the adjacent skin or nail fold (i.e., Hutchinson's sign) [6, 7].

17.4 Diagnosis and Histopathology

Excisional biopsies of suspicious lesions are often not feasible given the limited skin laxity and large size at presentation. Therefore, an incisional biopsy of the clinically most suspicious area within the lesion, or multiple punch biopsies is recommended. It is also worth noting that incisional biopsies should be oriented perpendicular to the dermatoglyphics, and specimens should be similarly cut perpendicular to the ridges and furrows to avoid the falsely positive pathologic interpretation [7].

Histologically, AM is characterized by broad, confluent single-cell melanocytic proliferation along the dermo-epidermal junction in early-stage disease [10]. As the tumor progresses, large junctional nests composed of atypical melanocytes are seen, as well as pagetoid spread.

The histologic diagnosis may be difficult to confirm, as acral melanocytic nevi have some overlapping features with AM, including nuclear atypia, upward scatter, and nesting [10]. Unlike the vertically oriented, uniform nests in melanocytic nevi, however, AM nests are frequently horizontally oriented, pleomorphic, non-cohesive, and poorly circumscribed [10]. In addition, the pagetoid spread is present within the furrows in acral nevi, compared to its presence within the ridges in AM. Therefore, sectioning specimens perpendicular to the ridges and furrows is of paramount importance in aiding diagnosis. Immunostaining for HMB-45 and MART-1 may also be of benefit in confirming the diagnosis of AM [10].

In diagnostically challenging cases, fluorescence in situ hybridization (FISH) should also be considered. Several tests have been developed to test for specific molecular aberrations seen in AM, including telomerase reverse transcriptase gene (TERT), aurora kinase A gene (AURKA), CDKN2A, ras responsive element binding protein 1 gene (CEP6) on 6p25, MYB on 6q23, and centromere of chromosome 6 gene (CEP6). Targeting various combinations of the aforementioned genes yielded a sensitivity of 80–97% in the detection of AM [7].

17.5 Management

17.5.1 Surgery

Surgical management is the standard of care for the treatment of AM, with wide local excision being most commonly employed [11]. Despite the variation in the molecular landscape and the overall inferior outcomes in AM, the recommended surgical margins are largely based on studies of other melanoma subtypes [11]. One of the few studies assessing surgical margins in AM is a retrospective cohort study of 129 patients with AM. For thin AM (Breslow depth < 1 mm), no difference in outcomes was noted between margins 1 cm or less compared to margins >1 cm [12]. In contrast, for thick melanomas (Breslow depth > 1 mm), a multivariate analysis demonstrated a lower risk of local recurrence in patients who underwent WLE with 2 cm margins compared to <2 cm. However, no difference in nodal/distant spread was noted [12]. The authors, therefore, concluded that while 1 cm margins appear to be adequate in treating thin AM, 2 cm margins may be considered for T2 melanomas, in addition to more advanced melanomas (T3–T4) [12].

In cases of subungual melanoma, phalangeal amputation is typically recommended for thick AM, whereas more conservative surgical management with a WLE at the distal phalanx and reconstruction may be considered for in situ disease or thin invasive disease [12, 13]. No difference in outcomes has been noted when comparing amputation versus WLE for early-stage disease [13].

17.5.2 Medical Management

17.5.2.1 KIT Inhibitors

Given the higher rate of KIT mutations in AM, several KIT inhibitors have been investigated for advanced or metastatic disease. Several phase II studies evaluating the KIT inhibitors imatinib or nilotinib in metastatic melanoma demonstrated an ORR of 17–30% and a DCR of 35–57% [14–19]. However, the studies included a significant percentage of non-acral melanomas (up to 71%),

and most of the responses were of limited duration. Interestingly, some of the studies demonstrated a trend toward improved responses in patients with KIT mutations versus amplification alone [18, 19]. Individualized therapy based on each patient's specific molecular aberrations is essential to optimize outcomes and improve prognosis in metastatic disease.

17.5.2.2 BRAF Inhibitors

BRAF inhibitors (BRAFi) have yielded impressive clinical efficacy amongst several melanoma subtypes. Data for AM, in particular, is lacking due to its rare incidence and low typically BRAF mutation rate. In one of the few studies evaluating BRAFi for acral and mucosal melanomas, 28 AM patients were included as part of the retrospective review, with 21/28 patients having follow-up data available [20]. The study reported a median PFS of 3.6 months (95%; CI 3.0–6.4), median OS of 6.2 months (95%; CI 6.1–12.1), ORRs of 38.1% (8/21 patients), and DCR of 81.0% (17/21) [20]. BRAFi were well tolerated, and grade 3/4 AEs were relatively rare. One patient developed grade 3/4 rash, and 2 patients developed grade 3/4 thrombocytopenia. The authors concluded that BRAFi has acceptable efficacy and good tolerability in BRAF-mutant AM [20].

17.5.2.3 Immunotherapy

PD-1 and CTLA-4 inhibitors have revolutionized the treatment of numerous types of advanced malignancies, including metastatic melanoma. While studies evaluating AM specifically are limited, early results are promising. A retrospective study evaluating 25 AM patients demonstrated an ORR of 32%, with 2 achieving CR, 6 PR and 7 SD [21]. The median PFS was 4.1 months, and only 2 patients discontinued treatment due to side effects [21].

17.5.2.4 Imiquimod

Imiquimod is a toll-like receptor 7 ligand that stimulates an anti-neoplastic, TH-1 mediated immune response. The topical medication has been extensively studied for lentigo-maligna melanoma (LMM) with impressive efficacy. Given the overlap in morphologic and histologic presentation between LMM and AM, imiquimod is an intriguing therapeutic option for non-surgical candidates. However, only scattered case reports have been published on the use of imiquimod for the treatment of AM, with favorable outcomes [22, 23]. Large RCTs are needed to confirm its efficacy and safety in this clinical setting.

17.6 Outcome of Acral Melanoma

AM is known to have a worse prognosis when compared to other CMM subtypes [1, 2]. Even when accounting for tumor thickness and stage, AM is associated with lower rates of overall survival. The 5- and 10-year disease-specific survival rates were recently demonstrated to be 80.3% and 67.5%, compared to 91.3% and 87.5% in CMM, respectively ($p < 0.001$) [1]. The 5- and 10-year AM-specific survival rates were highest in Non-Hispanic Whites (82.6% and 69.4%), Blacks (77.2% and 71.5%), and lowest in Hispanic Whites (72.8% and 57.3%) and Asian/Pacific Islanders (70.2% and 54.1%) [1]. Compared to other ethnicities, Asians/Pacific Islanders and Hispanics presented with the highest percentage of Stage II and III disease, which translated to lower overall survival rates [1].

Approximately 70% of CMM were thin at the time of diagnosis (0.01–1.00 mm) with 68% of cases being stage I. In contrast, only 41% of AM were classified as thin on presentation, and 38% were stage I [1]. When controlling for thickness and stage, the 10-year survival rates for AM tumors <1.00 mm and those 2.00–4.00 mm were still approximately 10–20% lower than for CMM overall, which suggests a biologic difference in the behavior between AM and other melanoma subtypes [1]. As discussed previously in the book in the "Pathogenesis of Melanoma" chapter, there are known differences in mutations when comparing AM to CMM.

Currently, the factors that make minority populations most vulnerable to AM are unknown.

Some hypotheses include a lack of access to adequate dermatologic care, lack of trust in the healthcare system, and a lack of awareness amongst patients and non-dermatologist physicians regarding AM. Improved surveillance in these patient populations is a potential method to decrease their vulnerability to AM. A retrospective study of AM patients in a Japanese hospital over 28 years demonstrated that increasing awareness of AM through public health programs was clinically correlated with detection of AM at earlier stages and better survival rates [2]. Educational campaigns and greater surveillance of cutaneous glabrous changes in people of color may be beneficial in improving overall survival rates in AM.

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Mucosal Melanoma

18

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18.1 Introduction

Primary mucosal melanomas are rare, aggressive neoplasms arising from melanocyte lineage cells, typically at mucocutaneous junctions at various anatomic sites in the body. First described in 1859 by Weber [1], mucosal melanomas (MM) account for less than 1.4% of all melanomas diagnosed in the USA [2–4]. While the incidence rates of cutaneous melanoma have steadily increased over time, the rate of MM has been stable; implying the presence of intrinsically dissimilar risk factors to those associated with cutaneous melanoma [4, 5]. These factors, combined with the biologically aggressive nature of MM and the relatively advanced nature of these tumors at the time of diagnosis, have rendered poor prognoses despite ever-increasing knowledge regarding these cancers [6]. Furthermore, MM also exhibits molecular features that are somewhat divergent from those classically associated with cutaneous melanoma, though recent advancements in whole genome sequencing have uncovered shared similarities between these two neoplastic entities that hint at shared biologic origins. Clinically, MM pose significant diagnostic and therapeutic challenges, owing to the anatomic locations in which they arise, the variability of their presentations, and difficulties related to their staging, partly owing to a lack of a universal staging algorithm, and partly owing to the diverse biology and pathology demonstrated by this disorder. This chapter will address the epidemiology, clinical features, and management considerations of MM, including those of the head and neck, genitourinary, and gastrointestinal tracts.

18.2 Epidemiology

MM is a rare clinical entity, with an incidence of 2.2 cases per million per year, in comparison to 153.5 cases per million for cutaneous melanoma in the USA [7–9]. They represent 0.03% of all cancers diagnosed annually, and unlike cutaneous melanoma, whose incidence has been steadily increasing since the 1990s, the incidence rates of MM appear to have remained stable, suggesting its own unique etiological factors [2, 7, 8, 10]. Unfortunately, no clinically significant modifiable risk factor for MM has been identified [7, 8, 10]. MM type based on anatomic location appears to vary with ethnicity and environment [5, 7]. A recent German study demonstrated that head and

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neck lesions comprised the bulk of their cases. In contrast, a contemporaneous Chinese study found that gastrointestinal (GI) MM formed the majority of their cases [11, 12]. Two large US studies using updated comprehensive data from the National Cancer Database (NCDB) and the North American Association of Central Cancer Registries found that genitourinary (GU) lesions were the most common subtype of MM, followed by head and neck lesions. This is dissimilar to an earlier study using similar data from the NCDB alone, in which head and neck lesions formed the bulk of the cases [2, 4, 5]. The general consensus, obtained using data from the largest population-based studies of MM in the USA, suggest that lesions of the GU tract are the most common in females, while HN lesions form the majority in males; with greater than 50% of head and neck MM arising in the nose and paranasal sinuses, and the oropharynx being the second most common site for MM of the head and neck [2, 4, 5, 7, 8, 10].

It should be noted that MM appears to be a disease of the elderly. The average age at diagnosis is >70 years, with a possible exception for lesions of the oropharynx in which the average age is lower [4, 12]. MM also appears to occur more frequently in female patients, with a female-to-male ratio of 1.85:1. This increased ratio is likely driven by the higher incidence rates of vulvovaginal mucosal melanoma, which make up GU melanoma, the most common type of MM in women [7, 8]. Previously, it was thought that there were no racial predilections for MM. This no longer appears to be the case, as higher numbers of MM cases are detected in Caucasians when compared to African Americans [4]. However, MM forms a higher proportion of all melanoma types in Asians, Hispanics, and African Americans when compared to Caucasians. This is likely a result of the lower incidence of cutaneous melanoma in these populations [2, 4, 5]. As mentioned earlier, an environmental predilection exists for specific subtypes of MM; for example, oropharyngeal mucosal melanoma occurs at a higher rate in Japanese patients when compared to the rest of the world [12–14].

Clinically MM carries a worse prognosis when outcomes are compared to its cutaneous counterpart [8, 15, 16]. Five-year survival rate for cutaneous melanoma for all stages at diagnosis approximates 80%; in comparison, the survival rate for mucosal melanoma is 14% [15–17]. This stark contrast has been attributed to multiple factors, including pathogenesis within "hidden" anatomic sites not amenable to regular screening efforts, especially in the case of gastrointestinal lesions; this likely contributes to the frequently advanced nature of the disease at diagnosis [5]. This is compounded by the fact that the locations of MM are often rich in lymphovascular supply, which make complete resection difficult, in addition to increasing the risk of metastatic spread [7, 10]. MM appears to be biologically more aggressive than its cutaneous counterpart even when the clinical aspects of delayed diagnosis are accounted for. For example, in the context of invasive metastatic disease, MM patients experienced shorter median overall survival than those with cutaneous melanoma [15].

18.3 Pathogenesis and Molecular Characteristics

The pathogenesis of MM remains poorly characterized, and this has hampered efforts to develop effective therapeutics specific to mucosal melanoma. The problem is further compounded by the rarity of MM [7, 8, 10]. It is, however known, that MM arise directly from resident melanocytes in the mucosa and not from the extension of cutaneous lesions either directly or via metastatic spread [10, 18–21].

Given its dissimilarities to cutaneous melanoma, it comes as no surprise that MM has distinct mutations and molecular characteristics. It is well known that the vast majority of cutaneous melanomas (94%) have driver mutations in the canonical mitogen activated protein kinase (MAPK) signaling cascade via mutations in *BRAF, NRAS, or NF1* [16, 17, 22, 23]. Conversely, only 28% of MM appear to harbor MAPK mutations, with driver mutations being identified in

the tyrosine kinase *KIT* upstream of the MAPK cascade in 15–39% of MM [7, 17]. Intriguingly, it also appears that MM are chromosomally unstable with high mutational loads and frequent focal amplifications and deletions, often resulting in loss of critical tumor suppressors such as *PTEN* or *CDKN2A* along with amplification of pro-growth genes such as *CDK4* [16, 23–25]. The cause of this chromosomal instability and genomic alterations is ambiguous, especially given that melanocytes for MM are effectively shielded from UV-B radiation and other similar exogenic genotoxic insults [26]. One possibility that has been postulated involves the whole chromosome doubling events during pathogenesis, possibly involving mitotic errors such as cytokinesis failure or endoreduplication, which data from whole genome sequencing of MM appears to support [16, 23, 27–29]. Lastly, it should be mentioned that MM is not entirely molecularly distinct from its cutaneous cousin; recent studies, especially involving whole genome sequencing, have demonstrated shared genomic alterations between mucosal and cutaneous melanomas, especially in those involving the gene *TERT*, suggesting that shared melanocyte precursor lineages predispose these subtypes of melanoma to similar patterns of genomic alterations at least in part, hinting at shared vulnerabilities that could be adapted for therapeutic advantage [23, 30].

Immunohistochemically, confirming a diagnosis of MM is similar to that for cutaneous melanoma. Due to their shared lineages, MM have been shown to be positive for a variety of markers commonly in use for the diagnosis of cutaneous melanoma, including S-100, HMB-45, Melan-A, and Mart-1 [7, 31, 32]. A recent study assessing pathologic features of sinonasal MM found that *MITF* staining, another marker commonly used for the pathologic confirmation of melanoma, was not only helpful in the diagnosis of mucosal melanoma, but also in identifying tumor-associated intraepithelial melanocytosis and hyperplasia [33]. It should be mentioned, however, that due to the invasive nature of mucosal melanoma, ulceration, and fragmentation of samples are frequent, which can make confirmatory staining challenging [34]. As such, clinicopathologic correlation is often essential in the diagnosis of MM, especially when using a negative stain or pathologic study to rule out this malignancy.

18.4 Clinical Presentations

As with cutaneous melanoma, MM can present with features embodied by the classic "ABCs"—asymmetry, border irregularity, and color variation. However, due to their typically inaccessible anatomic location, obtaining a history of lesion evolution from the patient can be difficult, if not impossible [10]. At least initially, most MM will appear as isolated pigmented lesions surrounded by seemingly healthy mucosal tissue, although on examination, the clinician may also note changes in the region surrounding the lesion, such as nodularity or thickening of the mucosa. Undiagnosed, they may progress and eventually present more like a visceral tumor, causing symptoms specific to the location in which the MM arises from [7, 10].

18.4.1 Head and Neck Mucosal Melanomas

More than 50% of HN MM arise in the nose and paranasal sinuses, with the oral cavity being the second most common site [7, 9].

18.4.1.1 Sinonasal Mucosal Melanoma

Initial symptoms associated with sinonasal lesions may be non-specific, but the most common symptoms for which patients seek clinical evaluation are epistaxis, a new nasal mass, or symptoms of nasal obstruction (most frequently unilateral) [32, 35, 36]. It should be noted that the nasal cavity has been shown to be the most common site for sinonasal mucosal melanoma, especially along the septum and lateral wall [32, 35]. As such, disease progression can exert a mass effect on nearby facial structures, leading to focal neurologic symptoms such as diplopia, proptosis, facial pain, as well as other visual changes [7, 35]. Given the often highly vascular nature of

MM, recurrent epistaxis is often the inciting complaint about those seeking care and should be suspected in any patient with recurrent epistaxis who presents with a new mass lesion in the nasal cavity [37].

On examination, sinonasal MM often appear as brown or black-pigmented, polyploid masses rather than flat pigmented lesions [36]. The clinician must be cautious as the mass may be amelanotic and appear similar to more benign conditions, such as an atypical nasal polyp. As such, any patient who presents with an atypical or polyploid mass in the nasal cavity, even if non-pigmented, should be biopsied to rule out MM. Patients presenting with larger tumors (>3 cm) have a poorer prognosis [32]. Lesions arising from the paranasal sinuses often confer a poorer prognosis than those arising from the nasal septum or lateral wall, largely due to the fact that paranasal lesions may often be asymptomatic until the advanced disease causes obstructive symptoms via the mass effect on nearby critical structures [38, 39].

Once a diagnosis of sinonasal MM has been made via biopsy, further diagnostic work-up includes nasopharyngoscopy to assess the nasal and paranasal sinuses, as well as delineate the limits of the tumor three-dimensionally [3]. Imaging studies, including CT and MRI, can assist with assessing the extent of tumor spread within the nasal cavity, as well as a possible invasion into the orbit or the CNS [35]. It is also imperative to assess for the metastatic spread at this time, with a whole body PET-CT and brain MRI [3].

18.4.1.2 Oropharyngeal Mucosal Melanoma

Oropharyngeal MM can occur at any site of the oral cavity, but are most commonly found on the maxillary gingiva and the hard palate [7, 13, 14, 40]. Patients are often asymptomatic, and in contrast to the more mass-like presentation of the sinonasal lesions, oropharyngeal lesions often begin as flat pigmented lesions that progress to ulceration, localized invasion, and lymph node metastases [7]. The most common symptoms for which patients seek care are therefore often dental in origin, ranging from frequent gum bleeding to tooth mobility [7]. Unfortunately, amelanotic lesions in the oropharynx are not infrequent, which has contributed to the difficulty in diagnosis and a poorer prognosis [41, 42]. Almost a quarter of all patients with oral lesions have regional lymph node metastases at the time of diagnosis [43]. The average age at diagnosis for oropharyngeal lesions is also lower when compared to other subtypes of MM, at 59.2 years, and in contrast to other subtypes, appears to have a predisposition for the male sex [44, 45].

Once a lesion suspicious for oral melanoma has been identified, a biopsy is imperative, though prophylactic excision may also be warranted, as almost one-third of oral melanomas appear to originate from a precursor pigmented oral lesion [9, 13, 40]. Similar to their cutaneous counterparts, oral melanomas >4 mm in thickness have been shown to have a high metastatic potential [40]. Furthermore, nodal involvement effectively cuts median survival to approximately a third of those without nodal involvement (18 months vs. 46 months) [40]. Palatal involvement has been shown to confer a poorer prognosis than gingival involvement [7, 40, 46]. Given the frequency with which this cancer presents with advanced disease, assessing for metastatic spread, including assessment of regional lymph nodes, is essential [43].

18.4.2 Gastrointestinal Mucosal Melanomas

MM of the gastrointestinal tract primarily arise in the anorectal region and is the third most common site for MM overall [4, 5, 47]. Similar to other MM, anorectal lesions occur in the elderly with a predisposition for the female sex; it also appears to have a higher prevalence among Caucasian patients [4, 48]. Lesions may affect the anal canal and/or the rectum, such that the most common presenting symptom is recurrent rectal bleeding, as well as anorectal pain secondary to mass effect from the lesion [7, 49]. Other

common complaints may include pruritus and changes in bowel habitus. The tumor may also cause prolapse of the anus with resultant fecal incontinence, especially as it becomes advanced locoregionally [49]. Similar to sinonasal MM, anorectal lesions appear most often as polyploid, frequently friable tumors that may be pigmented or amelanotic; it should be noted that up to 30% of anorectal MM have been found to lack pigmentation, and cautious work-up and biopsy-driven diagnosis is key to ensure that this invasive disease is not misidentified as a more benign condition, such as hemorrhoids or anorectal polyps [7, 49–51]. Management centers around wide local excision with selective lymphadenectomy, with appropriate imaging and follow-up to monitor for local recurrence of the tumor and metastatic spread [52–54]. This is particularly important as early aggressive management may significantly impact patient survival, with median survival ranging between 14 and 24 months depending on nodal involvement [54].

MM of the esophagus, stomach, and small intestines are generally rare, though esophageal lesions appear to have a higher than expected incidence among Japanese patients [7, 55, 56]. Presenting symptoms are largely dependent on their sites of origin. Patients presenting with esophageal tumors often present with progressive dysphagia; other symptoms include weight loss, epigastric, or retrosternal pain, and more rarely, hematemesis or melena [7, 57, 58]. Interestingly, esophageal lesions appear to be less friable than other mucosal melanomas, which may be due to the tendency of these tumors to present as flat or elevated pigmented lesions in the esophageal walls on the exam, rather than polyploid masses like those occurring in the sinonasal or anorectal tracts [7, 59].

Primary lesions of the stomach are rarer still, as are those of the small intestine. Again, symptoms largely depend on the site of origin; gastric mucosal melanomas may present with abdominal pain and anemia secondary to ulceration and bleeding from the lesion, while small intestinal lesions often present with symptoms secondary to localized ileus and bowel obstruction as the mass continues to grow [60–62]. Both gastric and small bowel tumors may also cause non-specific complaints, such as nausea, vomiting, and weight loss [60–62]. The ileum appears to be the most common site of occurrence for small bowel lesions [62]. Both lesions of the stomach and the small intestine can cause secondary anemia due to friable lesions that cause upper GI bleeding, which may be mistaken initially for other conditions, such as peptic ulcer disease [7, 60, 62]. It should be noted that some controversy remains regarding whether or not gastric and small intestinal melanomas reflect true primary lesions or if they are metastatic lesions from another site, mainly owing to their extreme rarity; notably, less than 20 cases of primary gastric mucosal melanoma have been reported to date [7, 60]. Prognosis for these rarer subtypes of gastrointestinal MM are typically very poor, even when compared to other mucosal melanoma subtypes such as those of the head and neck and the genitourinary tracts, with a median survival of 16 months for small bowel lesions, 5 months for gastric lesions, and 12 months for esophageal lesions [47]. As with other MM, surgical resection remains the mainstay of therapeutic management, though locoregional involvement and tumor resectability vis-à-vis anatomic accessibility may impact clinical decision-making [47].

18.4.3 Urogenital Mucosal Melanoma

MM of the urogenital tract predominantly occur in women, though rare cases of penile MM have been reported [63]. In particular, female urogenital MM account for 18–44% of all MM cases, with the bulk of such cases being attributed to vulvar (76.7%) and vaginal (19.8%) melanomas [2, 4, 5]. As with other MM subtypes, vulvovaginal melanomas are a disease of elderly women with a median age of 68 years at diagnosis and a striking predilection close to 90%, for Caucasian patients [64]. The most common symptoms at presentation may include bleeding, pruritus, dyspareunia, dysuria, and a new vulvar or vaginal

mass [65–67]. Generally, lesions of the vulvovaginal region are most commonly noted during routine exams, though the relatively high frequency of amelanotic mucosal melanomas in this region, particularly in tumors originating in the glabrous skin of the vulva, mean that special care must be taken to avoid misdiagnosis for other neoplastic or benign disorders of the female urogenital tract [65]. Satellite lesions are also common in these lesions, occurring in over 22% of patients [65]. In lesions originating in the vagina, masses were most often found in the anterior wall of the lower third of the vaginal canal. Vaginal masses are frequently more friable than those originating in the vulvar mucosa, with frequent ulceration and bleeding, likely due to the fact that vaginal lesions more often present as masses, whereas vulvar lesions may initially begin as plaques at mucocutaneous junctions of the vulvar skin [65, 67, 68].

For both vulvar and vaginal MM, as well as those arising in other portions of the urogenital tract, surgery remains the mainstay of therapy [69]. Similar to other melanomas, tumor thickness/size, ulceration, and nodal involvement are strong predictors of survival [65]. As locoregional involvement is common at the time of diagnosis, standard metastatic work-up and assessment of local lymph nodes for tumor involvement is recommended [64]. Interestingly, there is data to suggest that radical surgical approaches do not translate to improved outcomes in vulvovaginal lesions. This may be explained by an increased morbidity associated with a more radical surgical approach, as well as the proclivity of these cancers to be relatively advanced even at times when they appear to be "early" clinically [69]. These principles hold true for the less common subtypes of urogenital mucosal melanomas, including those arising at the cervix, as well as the urethra. Symptoms for these rarer variants mimic those for vulvovaginal lesions, though urogenital tumors may present earlier with symptomatic urinary incontinence and/or urinary tract obstruction, depending on its anatomic location [69, 70].

18.5 Survival Differences and Metastases

It should be noted that relatively stark survival differences exist between different subtypes of MM [5]. A current review of the literature on MM survival rate and median survival has demonstrated that gastrointestinal MM appears to have the worst prognosis when compared to sinonasal and urogenital tumors, though it is unclear whether this discrepancy is driven by a true difference in biologic aggressiveness between tumor subtypes, or whether the relatively insular nature of the anatomic locations in GI lesions makes expeditious diagnosis and complete surgical removal difficult [5]. It is known that the accessibility and visibility of a subtype certainly affect survival outcomes in mucosal melanoma; for example, sinonasal tumors and vulvar tumors, which are the most easily visualized and thus the most easily diagnosed, have the best prognoses, with 5-year survival rates of 25–42% for sinonasal tumors and 24–68% for vulvar tumors depending on nodal involvement [32, 39, 64, 71]. In comparison, 5-year survival rates for oropharyngeal and gastrointestinal tumors are less than 20%, even in the absence of nodal involvement at diagnosis [40, 47, 59]. Of note, however, anorectal MM, which is anatomically more accessible than oropharyngeal or gastrointestinal melanoma, still has a low 5-year survival rate below 30%, with a median survival of 14–20 months, even with optimal surgical and medical management [54]. The most likely explanation is that these survival differences are driven by a combination of biologic variations, local tumor-environment interactions under different anatomic contexts, and the ease of both diagnosis and treatment. Clinically, this should translate into a more aggressive management in patients whose prognoses are intrinsically worse by virtue of their anatomic involvement.

As mentioned above, metastatic disease is exceedingly common in MM, and a standard metastatic work-up should be part of the "mucosal melanoma battery," involving both whole

body PET-CT and brain MRI, with laboratory panels to assess for serum lactate dehydrogenase (LDH), and a comprehensive metabolic panel. Generally, MM appear to show metastatic avidity for the lungs and liver, in particular for GI and GU tumors [12, 72]. Less commonly, tumors may also metastasize to bone and the CNS, with a consequent increase in both morbidity and mortality for these patients [73]. Regional lymph node involvement is also exceedingly common and is often found at the time of diagnosis, although cases of distant metastases in the absence of nodal involvement have also been reported [10, 74]. In very advanced cases, peritoneal involvement may also be seen [74, 75]. Metastatic disease imparts a dismal prognosis, with 5-year survival rates in the single digits for most subtypes following confirmation of distant metastases [2, 10, 15, 38].

18.6 Staging in Mucosal Melanoma

A clinical challenge in patients with mucosal melanoma is the lack of a universal staging system. One major reason for this lack is the rarity of this cancer type as a whole, which, when divided into anatomic subtypes, further decrease total case numbers, in addition to introducing subtype-specific challenges to establishing a comprehensive diagnostic and staging algorithm [5, 8, 10]. Currently a limited staging system introduced by Ballantyne in 1970 is in use, which divides mucosal melanomas into three stages; stage I for localized, stage II for regional, and stage III for metastatic disease [76]. The simplicity of this system allows for its use across multiple different subtypes of mucosal melanoma, but the fact remains that this is too simplistic an algorithm to capture the clinical diversity and complexity of clinical presentation appropriately. Indeed, recent studies have shown that this simplified system portends a worse prognosis for the patient when compared to the new TNM staging system introduced in the seventh AJCC staging manual [39, 77–79]. The AJCC staging algorithm, however, also suffers from some critical drawbacks. For one, the T1 and T2 categories are entirely omitted owing to the poor prognosis of even localized disease, with staging beginning at T3 instead. This renders prognostication based on TNM staging more challenging, in addition to inappropriately capturing disease that might be truly localized and more reflective of an earlier stage.

There is tremendous variation in the way that MM subtypes are classified for staging; for example, vulvar (but not vaginal), mucosal melanomas have been staged using the traditional TNM classification system in use for cutaneous melanoma; with fairly good prognostic value [10, 35]. Vaginal lesions, however, are generally assessed on the size of the primary tumor, with data suggesting poorer prognosis in primary tumors greater than 3 cm [80]. Gastrointestinal MM lack a unified classification system, while anorectal lesions use the Ballantyne system from 1970 [5]. These factors combined further impede the accurate clinical staging and prognostication of these aggressive diseases. Additionally, the absence of a universal staging algorithm has made a comparative analysis of data from various studies difficult, and staging information is frequently omitted or reported as "missing" in larger databases [5]. As research continues to advance on MM, a universal staging system for MM, irrespective of anatomic origin, will be critical in allowing for more accurate prognostication and communication and also to facilitate comparative research incorporating multi-institutional and multi-national datasets.

18.7 Treatment of Mucosal Melanoma

18.7.1 Surgical Resection

Despite recent advancements in our understanding of the basic biology of melanoma, as well as the development of more efficacious systemic therapeutic agents, surgical resection of the primary tumor remains the mainstay of therapy for all subtypes of MM. Indeed, complete resection

with clean margins is always the goal of surgical therapy, but this may be hindered or may need to be adjusted with the clinical presentation and surgical options available.

For sinonasal tumors, critical structures surrounding the primary tumor, as well as invasion of the tumor into sensitive anatomic locations, may hinder obtaining negative margins [7, 32]. Traditionally an open approach has been utilized involving the cribriform plate with either orbital or nasal exenteration depending on locoregional disease involvement [77]. However, in recent years, endoscopic techniques for the management of sinonasal mucosal melanoma have been investigated and found to be potentially superior in reducing morbidity, with better postsurgical functional outcomes when compared to open approaches [81–83]. Furthermore, it was demonstrated that using an endoscopic approach was not inferior in terms of disease control and survival outcomes when compared to open surgery [81].

For anorectal MM, the primary goal of surgery is to spare the anal sphincter while removing the tumor with negative margins [52–54]. Traditionally, abdominoperineal resections were performed but did not improve outcomes in patients with localized disease. This form of radical surgery is now typically reserved only for cases where there is evidence of local recurrence or regional invasion [54, 84]. Depending on the extent of nodal involvement, selective lymphadenectomy may also be performed in addition to tumor resection [54].

The mainstay of surgical therapy in vulvar MM previously involved aggressive pelvic exenteration, with en bloc resection of all major pelvic organs [7, 10]. However, due to the significant morbidity incurred by such an intervention, along with the findings that overall outcomes were not significantly improved in comparison to more conservative approaches, wide local excision has become the more favored approach [69]. Nonetheless, in cases of vaginal MM in which clean negative margins are difficult to obtain, pelvic exenteration may still be considered [10, 69, 85]. Interestingly neither sentinel lymph node biopsy nor regional lymphadenectomy in vulvovaginal mucosal melanomas was shown to provide a survival benefit, such that these procedures are seldom performed, especially in cases of locally limited disease [8, 80, 86, 87].

For rarer subtypes of MM (e.g., small bowel or stomach) aggressive, radical en bloc resections of the affected organ and surrounding structures are favored, though there is a paucity of evidence to suggest these approaches improve outcome [47]. Conversely, a recent study did note that surgical management appears to confer a survival advantage in patients with MM over non-surgical therapy; this may mean that for biologically aggressive subtypes with poorer prognoses, an active surgical approach may provide some benefit for patients, although this may be secondary to a staging bias more conducive to surgical intervention [5]. Indeed, in cases of locoregional recurrence without metastases, salvage with another surgical procedure is often considered standard of care, especially if the recurrent tumor appears to be resectable [10].

18.7.2 Radiation Therapy

Despite its frequent use in the postsurgical adjuvant setting to provide local control, there is little evidence to suggest that primary radiation therapy provides a benefit to patients in terms of survival outcomes [7, 8, 10]. In prior years, when there was a lack of systemic therapeutic options available to patients with mucosal melanomas, radiation therapy may have been considered for those presenting with unresectable or widely advanced disease. However, as newer systemic agents have entered the cutaneous oncology field, the role of radiation therapy has diminished [8, 10]. Moreover, although adjuvant radiation therapy has demonstrated improved local control, especially in lesions of the head and neck, this is limited by the fact that a relatively high dose of radiation is required to obtain such control. Also, the bulk of the morbidity and mortality in MM arise from distant metastases, for which radiation therapy has not been shown to improve the rate of metastatic spread or survival outcomes [35, 88–90]. In general, the main role of radiation therapy

in MM patients is in the setting of palliative care, especially in those presenting with the symptomatic disease that is not amenable to surgical options [8, 91].

18.7.3 Systemic Therapy

Until 2011, the only chemotherapeutic options approved by the FDA for any type of melanoma were dacarbazine and high-dose Interleukin-2 (IL-2), neither of which were associated with significant overall survival outcomes [92]. Melanoma as a whole has been historically recalcitrant to cytotoxic systemic agents, with MM holding fast to this general principle [8, 35, 93]. Recently, however, the discovery and development of immune checkpoint inhibitors in the form of monoclonal antibodies targeting either PD-1/PD-L1 (Programmed cell Death-1/Programmed cell Death-Ligand 1) or CTLA-4 (Cytotoxic T Lymphocyte Antigen-4) have significantly expanded systemic therapies available to patients with MM [94–96]. Unfortunately, MM was not shown to have as robust a response to checkpoint inhibition when compared to cutaneous melanoma, though it was noted that combination therapy with nivolumab and ipilimumab demonstrated improved efficacy with a respectable objective response rate of 37.1%. Combination immunotherapy is therefore recommended in the treatment of advanced MM [95–97]. Currently, there is little data to support the use of immune checkpoint therapy in the context of adjuvant therapy after surgical resection, though limited data from one group in China posits its encouraging biologic rationale for this therapeutic approach [98, 99].

Other systemic agents that can be employed include *BRAF-V600E* specific small molecule inhibitors, such as vemurafenib or dabrafenib, as well as the *MEK* inhibitors cobimetinib and trametinib [8, 10]. In the less common cases where mutational analysis reveals a *BRAF*-mutant status in mucosal melanoma, patients should be offered a combinatorial *BRAF-MEK* inhibition approach. Other mutations that are common in MM include those in *KIT*, a tyrosine kinase upstream of the MAPK signaling cascade. Although only 15–39% of MM harbor mutations in *KIT*, nearly 40% of these were shown to respond to systemic inhibition of this tyrosine kinase, most often through imatinib, which has been used to some clinical success in the treatment of gastrointestinal stromal tumors (GIST) harboring *KIT* mutations [10, 25, 100–104]. Other tyrosine kinase inhibitors, including sunitinib, dasatinib, sorafenib, nilotinib, and masitinib are being studied for the systemic management of MM [105–109]. However, it should be noted that much like the experience in the early days of the vemurafenib trials, monotherapy with a single small molecule inhibitor such as imatinib almost always results in therapeutic resistance, and thus should not be relied upon as the singular systemic modality [10]. Other targeted therapies under investigation currently include co-inhibition of MEK with PI3K-AKT and/or CDK4/6 [110, 111]. Further studies to assess mechanisms underlying treatment failure and inhibitor resistance in MM will be key in better characterizing the biochemotherapeutic vulnerabilities of this unique disease, with the goal of developing an efficacious multi-modal treatment approach that combines surgical resection with combinatorial targeted and/or checkpoint inhibitor therapy.

18.8 Conclusion

In sum, MM is a highly aggressive, clinically and genetically distinct neoplastic disorder that confers a particularly poor prognosis for patients diagnosed with it. Due to its aggressive biologic features, combined with the relatively advanced stages at which it typically presents, an active clinical plan for management is key, combining multi-disciplinary approaches for the diagnosis, treatment, and long-term management of this cancer. Specific anatomic sites of origin, such as the GI tract, portend worse clinical outcomes, and management should be adjusted accordingly in such cases. Currently, the lack of a universal staging system provides a significant barrier to both effective research efforts as well as accurate

prognostication. The current mainstay of therapy for MM remains surgical resection with negative margins, though using more conservative approaches including endoscopic methods and wide local excisions, have begun to replace more radical exenterations and en bloc resections due to comparable survival outcomes with improved morbidity. The advent of new systemic agents, including immune checkpoint inhibitors and targeted therapy (e.g., *KIT* inhibitors) have significantly expanded the options available for medical management of this malignancy, though further research to characterize targetable molecular features and unique biochemical vulnerabilities are needed.

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Melanoma in Pediatric Patients

19

Hilary Haimes, Lisa Y. Shen, and Margaret S. Lee

19.1 Introduction

Pediatric melanoma (PM), while sharing a number of attributes with adult melanoma, possesses a number of characteristics that make it distinct in both presentation and clinical course. These unique qualities, compounded by PM's relatively low incidence as compared to adult melanoma, contribute to its diagnostic challenges and the consequent risk of a delay in initiation of therapy. An additional challenge in diagnosing and managing PM is the notable variety in behavior patterns among the different pediatric age groups. This chapter reviews the distinctive clinical features, management options, and prognosis of PM.

19.2 Incidence

Pediatric melanoma (melanoma diagnosed between birth and age 18) is a rare disease with an incidence of approximately 5 per million pediatric patients per year in the United States, comprising 0.4–4% of all melanoma cases [1–3]. It is the most common pediatric skin cancer and represents 1–3% of pediatric malignancies [1, 4]. Longitudinal studies have demonstrated an increase in the incidence of PM since the 1980s, though more recent studies have revealed a relative decline in PM diagnoses since the turn of the century [1, 2, 4]. The 2007 National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database trended the incidence of PM from 1988 to 2007 and found an increase in incidence of 50% over the 20-year period [2]. Subsequently, a more recent examination of SEER data revealed a decreasing incidence in PM from 2004 to 2010, most notably in the adolescent age group (ages 15–19 years) [5].

A proposed etiology for this recent downtrend in PM cases is changes in sun-related practices in the setting of successful public health campaigns to promote photoprotection [1, 5]. These behavioral alterations may be more effective at mitigating PM risk in the adolescent population, as ultraviolet radiation (UV) exposure is noted to be a particular risk factor in these individuals as compared to younger patients (see "Risk Factors" section).

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19.3 Risk Factors

19.3.1 Family History of Melanoma

A number of risk factors have been associated with the development of pediatric melanoma. Genetic predisposition is considered a key contributor. Family history increases the risk of melanoma in patients of all ages by 5–10%, and familial cases are diagnosed at a younger age than cases in the general population [1, 4, 6]. A prospective study by Goldstein et al. followed 60 families in which at least three individuals possessed a history of melanoma and found that the risk of developing melanoma before age 20 years was 6–28 times higher than in the general population (based on SEER data) [3].

19.3.2 Genetic Mutations

A number of genetic mutations confer varying degrees of risk for the development of melanoma. In xeroderma pigmentosa, an autosomal recessive disorder characterized by UV exposure sensitivity due to impaired DNA repair mechanisms, patients have a 2000-fold increased risk of melanoma compared to the general population, and the mean age of melanoma development is 17–18 years [7, 8].

Alterations in the cyclin-dependent kinase inhibitor 2A (CDKN2A) gene are the most prevalent genetic mutation identified among PM patients, seen in 10–40% of familial cases [3, 6]. In families with a history of this high-risk susceptibility gene, children and adolescents are significantly more likely to develop melanoma compared to CDKN2A-negative families (11.1% v. 2.5%) [3]. Familial atypical multiple mole and melanoma (FAMMM) syndrome, in which patients have greater than 50 melanocytic nevi and a family history of melanoma, is a particular genodermatosis associated with the CDKN2A mutation. In examining patients who possess the CDKN2A gene mutation and have family members diagnosed with FAMMM, researchers have found the penetrance of melanoma to be 58–92% [9]. The development of melanoma in these patients occurs at a younger age than the general population [9, 10]; however, CDKN2A-associated PMs are still rare, accounting for only 1–2% of melanomas in adolescent patients [3, 6].

19.3.3 Preexisting Nevi

As in adult patients, pediatric patients with a large number of acquired melanocytic nevi and dysplastic nevi are at higher risk of developing melanoma [1, 10, 11]. These nevi may act as precursors to melanoma in some cases, but they may also simply serve as markers for increased risk of melanoma elsewhere on the body [11]. Adolescents with more than 100 acquired nevi are 34 times more likely to develop melanoma than those with fewer than 25, and those with 10 large nevi are 15 times more likely to develop melanoma than those without large nevi [12]. The presence of congenital melanocytic nevi also increases the risk of PM, which will be discussed further in the "Etiology" section. Still, the majority of PM cases arise in patients with no family history of melanoma and in normal skin, rather than preexisting nevi (atypical or congenital) [13].

19.3.4 Ultraviolet Radiation

UV radiation exposure is a risk factor for the development of melanoma in patients of all ages. Patients with lighter skin types are more likely to develop melanoma, and the vast majority of melanoma patients are Caucasian [1, 11]. Notably, UV exposure (including sunburns and tanning bed use) has been found to play a larger role in the development of melanoma in adolescents than in younger patients [1, 14]. This trend may be partially due to the greater role that genetic predisposition plays in the development of melanoma in younger patients.

19.3.5 Immunosuppression, Prior Malignancy, and Iatrogenesis

Pediatric patients with inherited immunodeficiencies are three to six times more likely to develop melanoma, and those with a history of organ transplantation maintained on immunosuppressive medications have a fourfold increased risk of acquiring the disease [10, 11]. In addition, a history of childhood malignancy (particularly leukemia and lymphoma) confers a 2.5-fold increased risk of subsequent melanoma diagnosis [10, 15]. Finally, antimicrobials have also been implicated in the development of melanoma [10]. Case reports have shown that long-term voriconazole use increases risk of cutaneous malignancy (most frequently squamous cell carcinoma but also malignant melanoma), which is likely due to the medication's photosensitizing effects [16, 17].

19.4 Etiology

Pediatric melanoma may arise de novo, from precursor lesions such as acquired or congenital melanocytic nevi, or, rarely, via transplacental transmission. A retrospective study by Schmid-Wendtner et al. [18] of 36 PM cases revealed that 25% of melanomas originated from acquired nevi. The risk of developing melanoma from congenital melanocytic nevi (CMNs) depends on the size of the CMN and is significantly higher in larger lesions. Small CMNs are defined as those that reach a size of less than 1.5 cm by adulthood, whereas large CMNs are those that reach greater than 20 cm by adulthood. Some recognize a further classification of giant CMNs, those larger than 40 cm by adulthood [19, 20].

One percent of neonates have CMNs, and only one in 20,000 newborns develop a CMN greater than 10 cm [21]. The lifetime risk of developing melanoma from a smaller CMN is controversial but is likely in line with the lifetime risk in the general population. Studies suggest that small CMNs may serve as precursors to PM in rare instances, but these malignancies rarely develop in the pediatric period [22, 23].

Large and giant CMNs, on the other hand, are associated with a higher risk of PM than that of the general population. Watt et al. [24] found that 2.8% of patients with CMNs greater than 20 cm underwent malignant transformation and Vourc'h-Jourdain et al. [25] calculated melanoma incidence in those with large or giant CMNs to be 2.3 per 1000 patient-years. A prospective study by Marghoob et al. [26] found a lifetime risk of 4.5% in patients with CMNs greater than 20 cm.

Historically, NRAS mutations were thought to play a role in the development of malignancy and/or neurocutaneous melanosis (an entity discussed in the "clinical presentation" section) among patients with large or giant CMNs [27]; however, more recent data suggest that, while giant CMNs are associated with NRAS mutations, no direct relationship exists between this genotype and malignancy or neurologic pathology [28].

19.5 Clinical Presentation

19.5.1 Clinical Characteristics

Pediatric melanoma most commonly arises in teenage patients and is rare in young children. Among the 256 cases of PM in the Colorado Cancer registry, the mean age of onset of PM was 16 years and no cases were diagnosed under the age of 5 years [29]. Notably, characteristics of melanoma vary by age. For example, the incidence of amelanotic melanoma is greater than that of pigmented melanoma in children aged below 10 years, whereas rates are equal in adolescents [1]. Younger children tend to develop melanomas on the head, neck, and extremities while teenage patients present with melanoma most often on their trunk [1, 2, 29, 30]. There is no gender predominance in younger children, but adolescent melanoma patients are more frequently female [1, 29].

There are a number of distinctive features of PM that differ from adult melanoma. PM is often thicker at time of diagnosis than melanoma in adults, which is likely multifactorial, due to both differences in growth dynamics and delayed

detection [1, 11, 31, 32]. PM is also more often grossly amelanotic, pedunculated, and/or nodular, especially in the pre-adolescent age group. A study by Ferrari et al. [31] retrospectively analyzing 33 patients age 14 years and younger, found that this cohort had a higher frequency of atypical features (amelanotic, verrucoid, nodular) compared to prior studies in adults. Lesions were amelanotic in 50% of cases and raised in 73% [31].

The clinical differences between pediatric and adult melanoma raise the question of whether standard approaches to diagnosing adult melanoma can be utilized in pediatric patients. Cordoro et al. [14] evaluated whether the well-established "ABCDE" melanoma detection criteria (*a*symmetry, *b*order irregularity, *c*olor variegation, *d*iameter > 6 mm, *e*volution) effectively identifies pediatric melanoma. They found that 60% of younger children (< age 10 years) and 40% of older children (ages 10–19 years) did not meet conventional ABCDE criteria. An additional "ABCD" diagnostic tool was proposed (to be used in conjunction with the traditional criteria), based on alternative features exhibited by melanomas in these cases: *a*melanosis, *b*leeding, "*b*umps," uniform *c*olor, variable *d*iameter, and de novo development.

Cordoro et al. [14] found that, while their study population failed to demonstrate a number of the classic features encapsulated in the original ABCDE measures, there was one notable exception. A history of recent lesional evolution was nearly universal among the subjects examined, emphasizing the reliability of this criterion in supporting a diagnosis of melanoma of all ages. Still, given the dynamic nature of benign nevi during childhood, it may be challenging to distinguish between expected and pathologic lesional changes [33].

19.5.2 Spitzoid Melanoma

Spitzoid melanomas, malignant melanocytic proliferations consisting of spindle and epithelioid cells on histopathology, represent a unique subset of malignant melanomas. These tumors occur most commonly in children. They exist on a spectrum of spitzoid proliferations, with Spitz nevi on the benign end and spitzoid melanomas on the malignant end. Straddling these two extremes is a group of spitzoid proliferations termed atypical Spitz tumors (ASTs), which encompass a broad range of atypia [32, 34].

Spitz nevi display a distinct phenotype when compared to classical benign melanocytic nevi. They are often flat or dome-shaped papules or nodules that range from amelanotic to pink, red, or dark brown, and they often demonstrate a rapid growth stage followed by a stagnation in growth [34]. A heavily pigmented variant of Spitz nevi, the pigmented spindle cell nevus of Reed, possesses a particularly characteristic clinical appearance consisting of jet-black coloration and starburst configuration on dermoscopy. These features may mimic melanoma, but their symmetry and uniformity are often reassuring.

Spitzoid melanomas also have distinctive qualities. In a retrospective analysis of 52 PM cases, Carrera et al. [32] found that, in comparison to non-spitzoid melanomas, spitzoid melanomas presented earlier (at a mean age of 12.5 versus 16.3 years), more frequently arose de novo, and were more commonly located on the extremities (rather than the trunk). Spitzoid melanomas are also quite rare. A retrospective study conducted by Bartenstein et al. [34] of 622 histopathologically diagnosed spitzoid proliferations revealed a melanoma rate of just 0.5 percent. In addition, Lallas et al. [35] conducted a retrospective study of 384 patients aged 12 to 85 years with clinically diagnosed Spitz nevus that were excised upon identification (per hospital protocol) and found that 87% of such lesions were histopathologically consistent with Spitz nevi. Only 13% were found to be melanoma, and none these cases were discovered in the pediatric population (all over age 20 years). Given the favorable prognosis of pediatric patients with spitzoid proliferations, Bartenstein et al. suggest that monitoring lesions that are banal-appearing both clinically and dermoscopically, rather than empirically excising them, may be appropriate [34].

19.5.3 Neurocutaneous Melanosis

In addition to cutaneous melanoma, patients with CMNs are also at risk of developing neurocutaneous melanosis (NCM), an entity characterized by cutaneous melanocytic lesions and benign or malignant melanocytic proliferations within the leptomeninges or brain parenchyma. NCM may manifest as solid tumors of the brain parenchyma or as diffuse and progressive proliferations within the leptomeninges [27, 36]. Histopathologic evaluation of the melanocytic deposits is ultimately necessary to rule out CNS melanoma in the appropriate clinical context.

Risk factors for CNS involvement include the presence of numerous CMNs, multiple satellite nevi, giant CMNs, or CMNs in the paravertebral or axial location [10, 36]. In patients with such risk factors, symptomatic NCM develops around 4% of the time, and asymptomatic NCM (based on brain imaging findings) arises 5% to 25% [36, 37] of the time [5, 26]. In symptomatic patients, neurologic manifestations include hydrocephalus, seizures, and focal neurologic defects, and onset of symptoms often appear by age two [10, 27, 36]. In their cohort of 450 patients with CMNs, Kinsler et al. [27] report a cutaneous melanoma rate of 12% among the 51 patients with MRI findings suggestive of NCM.

The indications for imaging patients with CMNs depend on whether they are symptomatic. For patients who develop new neurologic signs or symptoms, Kinsler et al. [27] recommend gadolinium-enhanced MRI of the brain and spine with contrast to evaluate for evidence of NCM, including leptomeningeal enhancement, hydrocephalus, or intraparenchymal tumor. Ideal timing of the MRI is within the first six months of life, before the brain is fully myelinated [27] and when infants may tolerate imaging while being swaddled after feeding (rather than requiring sedation) [38].

For asymptomatic children with CMNs, the decision to pursue CNS imaging for surveillance of NCM is more controversial. A retrospective study by Waelchli et al. [39] looked at the screening MRIs performed on 376 children with at least two CMNs and found that 21% of patients had an abnormal MRI. Furthermore, they found that MRI results served as effective predictors of subsequent neurodevelopmental abnormalities. Based on this study, Kinsler et al. [27] recommend obtaining CNS MRIs for all infants with two or more CMNs of any size. The goals of this guideline are to establish baseline imaging should patients develop neurologic symptoms over time, and prognosticate patients early. However, this recommendation is controversial, as the risks of sedation may outweigh the benefits of early imaging in certain cases.

19.5.4 Neonatal Melanoma

Neonatal melanoma (NM), which is particularly rare, may arise in the setting of large-to-giant CMNs (in 57% of cases) or via transplacental transmission (in 13% of cases). NM is most often seen on the head and neck (43% of cases) [30]. Of note, in a study of 87 cases of transplacental metastasis of malignancy of any kind, 31% were attributed to malignant melanoma. This finding suggests that melanoma has an increased tendency to metastasize to the fetus compared to other tumor types [40].

19.6 Diagnosis

There is often a delay in the diagnosis of PM, given that providers tend to have a lower index of suspicion for melanoma in pediatric patients and PM does not always exhibit the classic "ABCDE" features seen in adult melanoma [14]. Diagnostic delays and/or initial misdiagnosis have been reported to occur in 50–60% of cases [41, 42].

19.6.1 Clinical History and Physical Examination

The first step in diagnosis of pediatric melanoma is the identification of a suspicious lesion. As discussed in the "Clinical Presentation" section, employing the conventional "ABCDE" criteria in conjunction with the additional "ABCD" criteria

proposed by Cordoro et al. [14] may aid in detecting lesions of concern. Still, even the "ABCD" diagnostic tool is somewhat limited. A retrospective study of 52 PMs conducted by Carrera et al. [32] found that only 25% of lesions met the supplemental "ABCD" criteria. The modified "ABCD" criteria may have higher sensitivity in younger children, whose melanomas more often demonstrate non-classic appearances and behavior, while the classic "ABCDE" criteria may be more likely to identify melanomas in adolescents, whose lesions are more consistent with adult melanomas [1].

19.6.2 Dermoscopic Evaluation

Given the limitations in diagnosing pediatric melanomas based on history and physical examination alone, dermoscopy can be a useful adjunctive tool. Characteristic dermoscopic features identified in PM are similar to those in adult melanoma. Haliasos et al. [43] name ten classic dermoscopic findings, any single one of which should raise concern for melanoma. These include atypical networks, negative networks, streaks, shiny white structures, atypical dots and globules, irregular blotches, blue-white veils, regression structures, peripheral brown structureless areas, and atypical vessels. Of note, as PMs are more often amelanotic than adult melanomas, they more frequently display atypical vascular findings on dermoscopy, including dotted vessels, linear irregular vessels, or serpentine vessels [8, 43]. A study by Carrera et al. [32] found similar atypical vascular patterns on dermoscopy in Spitzoid PMs. In contrast, in non-Spitzoid PMs, they noted a "multicomponent pattern" consisting of irregular globules, a negative network, structureless white regression areas, and blue-gray regression.

19.6.3 Histopathologic Evaluation

The gold standard in diagnosis of malignant melanoma is histopathologic evaluation, and any lesions with suspicious features on clinical or dermoscopic evaluation should be biopsied. The preferred approach to obtaining tissue is complete excisional biopsy with 1–3 mm margins and sufficient depth to obtain an accurate assessment of tumor thickness [44]. In general, the same histologic criteria used to diagnose adult melanoma is used for PM.

Nodular melanoma is the most common histologic subtype of PM overall, though the incidence of particular melanoma subtypes varies based on age, which is expected given the differences in clinical presentation among younger and older pediatric patients. Nodular and Spitzoid subtypes are more common in children 10 years of age or younger, whereas conventional adult melanoma subtypes (most commonly superficial spreading melanoma) are most common in adolescents [1, 45]. Notably, a substantial number of PMs have been found to be histopathologically unclassifiable based on the known subtypes in adult melanoma [14]. Finally, on average, pediatric melanomas have greater Breslow thickness than adult melanomas, which may be due in part to delayed diagnosis and differing growth dynamics [11, 32, 45].

19.6.4 Genetic Testing

While extensive research has been devoted to the genetic mutations implicated in pediatric melanoma, molecular genomic testing is not currently standard of care and histopathologic diagnosis remains the gold standard [46, 47]. Genetic testing may be most useful in risk stratifying atypical Spitz tumors, as clinical and histologic findings are often less prognostically significant in these lesions (as compared to standard melanomas). For example, alterations in the TERT promotor have classically been associated with a poorer prognosis in ASTs [46, 48]. In addition, copy deletions in 6q23 identified on fluorescence in situ hybridization have been found to portend a favorable prognosis, whereas homozygous deletions in 9p21 predict a more aggressive clinical course [49, 50]. However, more recent evidence suggests that genomics may not consistently

differentiate between benign and malignant Spitzoid tumors in children [46, 48].

Genetic classification of Spitzoid tumors continues to evolve based on continuing research in this area. In 2018, the World Health Organization made a distinction between Spitzoid melanoma and Spitz melanoma [51]. The WHO suggested that Spitzoid melanomas with BRAF and NRAS mutations (which are associated with traditional melanomas) be recategorized as melanomas with Spitzoid features rather than Spitz melanomas. In contrast Spitz melanomas are characterized by driver mutations in HRAS and kinase fusions and are thought to be the malignant counterpart to Spitz nevi and ASTs. This recommendation is further supported by a study by Quan et al. [52] in which the categories of ASTs and Spitz melanomas become more cohesive and homogeneous (in terms of clinical features and more favorable prognosis) with the elimination of lesions with BRAF and NRAS mutations.

19.7 Differential Diagnosis

In addition to benign melanocytic nevi, a number of other benign proliferations may mimic pediatric melanoma.

19.7.1 Proliferative Nodules

Proliferative nodules (PN), which are benign proliferations of melanocytic cells that can arise within CMNs, may be mistaken for regions of malignant transformation [11]. They most often develop within giant CMNs and tend to be small dermal pink, brown, or black nodules. They may demonstrate rapid enlargement, sometimes with ulceration, though this is usually followed by a plateau and/or regression phase [1, 6]. Histopathologically, PNs consist of cellular dermal proliferations of spindled and epithelioid melanocytes that do not demonstrate mitoses, necrosis, expansile growth, or other classic melanoma features [6].

Given that PNs may appear atypical without being malignant, Kinsler et al. [27] recommend a conservative approach to monitoring these lesions. For a new lump or change within a CMN, providers are advised to perform a thorough exam and obtain high-quality photographs, which should be reviewed after one month. If no change is observed, providers may opt for continued clinical observation; if evolution is noted, the lesion should be excised and evaluated histopathologically.

19.7.2 Spitz Nevi and Atypical Spitz Tumors

Spitz nevi and atypical Spitz tumors may also be erroneously diagnosed as malignant melanoma in the pediatric population. In a retrospective analysis of 102 pediatric melanoma cases, Spatz et al. [42] sought to determine the accuracy of PM diagnosis. They found that 41% of cases were erroneously diagnosed as melanoma, and 26% of these cases were reclassified as Spitz nevus or ASTs. Thus, second opinions by dermatopathologists with expertise in pediatric pigmented lesions may be recommended in these situations.

19.7.3 Pyogenic Granuloma

Pyogenic granulomas (PGs) are also in the clinical differential diagnosis of PM, given that melanoma in younger children may present as amelanotic or pink, nodular, ulcerative lesions [1]. However, PGs have a distinct dermoscopic appearance including a red homogeneous area, vascular lucunae, peripheral white collarette, and sometimes white intersecting lines [53].

19.8 Management

19.8.1 Surgery

As in adult melanoma, the mainstay of treatment for pediatric melanoma is wide local excision. Margins are determined by tumor thickness of the primary lesion. Given the relative paucity of

data due to the rarity of PM, there are no age-specific guidelines for surgical intervention [1].

19.8.2 Staging

The approach to staging PM is the same as that used for adult melanoma. In line with the recommendations of the American Joint Committee on Cancer (AJCC), staging is based upon presence or absence of ulceration, tumor thickness, degree of lymph node involvement, and presence of metastases [54]. Of note, given that Breslow thickness is often greater in pediatric than adult melanoma [11, 32, 45] (see "Diagnosis" section), there has been debate about whether tumor thickness predicts survival in pediatric populations as it does for adult cases. Studies have shown that increased Breslow depth in PM is correlated with a worse outcome, including increased metastasis and decreased overall survival [1, 11, 31]; however, this trend may be specific to adolescent rather than younger PM patients. For example, a retrospective review of 137 PM cases conducted by Paradela et al. [11] revealed a lower mortality rate in patients age 10 years or younger (compared to adolescent patients) despite thicker primary tumors and higher rate of sentinel node positivity.

19.8.3 Sentinel Lymph Node Biopsy

The value of sentinel lymph node (SLN) biopsy in the detection of micrometastases for the pathologic staging of pediatric melanoma is controversial. Multiple studies have shown that younger melanoma patients have higher rates of SLN positivity than older patients, especially in the pre-adolescent age group [11, 55]. Livestro et al. [56] demonstrated that while pediatric melanoma patients aged 13 years or younger had a higher rate of SLN positivity compared to thickness-matched adults, there was no difference in ultimate survival rate. This suggests that SLN positivity may not predict a more aggressive clinical course in pediatric patients.

Other studies, however, demonstrate a correlation between positive SLNs and poor prognosis. In an examination of SEER data from 2004 to 2011, for example, Kim et al. [57] showed that pediatric melanoma patients with positive SLN biopsy had increased mortality compared to those with negative SLN biopsy (though still better prognosis than adult patients with positive lymph nodes). The National Comprehensive Cancer Network (NCCN) guidelines (which apply to all melanoma cases and do not address specific pediatric considerations) recommend considering SLN biopsy in all patients (adult or pediatric) with melanomas <0.8 mm thick with ulceration or > 0.8 mm thick regardless of ulceration.

19.8.4 Adjuvant Therapy

In adult melanoma, adjuvant systemic therapy is often initiated in more advanced melanoma cases. Preferred regimens include immune checkpoint inhibitors (such as ipilimumab, nivolumab, and pembrolizumab) and BRAF/MEK inhibitors, among others. However, clinical trials have not studied pediatric patients and these medications are not approved for children [1]. The challenge of studying these therapies in pediatric patients is highlighted by a phase II study conducted by Geoerger et al. [58] where investigators attempted to evaluate the efficacy of ipilimumab in adolescent patients (ages 12–17 years) with unresectable stage III or IV melanoma and were able to demonstrate a partial response after one year; however, they ultimately discontinued the study due to slow accrual of patients. Notwithstanding the above limitations, there have been small studies supporting the safety of adjuvant interferon and pegylated interferon in pediatric patients [59, 60] which some providers use in later stage pediatric melanoma cases. These management decisions are typically made on a case-by-case basis and vary by provider and institution.

19.9 Prognosis

Overall survival of pediatric melanoma patients is longer than that of their adult counterparts, with an expected 5-year survival rate of 70–94% (depending on the study) [1, 4]. Among PM cases, younger patients (aged 10 years or younger) tend to experience longer survival than adolescent patients [4, 61]. In a study by Averbrook et al. [61], the pre-adolescent cohort was found to have a 100% survival rate. Predictors of poorer prognosis include increased tumor thickness, presence of ulceration, positive lymph node status, and higher stage at diagnosis. In a retrospective study of PM cases from 12 institutions from 1953 to 2008, the 10-year overall survival rate was shown to be 97% in patients with tumor thickness ≤1 mm and 70–80% for thicker tumors. The 10-year overall survival rate based on AJCC stage was 94% for stage I disease, 80% for stage II disease, and 77% for stage III disease [61].

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Melanoma in Skin of Color

20

Nicole Patzelt and Neelam A. Vashi

20.1 Introduction

It is well-established that melanoma has a higher incidence in white patients; however, when those of darker skin phenotypes do present with melanoma, it often bears a worse prognosis. While most literature has been obtained from light-skinned persons and subsequently extrapolated to darker skin types, new research is starting to show that there are significant differences in melanoma, including how it is diagnosed and treated for different skin types. In this chapter, we will discuss differences in incidence, outcomes, and perceptions of melanoma in skin of color.

20.1.1 Fitzpatrick Skin Types

The Fitzpatrick phototype system, categorizing patients from type I to VI skin, is widely used in dermatology. It was initially developed to categorize sun sensitivity but in practice is often inaccurately assigned based on complexion alone [1]. Skin of color patients are often assumed to be type IV–VI skin, but studies that have measured skin pigmentation with a portable tristimulus reflectance colorimeter to directly evaluate the patient's minimal erythema dose show a wide range of pigmentation and sun sensitivity levels in skin of color patients [1–3]. Evaluation of sun sensitivity with quantifiable measurements in studies can provide a more accurate representation of risk factors and outcomes associated with specific skin types.

20.1.2 Research

There remains a lack of research on melanoma in skin of color. Many large studies rely on cancer registries, often which have incomplete ethnicity/race data or lack certain ethnic/racial categories altogether (i.e., including white and black but not Asian or Hispanic choices). Some of these registries also use a patient's surname to autopopulate his/her most likely ethnicity when not self-reported. This can lead to misrepresentation particularly among married women who are more likely to change their surname [4, 5]. Another factor is the relatively low number of darker-skinned patients with melanoma in some areas of the United States, making it inherently more dif-

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ficult to obtain the power to reach significant conclusions if attempting to study these populations [4].

20.2 Epidemiology

20.2.1 Incidence

As compared to other forms of skin cancer (e.g., squamous cell carcinoma and basal cell carcinoma), melanoma remains the least common amongst skin of color patients. Annual incidence varies by race/ethnicity; 2–7/100,000 for Hispanic patients, 1/100,000 for black patients, and 1–6/100,000 for Asian and Native American patients [1, 6–9]. This is significantly lower than the incidence in white patients at 18–46/100,000 depending on the database studied. Incidence rates increased at a rate between 2.9 and 7.3% annually in Hispanic patients from the 1990s to early 2000s based on studies of the California and Florida cancer registries; newer reports have noted a decline between 2003 and 2012 [1, 7, 10–12]. Similar incidence rates were noted in the northeast United States [5]. Incidence rates for black and Asian patients have remained stable over those time periods [1, 5].

20.3 Pathogenesis/Risk factors

20.3.1 Ultraviolet Radiation

Although Ultraviolet (UV) radiation exposure is a well-demonstrated risk factor for skin cancer development in white populations, there is conflicting data in skin of color patients. Some of the limited studies suggest UV radiation exposure is less important in darker-skin types [13]. One study found that increased UV exposure and living at lower latitudes were not significantly associated with the development of melanoma in skin of color patients [1, 14]. Although UV-induced DNA damage has been demonstrated in all skin types, more severe damage is noted in lighter skin which may explain the more important role it plays in melanoma development for those patients [15]. It has also been shown that increased melanin content can provide a natural sun protection factor of up to 13.4 in the skin of black patients [5]. The higher incidence of melanomas in non-sun exposed sites also suggests a possible decreased importance of UV radiation in melanoma development in skin of color [1].

In contrast, other epidemiologic studies have supported an association between UV exposure and melanoma development in skin of color patients, although much of the data did not reach statistical significance [1, 5]. One study found a significant positive correlation between melanoma incidence and annual mean UV index in black male patients [16]. Living at a lower latitude was similarly correlated with higher melanoma incidence for all races/ethnicities although this was only statistically significant among black male patients again [16]. A higher proportion of head and neck melanomas occur in older Hispanic male patients than any other Hispanic patients, which could also imply a role for UV exposure [7].

20.3.2 Genetics

Melanin content alone cannot explain the differences seen in incidence of melanoma between ethnicity/race. Genetic variability has been demonstrated in oncogenic pathways; there is decreased p16 expression in acral lentiginous melanoma in black patients for example [5]. Decreased p16 expression has also been associated with worse survival outcomes which may be one contributing reason to why black patients have worse survival rates as discussed later [5].

Genome-wide association studies have identified many loci associated with melanoma, and skin color has been shown to affect these loci. In a study of non-Hispanic Europeans, a significant overall heritability risk for developing a sporadic melanoma was noted [17]. When their data was further evaluated by accounting for patient skin color, certain melanoma-associated loci developed significance while others lost their signifi-

cance. This suggests that, like acral lentiginous melanoma noted above, the genetics in sporadic melanomas differ based on skin color [17]. This highlights the importance of including skin color data in studies on the genetics of melanoma, not just epidemiologic studies.

20.4 Clinical Features

20.4.1 Age

The mean age at diagnosis varies by race/ethnicity. Black men and women are diagnosed at 60 and 62 years of age, respectively; Asian men and women at 61 and 55 years of age, respectively; Hispanic patients at 53–56 years of age [1, 5, 7].

20.4.2 Location

The most common anatomic site for primary melanoma is the lower extremity except in Hispanic men in whom truncal melanomas are most common [1, 5, 7, 9]. The incidence of head and neck melanomas also increases in older Hispanic men and women [1, 7].

20.4.3 Histology

The most common histologic subtype is superficial spreading melanoma in all skin of color patients, but black patients have been noted to have the highest proportion of acral lentiginous melanoma compared to Hispanic or white patients [1, 5–7]. Black patients were also more likely to have ulceration [5].

20.5 Differences in Diagnosis

20.5.1 Advanced Stage at Presentation

There has been an overall improvement in melanoma survival in white patients likely, in part, due to improved diagnosis of early stage melanomas in addition to advances in treatment options. In some studies, nearly 90% of all primary cutaneous melanomas in white patients are diagnosed at stage I-II [6]. This improvement in early stage melanoma diagnosis has not been seen in skin of color patients though. In one study out of Miami-Dade County Florida, 48% of black patients with melanoma presented with advanced stage melanoma (with regional or distant metastasis) as compared to 22% of white patients [8]. In a similar study by the same group, 26% of Hispanic patients with melanoma presented with advanced stage melanoma as compared to 16% of white patients. White patients in this population were more likely to be diagnosed at earlier melanoma stages, with 84% diagnosed at the in situ or local stage [4]. These data are comparable to similar studies in Washington DC, California, Connecticut, and based on national databases [5–7, 10, 18, 19]. Each of these studies found a higher percentage of late stage melanoma diagnosis in black or Hispanic populations as compared to white patients. Asian patients are also more likely to present with stage IV melanoma than white patients [1].

Similar findings have been found in the pediatric population. In a study of pediatric melanoma patients in Texas, Hispanic pediatric patients were more likely to have an advanced stage melanoma at diagnosis as compared to white pediatric patients. More than 50% of the Hispanic patients were diagnosed at an advanced stage; only 23% of the white patients were [20].

20.5.2 Artificial Intelligence

Artificial intelligence via machine learning has been studied in its ability to detect skin cancer. Unfortunately, it has the potential to fail to detect skin cancers in skin of color patients if certain skin types are excluded from the training photographs used to teach the computer algorithms. This already appears to be the case as many programs currently in development use photo sets

comprised mostly of lighter skin types such as the International Skin Imaging Collaboration: Melanoma Project archives [21]. Machine learning for dermatology requires a high volume of good quality images to be able to perform well consistently; if images of skin diseases like melanoma in darker skin types are not included in the training data these patients can be misdiagnosed [21]. Melanoma and other skin diseases can look very different in darker vs lighter skin types so a computer algorithm trained almost solely on images derived from lighter skin types is destined to fail in skin of color. Artificial intelligence will only have utility if algorithms are formed from an incredibly diverse array of patient photos.

20.6 Disparities in Management and Outcomes

20.6.1 Mortality

Despite an overall improvement in melanoma survival in white populations, survival rates remain relatively low among Hispanic and black patients [4]. Whereas overall survival for white populations improved from 68% in the 1970s to 92% in the early 2000s, the rates for black patients only improved from 67% to 78% over the same time frame [4]. Rates for Hispanic patients improved to 77.2% for Hispanic men and 86.5% for Hispanic women [4]. Data have shown that black patients with melanoma have a 1 in 3 risk of dying from their melanoma whereas white men and women have a 1 in 7 or 1 in 11 risk, respectively [13]. Much of this difference can be attributed to the later stage at diagnosis as discussed in the previous section. Even when diagnosed with melanoma at the same stage though, white patients had significantly better survival as compared to black patients [6, 9]. This trend was also described after patients were stratified by age or histologic subtype [6].

Similar findings were also found in the pediatric population. Hispanic pediatric patients had a higher risk of mortality as compared to white pediatric patients, which are likely related to their increased risk of presenting at an advanced stage [20].

20.6.2 Surgical Delay

Surgical delay is defined as a surgical excision being performed more than 6 weeks after a diagnosis of melanoma is made, which is considered the upper limit for standard of care. Surgical delay can result in increased morbidity and mortality [22]. Patients with skin of color are at a higher risk of surgical delay than white patients [13, 22]. Nonwhite patients are also more likely to receive their melanoma diagnosis from a provider other than a dermatologist which may in part explain the higher surgical delay risk. Both diagnosis and treatment by a dermatologist are associated with a lower risk of surgical delay [22].

20.7 Prevention

20.7.1 Patient Education and Photoprotection

Skin of color patients often believe they are at no or low risk of developing melanoma. In one study, 65% of respondents felt they had no risk; in another, 46% believed they had no risk while 30% endorsed being at low risk [1, 23]. This belief can be perpetuated by skin cancer prevention programs that often emphasize the risk in white patients and those most susceptible to sunburn specifically. In one study, 65% of skin of color patients that reported being able to sunburn still felt they were at no risk of developing skin cancer and used sunscreen less frequently [1, 20, 24, 25]. Blacks and Hispanics are also more likely to believe there is little they can do to decrease their risk of skin cancer [26, 27]. These beliefs can explain in part the delay in diagnosis and worse mortality noted in skin of color patients as poor understanding of risks and treatment of melanoma are associated with a deeper Breslow depth [27].

Skin of color patients may be more likely to participate in risky sun exposure activities and less likely to participate in sun protective behaviors [1]. In one survey of US high school students, almost 8% of female Hispanic students used indoor tanning beds in the prior year [4, 7]. Hispanic and black individuals also noted less frequent sunscreen use with 47% of Hispanic respondents and 4% of black respondents endorsing wearing sunscreen in the last year [1, 20]. Hispanic workers with outdoor occupations reported more likely use of long sleeve shirts and hats than wide-brimmed hats or sunscreen [7]. This may be because black and Hispanic patients have been found to be less likely to believe skin cancer risk can be affected by sun protective measures [1]. Sunscreen use is also less frequently recommended to skin of color patients and what SPF value to recommend may be unclear [1, 28, 29]. Even when testing the same product, a reported SPF value may confer greater protection in light skin compared to darker skin [29].

Programs that use multicomponent initiatives have been shown to increase sun protection measures, specifically sunscreen use [26]. Although some educational initiatives aimed at skin of color patients have helped raise skin cancer risk awareness, no multicomponent programs have been studied that specifically target these patients [26]. These programs should also focus on education regarding skin cancer symptoms or lack thereof. Current beliefs about symptoms that are more prevalent among skin of color patients can be incorrect such as that skin cancers are always preceded by pain [27, 30].

20.7.2 Skin Cancer Screenings

Skin cancer examinations are performed less frequently for black, Hispanic, and Asian patients than for white patients. Whereas 8.9% of white patients reported having a recent skin examination by a physician, only 3.7% of Hispanic patients endorsed having had one recently [31]. Only 5% of black, Hispanic, or Asian patients reported ever having a full body skin examination in their lifetime as compared to 49% of white patients [1]. This may in part be due to socioeconomic factors including poverty and lack of insurance. Skin cancer screenings are also offered less frequently by providers to skin of color patients and are less likely to teach skin of color patients how to perform a skin self-examination [1, 5, 30]. Decreased skin cancer screenings can explain in part the delay in diagnosis noted earlier in skin of color patients.

20.8 Conclusion

Melanoma affects patients of all skin color, although at different rates. Education is essential to our skin of color population who often present late in disease and have an overall worse prognosis. The relative lack of dermatologists of color is another area that needs improvement. Dermatology has the second lowest percentage of underrepresented minority physicians, after orthopedic surgery [13]. The Skin of Color Society is focused on training more board-certified dermatologists of color and is working with the American Academy of Dermatology to help recruit residents to focus on skin of color work. In addition, other groups are working to help medical students find skin of color dermatology mentors [13]. Regardless, more research is needed regarding melanoma in skin of color to help patients understand the disease and improve outcomes.

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Melanoma in Pregnancy

21

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21.1 Introduction

Malignant melanoma (MM) is the most common malignancy reported during pregnancy. The impact of hormonal and immunologic changes during pregnancy is controversial. In the past, studies have reported variable prognosis regarding pregnancy-associated MM (PAMM). This chapter addresses multiple controversies regarding PAMM including pathogenesis, prognosis, and disease characteristics. Patient evaluation and management, treatment, as well as counseling patients considering oral contraceptives or hormone replacement therapy are reviewed.

21.1.1 Epidemiology

MM is the most common malignancy reported in pregnancy, which accounts for as many as one-third of malignancies diagnosed during pregnancy [1–3]. In addition, MM is one of the most common malignancies to affect young women as up to one-third of MM cases diagnosed are in patients of reproductive age [4, 5]. The incidence of PAMM may be increasing as MM becomes more common in younger women and women choose to delay childbearing [6]. A recent study in Australia, which has the highest rates of melanoma in the world, found the incidence of PAMM in women who gave birth increased from 37.1 per 100,000 in 1994 to 51.84 per 100,000 in 2008 [7]. While the authors attributed this trend to an increase in maternal age, the high prevalence of PAMM and increasing incidence demonstrate the importance of this issue.

21.1.2 History and Controversy

The controversy regarding the impact of pregnancy on MM began in the 1950s. Various case reports claimed pregnancy incited nevus transformation into MM [8–11] and posed an increased risk of metastasis [12]. Early investigators reported the adverse hormonal effect of pregnancy on MM was so pronounced that surgical sterilization was justified upon MM diagnosis [12]. However, other investigators found women who had previously been pregnant before MM diagnosis had a better prognosis than nulliparous women [13, 14]. Subsequent studies in the 1980s and 1990s found pregnancy had no effect on the

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outcome of patients diagnosed with MM [15–17]. Multiple systematic reviews and meta-analyses have attempted to synthesize the literature, but findings have varied across years and among research groups [18–20]. Much of the discrepancy can be attributed to variable terminology and inclusion criteria, both of which require standardization for meaningful comparison.

21.1.3 Terminology

The inclusion criteria for PAMM have varied dramatically across studies, which has resulted in discrepant findings among authors. Some authors aggregate MM diagnosed during pregnancy with MM diagnosed during the postpartum period in defining PAMM. Across studies the window of MM diagnosis may vary from diagnosis during pregnancy to diagnosis as far out as 5 years postpartum [21]. Though some studies perform subgroup analysis between MM diagnosed during pregnancy and MM diagnosed in the postpartum period, data are often incomplete. Herein, we differentiate between MM diagnosed before, during, and after pregnancy when appraising the literature on the effect of PAMM on patient prognosis.

21.2 Pathogenesis

Essential to the discussion of PAMM is an understanding of the immunologic and hormonal changes that occur during pregnancy. Pregnancy is thought to induce a state of immunosuppression, and theoretically may foster tumor progression [19, 22]. Increased metabolic activity, changes in hormone levels, increased lymphangiogenesis, and fetal cell microchimerism have also been proposed as contributors to a less favorable prognosis in PAMM. However, while some pregnancy-specific changes may increase a woman's risk of PAMM, others may be protective. We review each of these mechanisms separately and their respective levels of evidence in PAMM pathogenesis.

21.2.1 Immunosuppression in Pregnancy

The immune system of a pregnant woman must protect both mother and fetus from pathogens, without harming the fetus, which contains foreign paternal antigens [23]. Research has demonstrated that the regulatory adaptive immune system is enhanced in pregnancy, whereas the cytotoxic adaptive immune system is diminished. The mother's immune system shifts towards a T-helper 2 (Th2)-dominant phenotype to promote increased cellular tolerance despite a state of immunosuppression. The Th2 phenotype favors tumor survival and has been shown to be elevated in patients with metastatic versus resected MM [24]. In addition, fetal trophoblast cells survive through mechanisms that promote immune escape via regulatory T cells (Tregs) and natural killer (NK) cells [25].

The expansion of $CD4^+$ $CD25^+$ Tregs is essential for maternal tolerance of the fetus. Tregs also regulate maternal tolerance for cancer [22]. Tregs may be implicated in impaired antitumor immunity, suppression of effector T lymphocyte proliferation, and enhanced tumor vascularity [22]. Some investigators have proposed that depletion of Tregs from the tumor microenvironment will play a key role in producing immune responses against MMs [26]. Tregs have been correlated with worse outcomes in metastatic melanoma [27], but it is unknown whether the trophoblast alteration in Tregs affects surveillance and response to MM. Uterine NK cells are found in the decidua of the pregnant uterus and are the most common immune cells found at the maternal–fetal interface. NK cells are less immunomodulatory and less cytotoxic than Tregs. Uterine NK cells may contribute to tolerogenicity and angiogenesis in the decidua and placenta. As some malignancies have shown a similar reduction in NK cell cytotoxic activity [22], this immunologic change may increase the risk of PAMM development and progression.

While reduced cellular immunity and increased tumor tolerance would be expected to have an unfavorable effect on PAMM prognosis, the implications of this inflammatory reaction

have not been well-studied in humans. Currently, there is no specific evidence suggesting that the immunocompromised state in pregnancy leads to melanoma development or progression.

21.2.2 Metabolic Changes in Pregnancy

Pregnancy represents a state of increased metabolic activity. Mitotic activity may be increased in tumors associated with pregnancy. However, studies specifically investigating PAMMs do not reliably demonstrate increased tumor proliferation rates [28]. The most compelling evidence for the effect of increased metabolic activity on PAMM relates to pregnancy-associated plasma protein-A (PAPPA). PAPPA is a metalloproteinase, which modulates insulin growth factor and tumor migration. Serum levels of PAPPA have been shown to increase in pregnancy [29], which may indicate increased MM cell migration and unfavorable prognosis, especially for metastatic MM. While increased metabolic activity in pregnancy would appear to be associated with more aggressive tumor activity and worse patient outcomes, few studies have examined this association rigorously. Thus, there is no definitive evidence that increased metabolic activity in pregnancy is associated with PAMM development or progression.

21.2.3 Hormonal Changes in Pregnancy

Increased sex hormones in pregnancy have also been theorized to affect MM prognosis and outcome. Specifically, multiparity and female gender have been reported to be associated with improved MM outcomes [30, 31]. However, the association between increased parity and decreased MM risk has also been demonstrated in men, suggesting an impact of environmental factors over hormonal factors [32]. Data supporting MM as a hormone-responsive cancer include changes in pigmentation that occur during pregnancy and increased MM incidence after puberty [33, 34]. The effect of elevated estrogen levels on MM outcome is poorly understood. Treatment of metastatic MM with tamoxifen, an antiestrogen drug, does not affect outcome, suggesting the hormonal influence is not significant [35].

MM cells maintain estrogen receptors (ER), but the extent to which MM is a hormone-responsive tumor is unclear. While ERα does not appear to have significant expression in MMs, there is some evidence to suggest that loss of ERβ expression is correlated with increased Breslow depth in MMs [36, 37]. In one small study of G-protein coupled estrogen receptor (GPER), a non-classical ER, PAMMs had a higher expression of GPER versus non-PAMMs [38]. In most cases of PAMMs, ERβ was co-expressed, which correlated with favorable prognosis factors including fewer mitoses, lower Breslow thickness, and higher presence of peritumoral lymphocyte infiltration versus GPER−/ERβ-negative MMs. However, these favorable characteristics did not result in any difference in disease-free survival between PAMMs and non-PAMMs [38]. Thus, hormonal changes associated with pregnancy may have both theoretical positive and negative effects on PAMM prognosis though the net effect is not well understood.

21.2.4 Increased Lymphangiogenesis in Pregnancy

Pregnant mice with MM have been shown to have increased lymphatic vessels, larger tumors, increased metastases, and greater mortality versus nonpregnant mice [39]. Studies in pregnant women with MM have shown increased lymphatic vessel diameter and intra-tumoral lymphatic area compared to nonpregnant women. In addition, increased MM tumor lymphangiogenesis is associated with lymph node invasion and a higher likelihood of metastatic invasion to a sentinel lymph node [40]. Studies of the effect of increased lymphangiogenesis on PAMM have focused on advanced MM and further investigation is required.

21.2.5 Fetal Cell Microchimerism in Pregnancy

Fetal cell microchimerism (FCM), the process in which fetal cells enter the maternal circulation and act as progenitor cells, has been studied in PAMM progression with mixed results. Some MM tumors express endothelial cell markers and form new vessels suggesting that fetal cell-derived lymphatic progenitor cells may increase MM-associated lymphatics, causing more aggressive tumor phenotypes [41]; other studies have found FCM has a protective effect on the mother [42].

21.3 Maternal Prognosis

PAMM prognosis has been controversial since initial case reports in the 1950s suggested pregnancy induces malignant transformation in nevi and is associated with increased tumor metastasis [8–12]. Studies have used variable patient inclusion criteria with incomplete data sets and incongruent terminology, resulting in discrepant findings. A critical review of the literature requires separation of studies examining MM before, during, and after pregnancy, as these periods represent distinct physiological states. Analyses must also include important variables such as Breslow depth and stage of disease as well as appropriate control groups to make meaningful comparisons. Review of the literature on PAMM to-date largely suggests there is no difference in prognosis of women diagnosed with MM before pregnancy, during pregnancy, or in the postpartum period when compared to appropriate nonpregnant controls.

21.3.1 Malignant Melanoma Diagnosed Prior to Pregnancy

Few studies examine the prognosis and outcome of MM diagnosed prior to pregnancy. A study comparing 43 women who became pregnant within 5 years of MM diagnosis with 337 age-matched controls found no difference in survival in both univariate and multivariate models [43]. A more recent retrospective, population-based cohort study performed secondary analysis comparing 966 women with MM diagnosed prior to pregnancy with 4657 women without pregnancy after MM diagnosis. The study found MM diagnosis prior to pregnancy was not related to survival after adjusting for Breslow depth of tumor, tumor site, Clark's level, and age [44]. A study comparing 85 women who became pregnant after a MM diagnosis with 143 patients who completed their pregnancy prior to MM diagnosis found no difference in overall survival [17]. Overall, there appears to be no influence on survival when MM is diagnosed prior to pregnancy.

21.3.2 Malignant Melanoma Diagnosed during Pregnancy

Controlled studies on melanoma diagnosed during pregnancy are summarized in Table 21.1. The earliest studies reporting a poor prognosis for patients diagnosed with MM during pregnancy were case series performed in the 1950s [8, 12]. In 1985, [43] a retrospective cohort study in the USA of 100 cases of localized MM cases diagnosed during pregnancy demonstrated a significantly decreased disease-free interval (DFI) in pregnant women versus controls but no difference in overall survival. Using the same methodology and including additional study patients, a subsequent study had similar results [44]. The 88 patients diagnosed with localized MM during pregnancy had no significant difference in survival compared to a matched control group who were not pregnant at the time of diagnosis, but once again observed a shorter DFI. Both studies observed thicker MMs (although statistical significance was not stated) and increased risk of recurrence with spread to lymph nodes in the pregnant group versus nonpregnant group. The findings of these studies were limited by small sample size.

In 2008 [2] a single-institution retrospective chart review of 160 cases of PAMM was undertaken in Norway. They found an increased risk of cause-specific death, though this difference was

Table 21.1 Summary of studies on melanoma diagnosed during pregnancy

Article	Study type	Number of PREGNANT patients	Number of controls	Duration of follow-up	Did pregnancy influence survival?	Did pregnancy result in a shorter DFI?	Stage(s) of disease
Reintgen et al. 1985	United States retrospective clinic-based cohort study	58	585 not pregnant at diagnosis or within 5 years of diagnosis	5 years (mean)	No	Yes ($p = 0.04$)	I
McManamny et al. 1989	United Kingdom retrospective clinic-based cohort study	23	243 not pregnant at diagnosis or afterwards	2 months to 20 years	No	No	I
Wong et al. 1989	United States retrospective clinic-based cohort study	66	619 not pregnant at diagnosis; 66 matched for Breslow depth, anatomic location of primary lesion, and histopathologic subtype	5 years	No	N/A	I
Slingluff et al. 1990	United States retrospective clinic-based cohort study	100 (additional patients of Reintgen et al.'s patient base)	86 not pregnant at diagnosis	6.8 years (mean)	No	Yes	I
MacKie et al. 1991	United Kingdom retrospective clinic-based cohort study	92	143 women not pregnant at diagnosis or after diagnosis +68 women diagnosed with MM between pregnancies	N/A	No (after log-rank adjustment for tumor thickness)	No (after log-rank adjustment for tumor thickness)	I
Daryanani et al. 2003	Dutch retrospective clinic-based cohort study	46	368 not pregnant at diagnosis; matched for age and sex	9.1 years (median)	No	No	I/II
Lens et al. 2004	Swedish retrospective population-based cohort study	185	5348 not pregnant at time of diagnosis	11.6 years (median)	No	N/A	All

(continued)

Table 21.1 (continued)

Article	Study type	Number of PREGNANT patients	Number of controls	Duration of follow-up	Did pregnancy influence survival?	Did pregnancy result in a shorter DFI?	Stage(s) of disease
O'Meara et al. 2005	United States retrospective population-based cohort study	145	2451 not pregnant at time of diagnosis	N/A	No	N/A	All
Silipo et al. 2006	Italian case–control study	10	30 not pregnant at time of diagnosis (matched for age, localization, histopathologic subtype, and AJCC stage)	5 years	No	N/A	All
Stensheim et al. 2009	Norway retrospective population-based cohort study	160 (stage not stated; Breslow's depth available for only 55%)	4460 not pregnant at time of diagnosis or afterwards	11.9 years (median)	No	N/A	All
Moller et al. 2013	United Kingdom retrospective population-based cohort study	306	165,28 not pregnant at diagnosis or within 1 year	10 years	Yes; two-fold death rate for women who had given birth within 1 year before the cancer diagnosis (2.06; 1.42–3.01) though when adjusting for TMN stage HR reduced to 1.92 (1.32–2.79)	N/A	All
Johansson et al. 2014	Swedish retrospective population-based cohort study	247	5838 not pregnant at time of diagnosis or > 2 years postpartum at diagnosis	Up to 10 years	No	N/A	All (staging data available in 59%)
Jones et al. 2017	United States retrospective hospital-based case–control study	156	2025	For pregnant patients: 14.6 years (median), for controls: 11.1 years (median)	No	No	0-III

not significant when adjusting for tumor location. In accordance with the previous clinic-based cohort studies, there was also no difference in overall survival. Limitations of the study included the lack of staging data as well as incomplete data regarding Breslow depth. In 2015, [45] a retrospective hospital-based cohort study of 41 cases of PAMM (diagnosis during pregnancy or within 1 year of delivery) in the United States was published. The authors found a significant 5.1 times increased odds of death, 6.7 times increased odds of metastasis, and 9.2 times increased odds of local recurrence. However, only 19 of the 41 cases involved melanoma diagnosed during pregnancy, and the study was limited by discrepancies in staging. The study was also criticized for its methods, particularly the use of logistic regression instead of survival and progression-free analysis to evaluate mortality and recurrence [46, 47].

Since these population-based studies, two meta-analyses have been performed and reported an overall adverse effect of pregnancy on PAMM prognosis. Pooled data from 4 studies [20] found an increased risk of melanoma death. However, not all studies used strict inclusion criteria for PAMM as one study only included MM diagnosed in the postpartum period. Revised analysis failed to show a significant elevation in the study's hazard ratio (HR) [48]. A recent meta-analysis [49] which pooled data from 14 studies found an increased risk of mortality (HR 1.7 confidence interval 1.03–1.33) and decreased overall survival. The study also found decreased disease-free survival (HR 1.50 confidence interval 1.19–1.90). The authors used sensitivity analyses to account for study heterogeneity and the effect of PAMM on mortality remained; however, the overall grade for evidence quality has come into question [50].

A 1989 retrospective clinic-based cohort study [51] of 66 cases of stage I MM in the USA found no differences in histologic features, tumor location, or 5-year survival in patients diagnosed with MM during pregnancy versus MM not associated with pregnancy. A similar retrospective clinic-based cohort study in 1991 [17] analyzed 92 cases of stage I and II MM and found no effect on disease-free interval or overall survival after adjusting for patient tumor thickness. A United States retrospective clinic-based cohort study [52] of 45 cases of PAMM (diagnosis during pregnancy and up to 1 year postpartum) found better survival in PAMM patients than non-PAMM patients despite increased tumor thickness in PAMM patients. A retrospective-clinic based cohort study [53] of 46 patients diagnosed with localized MM during pregnancy in the Netherlands found pregnancy did not affect overall survival or DFI.

Data compared from 185 women diagnosed with PAMM to 5348 age-matched, nonpregnant controls with MM [54] found no statistically significant difference in survival between the two groups. A retrospective population-based cohort study [55] of 412 cases of PAMM (diagnosis of MM during pregnancy and up to 1 year postpartum) in the United States using the California Cancer Registry analyzed patients with all stages of MM in comparison to 2451 age-matched nonpregnant women diagnosed with MM and found no difference in survival. On analysis of the 145 women who were diagnosed during pregnancy and the 4 women diagnosed at delivery, pregnancy status was not related to death utilizing a Cox proportional Hazards model. In fact, mortality rate was lower in the group of pregnant patients (8.3% of those diagnosed with MM during pregnancy versus 9.8% in controls).

A retrospective population-based cohort study [21] of 1019 cases of PAMM (diagnosed with MM in pregnancy and up to 2 years postpartum) was undertaken in Sweden. Staging data was only available for 59% of cases. An analysis of 247 cases of MM diagnosed during pregnancy found no significant difference in mortality when compared to controls. Finally, in 2017, the largest single-institution cohort study [5] comparing 156 cases of MM diagnosed during pregnancy (pregnancy either self-reported or physician-reported) to 2025 patients who were not pregnant at diagnosis was reported. The study patients included those with stages 0 to III and key prognostic factors, such as Breslow depth. When these groups were compared, there was no significant difference in stage at diagnosis, Breslow depth, or site

of primary tumor. In terms of prognosis, there was no significant difference in overall survival, melanoma-specific survival, and DFI. One observation differed from previous studies; increasing gravidity was significantly associated with worse overall survival, melanoma-specific survival, and disease-free survival in women diagnosed with stages 0, I, and II MM.

Overall, the current body of evidence does not demonstrate a worse prognosis for women diagnosed with MM during pregnancy when compared with nonpregnant women.

21.3.3 Malignant Melanoma Diagnosed after Pregnancy

Much like MM diagnosed prior to pregnancy, there are few studies that evaluate the prognosis of MM diagnosed in the postpartum period. In 2005 [56] a retrospective population-based cohort study in the United Kingdom examined PAMM (diagnosis of MM up to 5 years postpartum), breast cancer, and Hodgkin's lymphoma mortality in the postpartum period using an English cancer registry. The authors found a significant increase in mortality for patients diagnosed with MM in the first year postpartum versus nonpregnant controls but did not find a significant relationship for patients diagnosed with MM in the second through fifth years postpartum. It has been postulated that fewer melanomas than expected are diagnosed during pregnancy and higher rates are diagnosed in the postpartum years, which may represent a rebound effect caused by delayed diagnosis rather than a true poorer prognosis [1]. Three retrospective cohort studies failed to show a difference in survival between women diagnosed with MM in the postpartum period versus controls [2, 17, 57]. More recently a 2014 study from the Swedish Cancer and Multi-Generation Registers [21] found there was no evidence of a worse prognosis for patients diagnosed with MM during pregnancy and up to 2 years postpartum. The analysis was extended through 5 years postpartum and did not demonstrate any significant differences in survival.

Overall, the evidence to-date does not suggest a worse prognosis for women who are diagnosed with MM up to 5 years postpartum.

21.4 Fetal Risks Associated with Malignant Melanoma

Much of the controversy regarding PAMM has centered around maternal risks and prognosis, but fetal effects also require consideration. In pregnancy-associated cancers, including advanced PAMM, the risk of Cesarean delivery and planned preterm birth are both elevated [3]. The most common adverse fetal outcome associated with PAMM is prematurity, though this is more common in advanced cases such as stage III/IV MM. However, the effect of PAMM on infant birth weight is not well understood as findings across studies have varied [3, 57]. Most adverse fetal effects associated with PAMM occur as a result of diagnostic procedures and treatments rather than the nature of the disease itself [50].

Melanoma is the most common malignancy to metastasize to the fetus. Approximately 58% of all metastatic cancers to the fetus occur from MM [58]. Fetal risk is greatest for advanced-stage MM in which the risk for placental and fetal metastasis is highest. In cases of fetal metastasis, microscopic evidence of metastatic MM is found in all placentas, particularly for stage IV MM with visceral metastases [58]; however, in only 22% of cases of documented placental metastases is there spread to the fetus [59].

21.5 Characteristics of Pregnancy-Associated Malignant Melanoma

Past studies have considered the effect of PAMM on Breslow depth, anatomic, location, and other clinicopathologic features which mediate prognosis. These issues will be addressed separately.

Breslow depth is one of the most important prognostic factors for MM and tumor thickness is

the single most important predictor of recurrence. A 2016 review of melanoma and pregnancy [46] evaluated 10 studies investigating the effect of PAMM on patient prognosis, which included Breslow depth in analysis. Only two studies reported women with PAMM as having thicker Breslow depths compared to nonpregnant controls [17, 52]. However, the two studies did not report decreased disease-free survival or overall survival in PAMM versus non-PAMM patients, suggesting this difference does not have significant clinical implications. One large, population-based cohort study [44] observed no significant difference in tumor depth overall in pregnant versus nonpregnant controls except for MM diagnosed in the third trimester. Thus, the evidence to-date does not suggest Breslow depth differs significantly between PAMM and MM in nonpregnant women.

Anatomic location is important as certain locations are associated with poorer prognosis for patients. A recent review [46] reported that only 2 of the large, population-based cohort studies to-date observed an increased frequency of MMs in poor prognostic sites. Though one study reported 45% of patients with PAMM had tumors on axial locations compared to 41% of nonpregnant controls in whom legs were the most common site, data from the analysis were not shown [2]. In the second study, PAMM patients were more likely than nonpregnant controls to have MMs on the trunk, but the difference was not found to be statistically significant [21]. A recent retrospective review examined the clinicopathologic characteristics of 34 MMs diagnosed during pregnancy or 1 year postpartum versus MMs in age and disease-stage-matched controls and found no significant difference in Breslow depth, ulceration, mitotic rate, stage of disease, anatomic location of MM, histologic subtype, Clark level, regression, necrosis, or vascular invasion [60]. Most evidence suggests tumor characteristics in patients with PAMM do not significantly differ from MM in nonpregnant women, which further supports the position that PAMM does not affect patient prognosis.

21.6 Patient Evaluation, Management, and Treatment

Principles for the evaluation and management of pregnant patients with MM are similar to those for nonpregnant patients and are based upon disease stage. In general, biopsies of suspicious lesions should not be delayed and excision of MM lesions with appropriate margins based on the tumor's Breslow depth should be completed in localized MM. However, as the stage of disease becomes more advanced, clinical decisions become more complex in order to ensure safety of both mother and the fetus.

A pigmented lesion during pregnancy that is of concern clinically or dermoscopically should be biopsied immediately. Lidocaine is considered safe for use in pregnancy "in small amounts" according to the American Academy of Dermatology's (AAD) 2016 Guidelines for the Use of Local Anesthesia in Office-Based Dermatologic Surgery [61]. Under the United States Food and Drug Administration (FDA) pregnancy guidelines, lidocaine may be used during pregnancy and risk of fetal harm is not expected based on limited human data.

The AAD also endorses the use of epinephrine as a vasoconstrictor in local anesthetic solutions. The use of local vasoconstriction in solutions minimizes serum levels of epinephrine and thus an effect on placental vessels is highly unlikely [62]. Under the FDA's pregnancy classification, epinephrine's benefits are noted to outweigh the risks during pregnancy though there is a possible risk of teratogenicity based on limited or conflicting human data. In addition, there is a theoretical risk of decreased uterine perfusion based on the drug's mechanism of action. However, the benefits of epinephrine use appear to outweigh the risks. The guidelines also recommend delaying "urgent surgery" until the second trimester, if possible, and if "large amounts" of anesthesia are necessary, recommend consultation with the patient's obstetrician [24]. If a wide local excision of a melanoma is to be performed, it should not be delayed but the patient's obstetrician should be consulted. Additionally, wide local excisions in which general anesthesia will be

administered require coordination of specialists in obstetrics, anesthesiology, and neonatology to ensure the safety of patient and fetus.

As in nonpregnant patients, once MM has been confirmed histopathologically, staging should be performed. When imaging is required, modalities without ionizing radiation should be used whenever possible. Magnetic resonance imaging (MRI) does not introduce ionizing radiation and may be useful when ultrasound or shielded chest radiograph is insufficient. MRI is safe in the second and third trimesters, though it should be used cautiously in the first trimester. In addition, studies such as computed tomography (CT) without contrast and nuclear medicine imaging studies can be performed as both are typically administered at doses that do not lead to fetal harm [59, 63].

Consideration of both maternal and fetal risks for diagnostic procedures, chemotherapy, surgery, and immunotherapy is important and largely depends on disease stage. For patients with T1a PAMM, a wide local excision under local anesthesia is appropriate [50]. For patients with T1b or T2 PAMM providers should perform a wide local excision and consider a sentinel lymph node biopsy (SLNB). There is controversy about use of blue dye alone, use of a radiocolloid (technetium-99) alone, or the use of both for SLNB in PAMM. Some cancer centers advocate against the use of blue dye due to risk for anaphylaxis [64, 65]. The European Society for Medical Oncology recommends avoidance of blue dye and the use of technetium-99 alone [66]. Some studies have shown radiation exposure to the fetus is minimal, even when the injection site is as close as 5 cm to the uterus [26]. Optimal procedures for SLNB in PAMM require further study.

While SLNB remains the most powerful prognostic factor for melanoma, there are currently no evidence-based guidelines regarding the utility of SLNB in pregnancy. In a European study of 290 "melanoma physicians," nearly half of respondents preferred to delay SLNB until after pregnancy [67]. One study observed no difference in survival if the interval between wide local excision and SLNB was a median of 47 days [68]. The Yale Melanoma Unit supports this position and recommends wide local excision under local anesthesia during pregnancy but delaying SLNB until after delivery if general anesthesia is required [69]. However, SLNB is not delayed across all institutions. Providers may also consider performing SLNB during pregnancy under local anesthesia, although this may be difficult in certain anatomic locations, such as deep nodes in the axilla or nodes in the inguinal and pelvic regions.

Ideally, SLNB should be discussed in an expert multidisciplinary setting. If the patient is at low risk for nodal involvement, SLNB may be postponed until after the delivery [69]. Patients in whom a SLNB is performed and the results are positive should undergo an MRI with or without a positron emission tomography (PET) scan [50] and be educated about options including surgery, targeted therapy, systemic therapy, immunotherapy, and radiation. For patients without advanced disease, premature delivery should be avoided to minimize fetal risks.

Patients with T3 or T4 PAMM represent the most complex cases. In all cases, the benefits of treatment versus the potential maternal and fetal risks and timing of interventions should be weighed [70]. For patients in the first trimester, at less than 20 weeks' gestation, providers may consider offering termination of pregnancy prior to staging and treatment as both can harm the fetus. In patients less than 34 weeks' gestation, providers may consider a wide local excision, SLNB, and MRI with or without a PET scan [50] in addition to treatment options such as surgery, targeted therapy, systemic therapy, immunotherapy, and radiation. For patients greater than 34 weeks' gestation, providers may consider induction of labor between 34- and 38-weeks' gestation before beginning these treatments [70].

In advanced PAMM, targeted therapy agents and checkpoint inhibitors may be teratogenic and therefore require careful consideration and consultation with expert providers. The FDA recommends avoidance of pregnancy and lactation during ipilimumab therapy and up to three months after the last dose as well as up to five months after the last dose of nivolumab. One case

of vemurafenib use in pregnancy reported a premature Cesarean delivery for fetal distress, though there were no fetal malformations noted [71]. Ipilimumab is known to cross the placenta and has been associated with urogenital tract malformations, spontaneous abortions, intrauterine fetal demise, premature births, and neonatal death in animal models [72]. Nivolumab has also been reported to cause fetal death in animal models [72]. Thus, immunotherapy requires further study in pregnant women.

Upon delivery, fetal and placental examination is essential to assess for metastasis. Both gross and microscopic evaluation of the postpartum placenta are indicated. Specifically, immunohistochemical staining for MM antigens may be beneficial [60]. Neonates without metastases noted at birth should be monitored for the next 24 months. Patients may benefit from total body skin examination and providers may consider a baseline chest X-ray and liver enzymes every 6 months [59].

21.7 Counseling Patients

Counseling of patients with MM depends on a patient's clinical history including tumor stage, patient variables, and future pregnancy goals. Currently, there are no evidence-based guidelines regarding future pregnancy after a previous diagnosis of MM. In the case of thin localized melanoma with favorable prognosis, a future pregnancy need not be delayed. For more advanced cases, tumor thickness remains the single most important predictor of recurrence. One study found less than 10% 5-year MM recurrence rate in tumors with a Breslow depth less than 1.5 mm in comparison with a 30% 5-year mortality risk for tumors with a Breslow depth of 1.5 to 3.5 [17]. Tumors thicker than 3.5 mm had greater than 50% mortality and an 83% rate of recurrence in stage II MM within 2 years of the initial treatment [17]. Thus, for patients with more advanced disease, providers should recommend waiting two to three years before becoming pregnant as recurrence of MM is most likely to occur in this time period. Patients may be concerned about fertility in cases of advanced age. Recommendations should be made on a case-by-case basis by carefully weighing a patient's eagerness to conceive and family planning goals with risk of MM recurrence. Potential effects on fertility should be addressed for patients in whom targeted therapy or immunotherapy are used. A 2018 study using the large database Truven Health MarketScan found women who received advanced treatment for MM had a lower rate of pregnancy than untreated women. However, women with thin melanomas who became pregnant after a MM diagnosis did not have an increased risk of requiring subsequent treatment for MM [73]. Likewise, adverse fetal outcomes are not increased for gestations occurring after a diagnosis of early stage MM [74]. Patients should be made aware that MM prognosis is not different in MM diagnosed before, during, or after pregnancy in comparison with women who have not been pregnant before.

Patients may inquire about the safety of oral contraceptive therapy for birth control given the theoretical effect of hormones on MM tumors. Currently there is no evidence for an increased risk of MM from the use of estrogen-progestin contraceptives, even with long duration of use [75]. Postmenopausal women may be concerned about the safety of hormone replacement therapy (HRT) for symptom management. 10 of 12 studies failed to identify an increased risk of MM from the use of HRT [33].

21.8 Conclusion

PAMM has been a controversial issue for almost seventy years since early reports of its poor prognosis in comparison to MM in nonpregnant individuals. The evidence to-date suggests MM prognosis does not differ from appropriate controls for those diagnosed before, during, or after pregnancy. Staging is essential to patient evaluation and management in order to inform treatment decisions. A multidisciplinary approach is essential to advanced cases of PAMM. Across the spectrum of PAMM, the assessment of disease severity and patient engagement is important in

considering future conception goals. Further investigation is required to establish best practices for the management of PAMM.

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