Clinical Presentations of Melanoma

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Contents

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Abstract

Cutaneous melanoma is unique among cancers in that it can be readily identified through visual examination of the skin surface. In this chapter, we detail patterns of melanoma presentation as well as appropriate clinical assessment to facilitate early diagnosis. The major histogenic types of melanoma are superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma; each differs in their associations with age, sex, race, anatomic site, ultraviolet exposure, and molecular profile. The cardinal clinical feature of all types of melanoma, however, is change in size, shape, and color, eventually becoming distinctly different from the remainder of a patient's skin lesions (i.e., the *ugly duckling sign*). Variant, uncommon clinical presentations of melanoma, such as amelanotic, desmoplastic, and spitzoid types, are summarized. Finally, we outline aids to the diagnosis of melanoma, including established tools, such as photography and dermoscopy, as well as emerging ones like reflectance confocal microscopy, artificial intelligence-based diagnostic systems, electrical impedance spectroscopy, and adhesive patch molecular assays.

Introduction

Prompt and accurate clinical assessment of melanoma remains an important strategy to reducing morbidity and mortality associated with this disease. Through increased public and physician awareness and knowledge of melanoma, there is a trend toward diagnosis of disease at an earlier stage with significant improvement in long-term survival (Rigel and Carucci 2000). As a result of progress in early detection and primary prevention, deaths from melanoma have recently decreased in younger cohorts but continue to increase in those over 55, especially men (Curchin et al. 2018) (see chapter ▶ "Clinical Epidemiology of Melanoma"). Increased detection pressure has been associated with rising incidence of melanoma in situ. Continued improvements in the early clinical recognition of melanoma are needed, especially for high-risk individuals, while simultaneously improving the specificity of diagnosis. This chapter broadly reviews a general approach to the early diagnosis of melanoma with attention to the varying presentations of the different histogenic subtypes. More details on risk factors, screening, and technologic aids to diagnosis can be found in chapters ▶ "Clinical Genetics and Risk Assessment of Melanoma," ▶ "Melanoma Prevention and Screening," and ▶ "Dermoscopy/Confocal Microscopy for Melanoma Diagnosis," respectively.

Patterns of Presentation

Several studies have addressed the pattern of melanoma detection and factors that have an impact on delays in diagnosis (Cassileth et al. 1988; Hennrikus et al. 1991; Negin et al. 2003; Oliveria et al. 1999; Richard et al. 2000a; Richard et al. 2000b; Schmid-Wendtner et al. 2002; Temoshok et al. 1984). Most melanomas currently are self-detected by either the patient or a member of the immediate family (Aviles-Izquierdo et al. 2016; Betti et al. 2003; Brady et al. 2000; Carli et al. 2004c; Fisher et al. 2005; Koh et al. 1992). However, physicians detect approximately 80% of second primary tumors (Fisher et al. 2005). The majority (~88%) of lethal melanomas are found by non-physicians (Aviles-Izquierdo et al. 2016). The major component of delay in patient-detected melanomas is lack of concern (Betti et al. 2003). A personal history of melanoma is more predictive of a thinner Breslow depth at the time the patient is first seen than a family history of melanoma

(Fisher et al. 2005). Women detect a higher percentage of melanomas than men, both in themselves and in their spouses (Koh et al. 1992). Given the importance of melanoma self-detection, public education campaigns aimed at raising awareness of melanoma and increasing knowledge of the early warning signs of melanoma have potential for reducing the melanoma mortality rate (see chapter ▶ "Melanoma Prevention and Screening"). To reduce patient delays in seeking treatment, educational messages should adequately stress the need for prompt referral to a physician once a suspicious pigmented lesion is self-detected. However, it has been noted that melanomas detected by a physician either in the screening or case-finding setting tend to be diagnosed at a thinner Breslow thickness (<0.75 mm) and earlier stage than those that are self-detected (Epstein et al. 1999; McPherson et al. 2006). There is suggestive evidence that point-of-care-based screening may improve early detection (Ferris et al. 2017b), but evidence for a reduction in mortality with population-based screening is inconclusive (Katalinic et al. 2012; Stang et al. 2016; Stang and Jockel 2016), and in the absence of sufficient assessment of potential harms from overdiagnosis, overtreatment, and associated costs, the US Preventive Services Task Force does not recommend population-based screening (Bibbins-Domingo et al. 2016). However, targeted specialized surveillance of high-risk individuals has been shown to be effective in improving early detection with a reduction in associated costs compared to standard community-based care (Watts et al. 2017).

A study examined the duration of the opportunity for early detection and the penalty in decreased survival for delays in detection (Liu et al. 2006). These investigators found that one third of all melanomas grew vertically in depth less than 0.10 mm per month, one third grew 0.10–0.49 mm per month, and one third grew 0.50 mm or more per month. The median monthly vertical rate of growth was 0.12 mm for SSMs, 0.13 mm for LMMs, and 0.49 mm for NMs. The penalty for diagnostic delay is particularly severe with a rapidly growing melanoma. Thick melanomas are predominantly of the nodular type and usually affect elderly men (Chamberlain et al. 2002). This elusive subtype frequently fails to fulfill the *ABCD* diagnostic criteria (see *Clinical Features* below) in that these lesions are more often uniform in color, are symmetrical, and are more frequently amelanotic (Chamberlain et al. 2003). Thus it has been proposed that *EFG* criteria (elevated, firm, growing for more than 1 month) be added for identifying nodular melanoma (Fox 2005; Kelly et al. 2003). Elderly men are more likely than women to develop rapidly growing tumors (0.28 mm per month versus 0.13 mm per month), as are those who lack the most important risk factors for melanoma, in particular large numbers of nevi (>50) and freckles (Liu et al. 2006). Together these studies and others (Chamberlain and Kelly 2004) suggest that men older than 50 years of age constitute a distinct group with a higher risk of undetected melanoma and should be targeted in special screening programs (Aitken et al. 2006; Geller et al. 2007; Janda et al. 2006).

Clinical Assessment

Elements of the clinical encounter relevant to early detection of melanoma are patient history, physical examination, and diagnostic aids.

Patient History

The key components of the patient history are questions pertaining to assessment of melanoma risk and questions pertaining to the detection of current melanomas. Risk-related questions include an assessment of family history of melanoma, personal history of skin cancer and/or nevus excision, sun exposure, and phototype. Questions pertaining to the presence of melanoma relate to a history of a changing, worrisome, or symptomatic lesion.

Multivariable risk prediction models for melanoma commonly include age, number of nevi, skin phototype, freckling, hair color, and sunburn history, and the few that have been validated show good discrimination (Olsen et al. 2018a; Usher-

Smith et al. 2014; Vuong et al. 2014). Integration of genetic determinants of risk into these models (e.g., *MC1R* genotype and melanoma susceptibility SNPs) may provide some improvement in discrimination, though further validation is required (Cust et al. 2013). An analysis of the American Academy of Dermatology Skin Cancer Screening Program indicates that 5 factors independently increased the likelihood of finding a suspected melanoma in the 362,804 people screened (Goldberg et al. 2007). They are represented by the mnemonic *HARMM*, which stands for history of previous melanoma (OR = 3.3; 95% CI 2.9–3.8), age greater than 50 years (OR = 1.2; 95% CI 1.1–1.3), regular dermatologist absent (OR = 1.4; 95% CI 1.3–1.5), mole changing (OR = 2.0; 95% CI 1.9–2.2), and male sex (OR = 1.4; 95% CI 1.3–1.5). Individuals at highest risk for melanoma (4–5 of these factors) composed only 5.8% of the total population, yet accounted for 13.6% of presumptive cases of melanoma and were 4.4 times (95% Cl 3.8–5.1) more likely to be diagnosed with suspected melanoma than those at lowest risk (0 or 1 of these factors).

Personal History of Skin Cancer

Patients with a personal history of melanoma (Bradford et al. 2010; Chen et al. 2015) or non-melanoma skin cancer (Wu et al. 2017) are at increased risk for developing subsequent melanomas. Approximately 1–8% of patients with melanoma will develop multiple primary melanomas according to retrospective studies (Stam-Posthuma et al. 2001). Atypical moles are strongly associated with increased risk of multiple primary melanomas (see chapter ▶ "Acquired Precursor Lesions and Phenotypic Markers of Increased Risk for Cutaneous Melanoma") (Marghoob et al. 1996; Titus-Ernstoff et al. 2006). A single institutional series of 4484 cases of melanoma found that 8.6% of patients had 2 or more primary melanomas when they were first seen (Ferrone et al. 2005). Among these patients, 59% had a second primary tumor within 1 year, and 21% had a family history of melanoma compared with only 12% of patients with a single primary melanoma ($p < 0.001$); 38% of patients with multiple primary melanomas had dysplastic nevi compared with 18% of those with a single primary melanoma ($p < 0.001$). Patients who had a positive family history of melanoma or dysplastic nevi had an estimated 5-year risk of multiple primary melanomas of 19.1% and 23.7%, respectively. The most striking increase in incidence for the population with multiple primary melanomas was seen for development of a third primary melanoma from the time of the second primary melanoma, which was 15.6% at 1 year and 30.9% at 5 years (Ferrone et al. 2005). Approximately one third of multiple primary melanomas are found concurrently (synchronous) with the diagnosis of the first melanoma, and two thirds are found sequentially (metachronous) during follow-up, with some being diagnosed more than 30 years after the first diagnosis. It stands to reason that a history of melanoma indicates that the person may have a genetic susceptibility to melanoma and/or have had the causative environmental exposure necessary to form melanoma. Germline mutations in *CDKN2A*, *CDK4*, and *MITF* have been associated with both family history of melanoma and development of multiple primary melanomas (Ferrone et al. 2005; Puig et al. 2005; Yokoyama et al. 2011). The genes, environment, and melanoma study identified several other low penetrance susceptibility loci associated with increased risk of developing subsequent melanomas (Gibbs et al. 2015). In patients with multiple cutaneous melanomas, synchronous or subsequent primary melanomas need to be distinguished from epidermotropic metastases, because the prognosis and treatment differ between the two (Abernethy et al. 1994; Gerami et al. 2006; Mehregan et al. 1995; White and Hitchcock 1998). There is conflicting evidence for the effect of multiple primary melanomas on survival given the inherent complexity in estimating survival in this group. The "delayed entry" approach has been advocated to avoid survival bias, and studies using this method have reported poorer survival in patients with multiple primary melanoma independent of other prognostic factors (Rowe et al. 2015).

Family History

It has been demonstrated that the validity of the family history of melanoma is poor (Weinstock and Brodsky 1998). This stems, in part, from the erroneous yet common interchangeable use of "melanoma" and "skin cancer." Therefore patients should be educated in the distinction between melanoma and other types of skin cancer before a history of melanoma is elicited from them. It is advisable to confirm the family history on a follow-up visit once the patient has had the opportunity to specifically question family members, with the added benefit of a greater understanding of the types of skin cancer. Confirmation of family history by pathology report is considered the gold standard. In patients with a positive family history or personal history of melanoma, it is appropriate to recommend screening of other family members. It is estimated that 5–10% of melanoma cases are hereditary, although this varies depending on the background incidence of melanoma in different regions (Leachman et al. 2009). *CDKN2A* germline mutations are strongly associated with familial melanoma although the penetrance varies by environmental exposures; mutations in *CDK4*, *BAP1*, *POT1*, *ACD*, *TERF2IP*, and *TERT* are rare and account for a small percentage of familial melanoma cases. It is estimated that a mutation in any one of the above genes is implicated in only 50% of melanoma dense kindreds (Read et al. 2016). The likelihood of a CDKN2A mutation being responsible for a familial melanoma cluster increases with number of family members affected, presence of multiple primary melanomas, early age of melanoma diagnosis, and familial cases of pancreatic cancer. In such cases where there is a strong family history (three or more first- or second-degree relatives) and other predictive factors present, genetic counseling and testing should be discussed (Leachman et al. 2009; Mann).

Phototype and Sun Exposure

Questions regarding burning tendency and tanning ability should be asked to determine the patient's phototype as described in Table 1. Patients should be questioned about their natural hair color and eye color, as these may be difficult to ascertain on physical examination because of canities and the use of hair dyes and colored contact lenses. A general assessment of occupational and recreational sun exposure, as well as a history of severe sunburn, should be elicited.

Signs and Symptoms

Patients should be questioned regarding the presence of any worrisome or changing skin lesions. A history of change is elicited more often in lesions that prove to be melanomas compared with lesions that are benign (Kittler et al. 1999). Specific questioning is often required to elicit a history of symptomatic lesions, for example, itching, bleeding, or lesions that are easily irritated. Questions regarding the presence of birthmarks and moles on unusual anatomic sites often can alert the physician to examine these areas more closely.

The cardinal clinical feature of cutaneous melanoma is a pigmented skin lesion that changes visibly over a period of months to years. Sometimes the change is so gradual that the patient is unaware of it. Changes in pigmented lesions that occur over the course of days are typically inflammatory or traumatic in nature. However, as a general rule, any lesion noted to have changed in color, shape, size, or elevation warrants medical attention. Some of the presenting signs are shown in Figs. 1, 2, 3 and 4. Bleeding, itching,

Table 1 Classification of skin phototype

Type	Description	Population affected
I	Always burns; never tans	Ivory white Caucasian (e.g., Celtic)
II	Always burns; sometimes tans	Fair Caucasian
III	Sometimes burns; always tans	Caucasian
IV	Rarely burns; always tans	Olive-skinned Caucasian
V	Burns and tans after extreme UV exposure	Dark-skinned Caucasian (Latino, Indian, etc.)
VI	Burns and tans after extreme UV exposure	Black

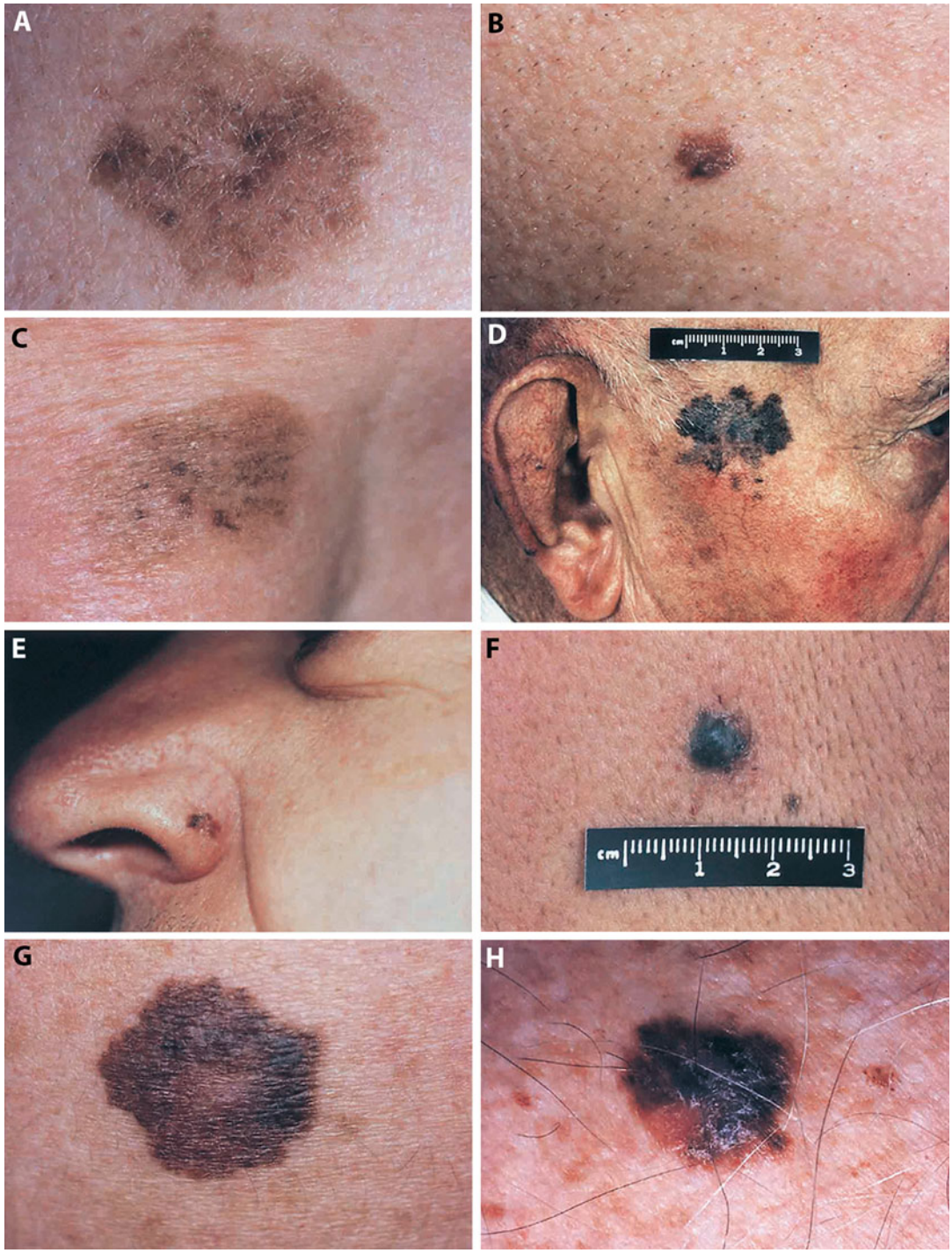

Fig. 1 (**a** and **b**) Melanoma in situ. Note variation in pigment pattern. (**c**) Lentigo maligna melanoma. Note variation in pigment pattern. (**d**) Lentigo maligna melanoma. Note highly irregular borders and background of chronic actinic damage. (**e**) Small melanoma exhibiting variation in color. (**f**) Melanoma exhibiting irregular borders. (**g**) Radial growth phase superficial spreading melanoma (0.64 mm). (**h**) Intermediate-risk superficial spreading melanoma (1.72 mm) (**a**, **b**, **c**, **g**, and **h** courtesy of R.A. Johnson, MD; **d** and **e** courtesy of C.M. Balch, MD)

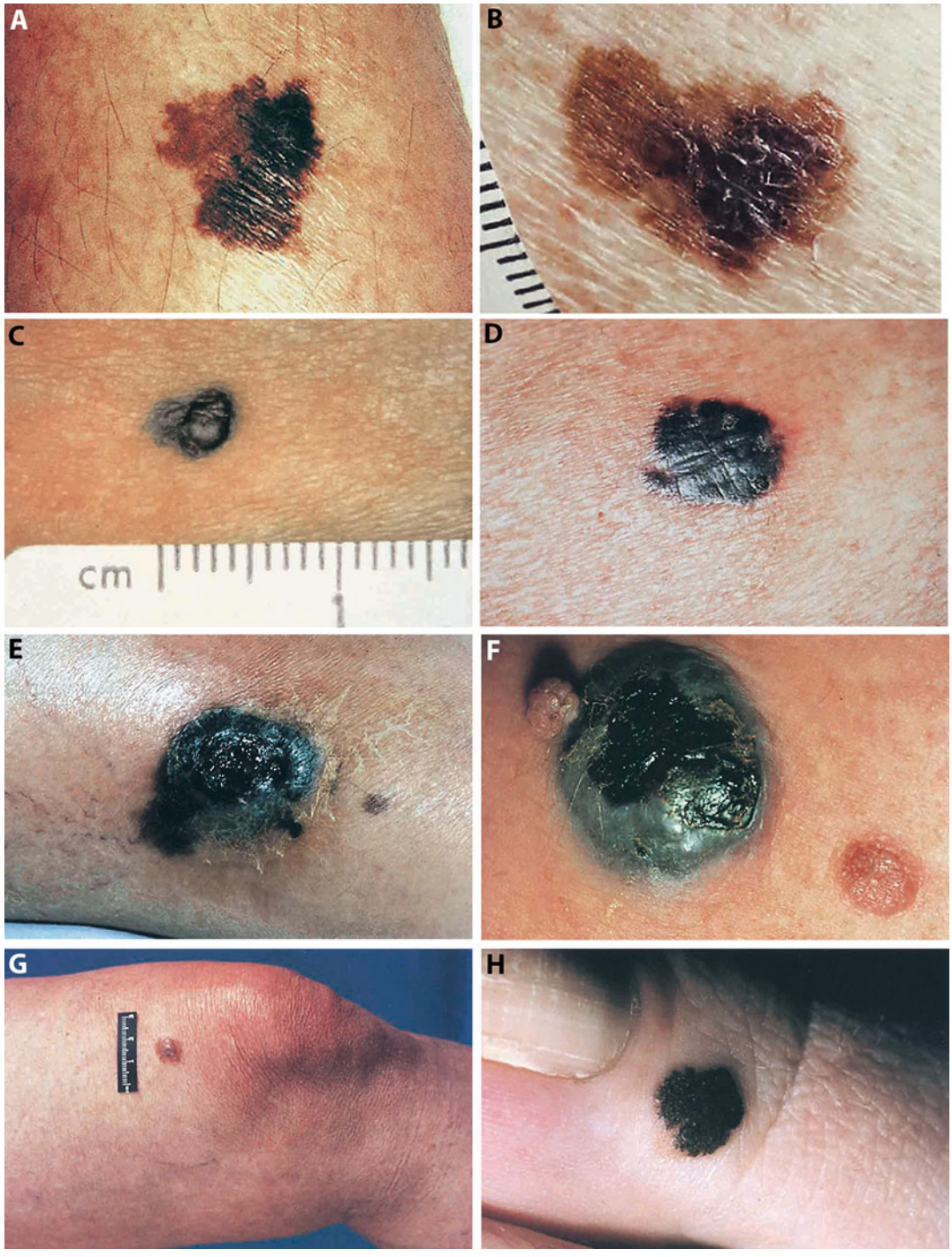

Fig. 2 (**a**) Advanced superficial spreading melanoma with asymmetry, irregular borders, and variation in color. (**b**) Melanoma with radial and early vertical growth phases clinically. (**c**) Melanoma with radial and advanced vertical growth phases. (**d**) Melanoma with irregular border and blue-black coloration. (**e** and **f**) Advanced melanoma with clinical ulceration. (**g**) Relatively lightly pigmented melanoma. (**h**) Acral lentiginous melanoma arising in a nevus (**a** and **g** courtesy of C.M. Balch, MD; **h** courtesy of R.A. Johnson, MD)

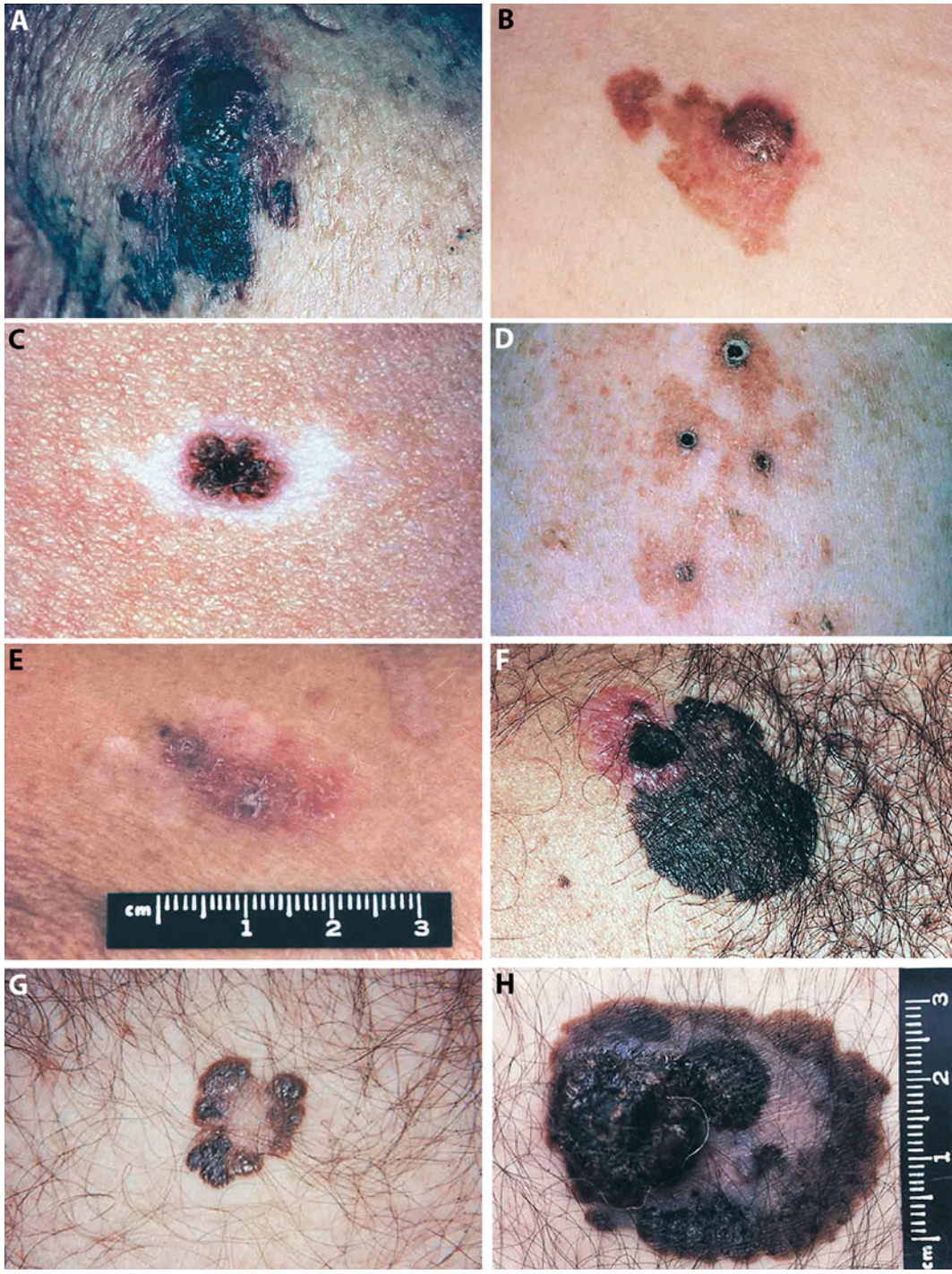

Fig. 3 (**a**) Advanced melanoma with highly irregular borders and variations in color and pigment pattern. (**b**) Relatively amelanotic melanoma with radial and vertical growth phases. (**c**) Halo melanoma. (**d**) Amelanotic superficial spreading melanoma, 1.2 mm thick. Note multiple punch biopsy sites. (**e**) Relatively amelanotic melanoma. (**f**) Superficial spreading melanoma with regression in upper left corner. (**g**) Melanoma with central regression. (**h**) Advanced melanoma with central regression (**b**, **g**, and **h** courtesy of C.M. Balch MD)

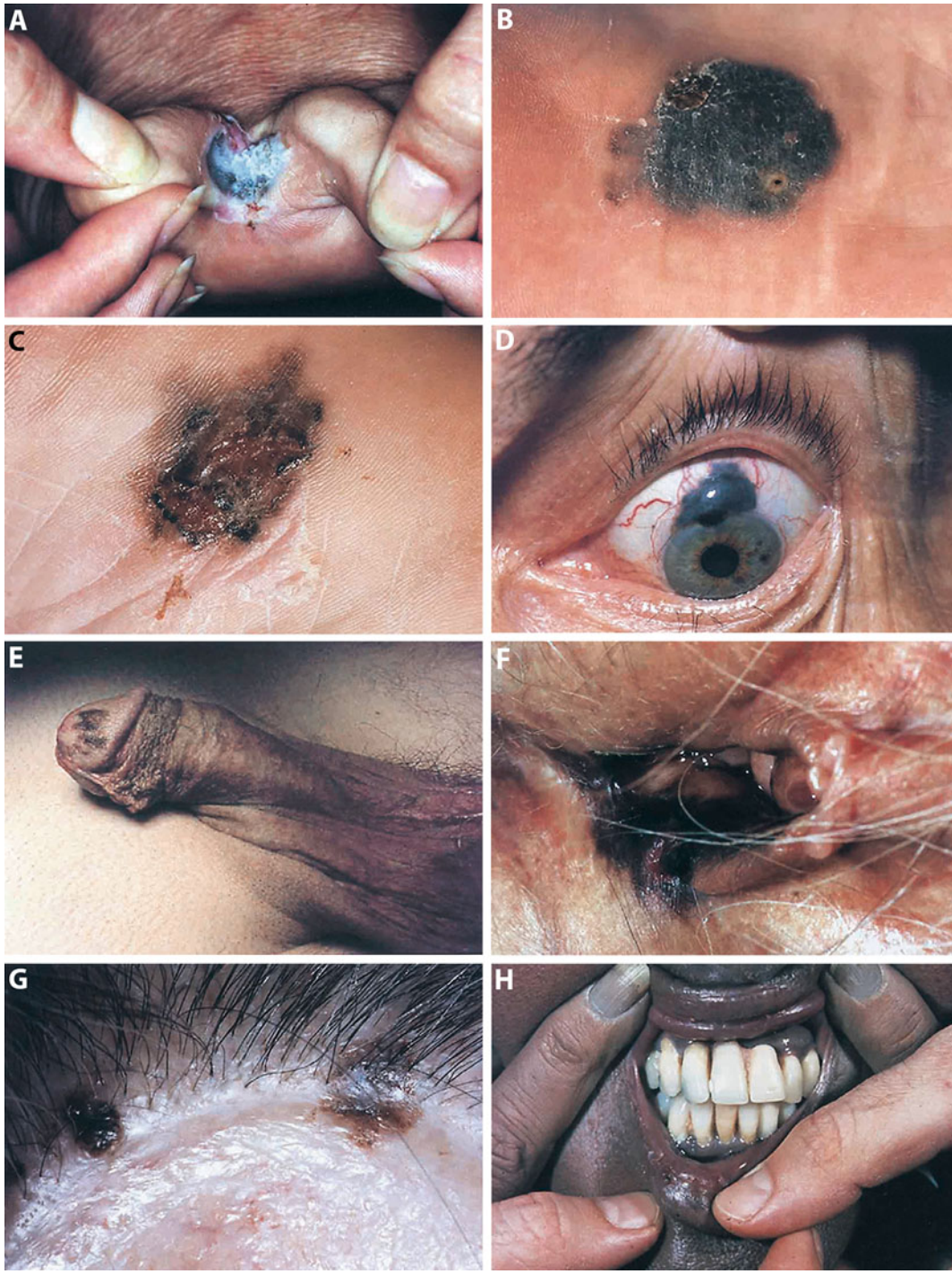

Fig. 4 (**a**) Acral lentiginous melanoma in situ in web space. (**b**) Advanced acral lentiginous melanoma on plantar surface. (**c**) Advanced clinically ulcerated acral lentiginous melanoma on plantar surface. (**d**) Conjunctional melanoma. (**e**) Penile melanoma. Patient had metastases to groin nodes. (**f**) Vulvar melanoma. (**g**) Recurrent melanoma in margin of skin graft. (**h**) Diffuse melanosis resulting from advanced metastatic melanoma. Note bluish-gray color of skin, gingiva, and nail beds (**a** courtesy of R.A. Johnson, MD; **c**, **d**, and **e** courtesy of C.M. Balch, MD)

tenderness, and ulceration can be associated with cutaneous melanoma. Bleeding and ulceration are typically signs of more advanced local disease. On the other hand, it is not uncommon for patients to report unusual sensations in early melanomas, including melanoma in situ. Although it is often difficult for patients to verbalize the exact nature of the sensation or the cause of their concern, lesions that are a source of concern to a patient should be taken seriously. It is not uncommon for melanomas that defy clinical diagnosis on morphologic grounds to be excised strictly on the basis of patient's insistence (Andersen and Silvers 1991). Furthermore, the presenting signs and symptoms of melanoma reported by patients differ between young and older patients. Younger patients have been reported to more often have a history of change in color or contour and have signs of itching (Christos et al. 2000), whereas older patients more often have a history of ulceration, which is a poor prognostic sign (Christos et al. 2000).

Physical Examination

Total body skin examination serves to ascertain melanoma risk factors, such as mole pattern, mole type, freckles, and so forth, and is essential for early detection of melanoma. In addition, total body skin examination performed by the physician demonstrates to the patient proper technique for skin self-examination. The examination should be performed with the patient fully disrobed and appropriately draped to permit a complete examination while addressing the issues of modesty and patient comfort. Lighting that is sufficiently bright is required and may be facilitated by a light source that can be readily manipulated during the course of the examination. Various poses and positions have been recommended for total body skin examination (Kopf et al. 1995). Regardless of the positions used, a systematic consistent approach is critical to ensure a comprehensive examination. All cutaneous surfaces including intertriginous areas, web spaces, and the scalp should be examined. Nails should be examined after all nail polish has been removed. Genital, ocular, and mucous membrane examinations should be performed or recommended as part of the patient's routine gynecologic, ophthalmologic, and dental examinations. When examining the oral cavity, it is important to remove any dentures that could obscure lesions (Dimitrakopoulos et al. 1998). Approximately 80% of melanomas arising in the oral mucosa occurred on the maxillary anterior gingival area, especially on the palatal and alveolar mucosa (Ebenezer 2006; Ulusal et al. 2003). Features to be noted on skin examination include the approximate number of nevi, the presence of atypical/dysplastic nevi, and the presence of actinic damage such as actinic keratoses, dermatoheliosis, solar lentigines, and poikiloderma. The presence of congenital nevi, halo nevi, acral nevi, and scalp nevi should be noted.

Some simple measures can aid in the examination of certain anatomic sites and lesions. For the scalp examination, some prefer to use a hair blower, whereas others prefer to use a comb to methodically part the hair. Examination of pigmented lesions of the nails, palms, and soles is facilitated by swabbing the surface with mineral oil or alcohol to render the nail plate or thickened stratum corneum translucent. Wood's lamp examination can be helpful in assessing the presence of halo nevi or leukoderma or defining the margins of atypical lentiginous lesions (Reyes and Robins 1988). When faced with a highly unusual macular pigmented lesion (Fig. 5), cleansing of the surface with an alcohol swab can prevent unnecessary biopsy of the occasional pseudo-lesion, such as a stain from hair dye or adherent dirt.

Clinical Features

The clinical features of melanoma vary by anatomic site and growth pattern; this is also referred to as *histogenic type.* These growth patterns, in turn, vary in incidence by sex, age, and race (Crombie 1979; Reintgen et al. 1982; Wang et al. 2016) (Table 2). The discovery of various molecular markers has offered the possibility of more detailed subclassification beyond growth

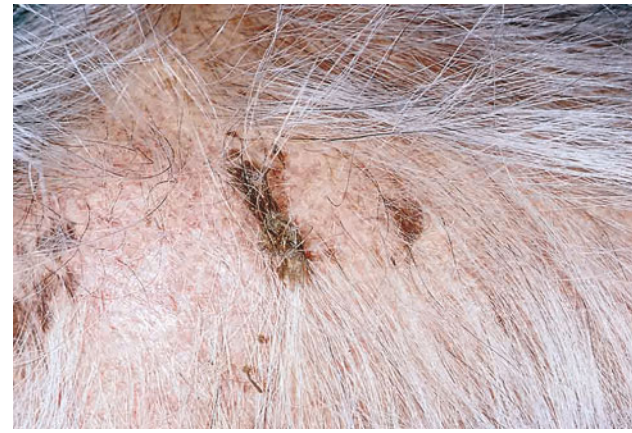

Fig. 5 Pseudolesion. This "pigmented lesion" on the scalp was referred for biopsy because of its irregularity and central regression. The "lesion" rubbed off during preparation with an isopropyl alcohol rub

Table 2 Age-adjusted US melanoma incidence rates per 100,000 person-years, stratified by race, age, and gender

	Non-Hispanic White	Hispanic White	Black	Asian	Total
Superficial spreading melanoma					
All ages	9.05	1.12	0.15	0.31	6.18
<40 years	3.35	0.35	0.04	0.11	1.96
40–64 years	14.73	1.81	0.20	0.47	10.04
65+ years	21.09	2.91	0.51	0.81	15.93
Male	10.23	0.98	0.18	0.34	7.20
Female	8.27	1.29	0.13	0.29	5.49
Nodular melanoma					
All ages	1.80	0.49	0.06	0.14	1.30
<40 years	0.38	0.08	0.01	0.04	0.23
40–64 years	2.31	0.51	0.06	0.14	1.60
65+ years	6.98	2.26	0.31	0.63	5.46
Male	2.51	0.60	0.07	0.19	1.84
Female	1.26	0.42	0.05	0.11	0.91
Lentigo maligna melanoma					
All ages	1.87	0.23	0.02	0.06	1.37
<40 years	0.05	0.01	0	0.01	0.03
40–64 years	1.83	0.17	0.01	0.05	1.26
65+ years	10.11	1.38	0.16	0.33	7.69
Male	2.97	0.33	0.04	0.09	2.21
Female	1.05	0.17	0.01	0.04	0.77
Acral lentiginous melanoma					
All ages	0.21	0.24	0.19	0.17	0.20
<40 years	0.04	0.02	0.02	0.02	0.03
40–64 years	0.25	0.26	0.21	0.17	0.24
65+ years	0.87	1.24	0.93	0.85	0.90
Male	0.22	0.25	0.22	0.20	0.22
Female	0.21	0.24	0.18	0.14	0.20

Diagnosed in the period of 1992–2011 in the SEER 13 database. In each cell, estimate (95% CI). Rates are age-standardized using the US 2000 Census population

pattern type. Divergent pathways of melanoma evolution have been proposed for melanomas developing on chronically sun-damaged (CSD) skin and those developing on non-CSD skin, which is supported by molecular data (Bastian 2014; Whiteman et al. 2003). Melanomas arising in chronically sun-damaged (CSD) skin are more common in older patients and have a high mutation burden from UV-induced DNA damage (Bastian 2014; Mar et al. 2013b). Melanomas arising in non-chronically sun-damaged (CSD) skin tend to occur in the third to sixth decades of life in people with multiple nevi, are associated with a lower mutation burden, and are more likely to harbor a *BRAF V600E* mutation compared to melanomas arising in CSD skin (Bastian 2014; Mar et al. 2013b). Although all of the clinicopathologic types of melanoma have been shown to have a similar prognosis for a given Breslow thickness, the categorization system is still considered to be useful based on distinct risk factors, natural history, site of predilection, and therapeutic implications.

The four major growth patterns of melanoma are lentigo maligna melanoma (LMM), superficial spreading melanoma (SMM), nodular melanoma (NM), and acral lentiginous melanoma (ALM). Table 3 highlights the salient characteristics of the different growth patterns. A biological explanation for the distinct histological patterns remains unclear. It has been suggested that these melanoma subtypes may arise from stem cells within the basal layer of the epidermis (SSM), outer sheet of the hair follicle (LMM), dermis (NM), and eccrine glands (ALM) (Okamoto et al. 2014; Zalaudek et al. 2008).

Several systems and mnemonics have been suggested as aids for the clinical recognition of melanoma. These include the *ABCD* (asymmetry, border irregularity, color variegation, large diameter) rule (Friedman et al. 1985), the three Cs (color, contour, change) (Moynihan 1994), the *ABCDE* rule *(ABCD* is same as previously listed; *E* stands for elevation, erythema, enlargement, or evolution) (Thomas et al. 1998), the Glasgow seven-point checklist (change in size, irregular shape, irregular color, diameter at least 7 mm, inflammation, oozing/bleeding, sensation) (Keefe et al. 1990), *Do UC* (different, uneven, changing) the melanoma? (Yagerman et al. 2014), the *AC* (asymmetry, color) rule (Luttrell et al. 2011), and *EFG* (elevated, firm, growing) (Fox 2005), among others (Weinstock 2006). Although the morphologic attributes highlighted by each of these diagnostic aids do show some degree of sensitivity and specificity for melanoma (McGovern and Litaker 1992; Whited and Grichnik 1998), the predictive value of these attributes is overwhelmed by the relative rarity of melanoma and the high prevalence of benign lesions that occasionally show these features. As mentioned earlier, a cardinal feature of melanoma is the rate of change in color, shape, and size of the lesion. When educating patients on skin self-examination, clinicians should emphasize the importance of change in size and color, as these two have been shown to be the most significant indicators of a patient's ability to self-detect malignant lesions (Liu et al. 2005). Any lesion noted to change significantly in these parameters over a course of months warrants serious consideration for biopsy, although the presence of change is not necessarily indicative of melanoma, especially in patients less than 50 years of age, because nevi in this age group commonly undergo changes. Another helpful feature for the recognition of melanoma is the *ugly duckling sign* (Grob and Bonerandi 1998; Scope et al. 2008); any lesion that stands out as distinctly different from the remainder of a patient's skin lesions merits clinical evaluation.

Growth Patterns

Superficial spreading melanoma (SSM) (Fig. 6) is the most common type of cutaneous melanoma occurring in the Caucasian population. SSM frequently arises in a pre-existing nevus (either banal or atypical/dysplastic), also known as a *precursor* nevus. Patients report a slowly evolving change, over years, in a precursor lesion followed by a rapid period of change in the months before diagnosis. Although a slight predilection for SSM on the back in men and the legs in women has been documented (Fig. 7), SSM can occur at any site. The mean age at diagnosis of SSM is 51 years, which is one to two decades earlier than that of

Table 3 Types of melanoma

Melanoma type	Mean age at diagnosis (year)	Anatomic site	Clinical features	Differential diagnosis
Superficial spreading	51	Any site, typically trunk or extremities, excluding palms and soles	Appearance of large lesion with asymmetry, notched irregular borders, multiple colors, (brown, black, pink, white/gray/blue), often arising in precursor mole	Dysplastic nevus, acquired common nevus, pigmented BCC, pigmented actinic keratosis/SCC, seborrheic keratosis, dermatofibroma
Nodular	56	Any site	Shiny, smooth nodule arising in normal skin or within a precursor nevus; often a single color throughout; does not demonstrate the ABCDs, often black/bluish hues or amelanotic (pink)	Spitz nevus, blue nevus, pigmented and nonpigmented BCC, Merkel cell carcinoma, AFX, hemangioma, thrombosed hemangioma, dermatofibroma, seborrheic keratosis, adnexal tumor, pyogenic granuloma, angiokeratoma, inflammatory nodule (e.g., arthropod bite)
Lentigo maligna	61	Chronically sun-exposed sites (scalp, face, ears, shoulders, extremities)	Asymmetric, irregularly pigmented patch or plaque, highly irregular borders; often appears as a solitary, *ugly duckling* lesion	Solar lentigo, macular seborrheic keratosis, lichen planus-like keratosis, ink spot lentigo, pigmented actinic keratosis, hair/dye/dirt-stained stratum corneum
Mucosal	67	Mucous membranes (oropharyngeal 55%, female genitalia 18%, anal/rectal 24%, urinary 3%)	May arise de novo or in pre-existing mucosal melanosis; often multifocal; can present as mass or bleeding in hidden sites	Mucosal melanosis, labial lentigo, mucosal nevus, amalgam tattoo, venous lake, Kaposi sarcoma, verruca, genital lentiginosis
Subungual	Unknown	Nail matrix/bed	Similar incidence across all races; common history of antecedent trauma; brown/black pigmented nail band >3 mm in width with variegated borders; most often thumbs and great toe nails; Hutchinson's sign (extension to hyponychium or nail fold)	Benign pigmented nail band (melanonychia striata) from lentigo or nevus, subungual hematoma, verruca, SCC, medication-induced pigmentation, pyogenic granuloma
Palmar/plantar	61	Palms and soles	Flat, irregular-bordered precursors, pigmentation masked by thickened stratum corneum	Nevus, lentigo, tinea nigra, verruca, hemorrhage in cornified layer, melanosis

Based on data from the National Cancer Database published in Cancer 1998
AFX atypical fibroxanthoma, *BCC* basal cell carcinoma, *SCC* squamous cell carcinoma

LMM or ALM (Fig. 8) (Chang et al. 1998). Several studies have shown that *BRAF*-mutant melanomas are more common in younger patients and that they are more strongly associated with SSM subtype, truncal location, and intermittent sun exposure (Adler et al. 2017; Broekaert et al. 2010; Curtin et al. 2005; Liu et al. 2007; Maldonado et al. 2003; Thomas et al. 2007).

The *ABCDs* of melanoma (asymmetry, border irregularity, color variegation, and large diameter)

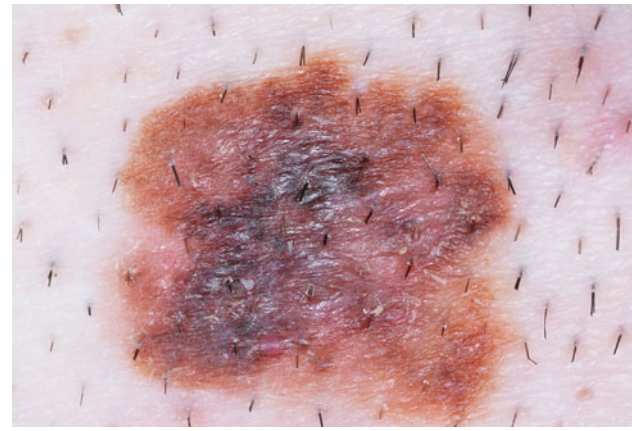

Fig. 6 Superficial spreading melanoma. This melanoma with a diameter of 2-cm harbors all of the ABCDs (asymmetry, border irregularity, color variegation, and large diameter). The central pink/blue area is a sign of regression

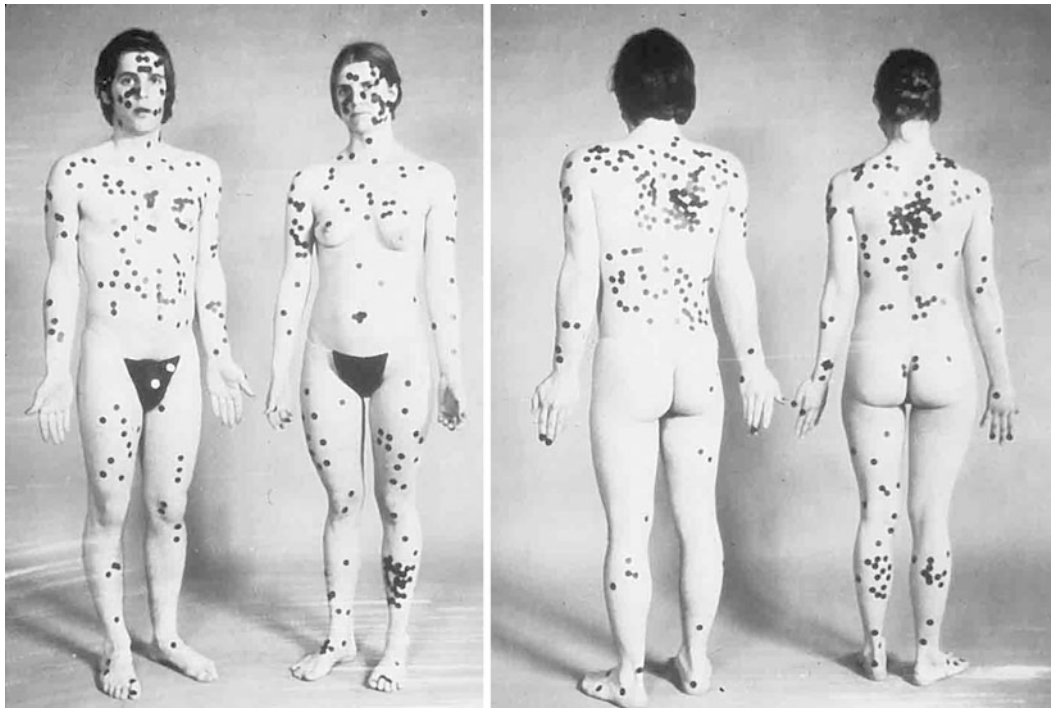

Fig. 7 Anatomic site distribution of melanoma by sex. (Courtesy of Melanoma Clinical Cooperative Group)

best describe SSM. However, the *ABCDs* are frequently present in atypical/dysplastic nevi as well, making it challenging to differentiate between them and SSM (Marghoob 1999). In trying to distinguish SSM melanomas from nevi, use of dermoscopy can be helpful (see chapter ▶ "Dermoscopy/Confocal Microscopy for Melanoma Diagnosis"). In a study of 205 nevi from 18 patients, 1 group found that 83% of patients harbored a dominant global dermoscopic pattern, defined as a pattern occurring in more than 40% of their nevi (Scope et al. 2006). Most of these patients also had one or two minor patterns, defined as occurring in 20–39% of nevi. Thus, in most patients, 80% or more of their nevi could be grouped into one, two, or three patterns, further validating the ugly duckling approach and supporting its clinical utility. A similar study of

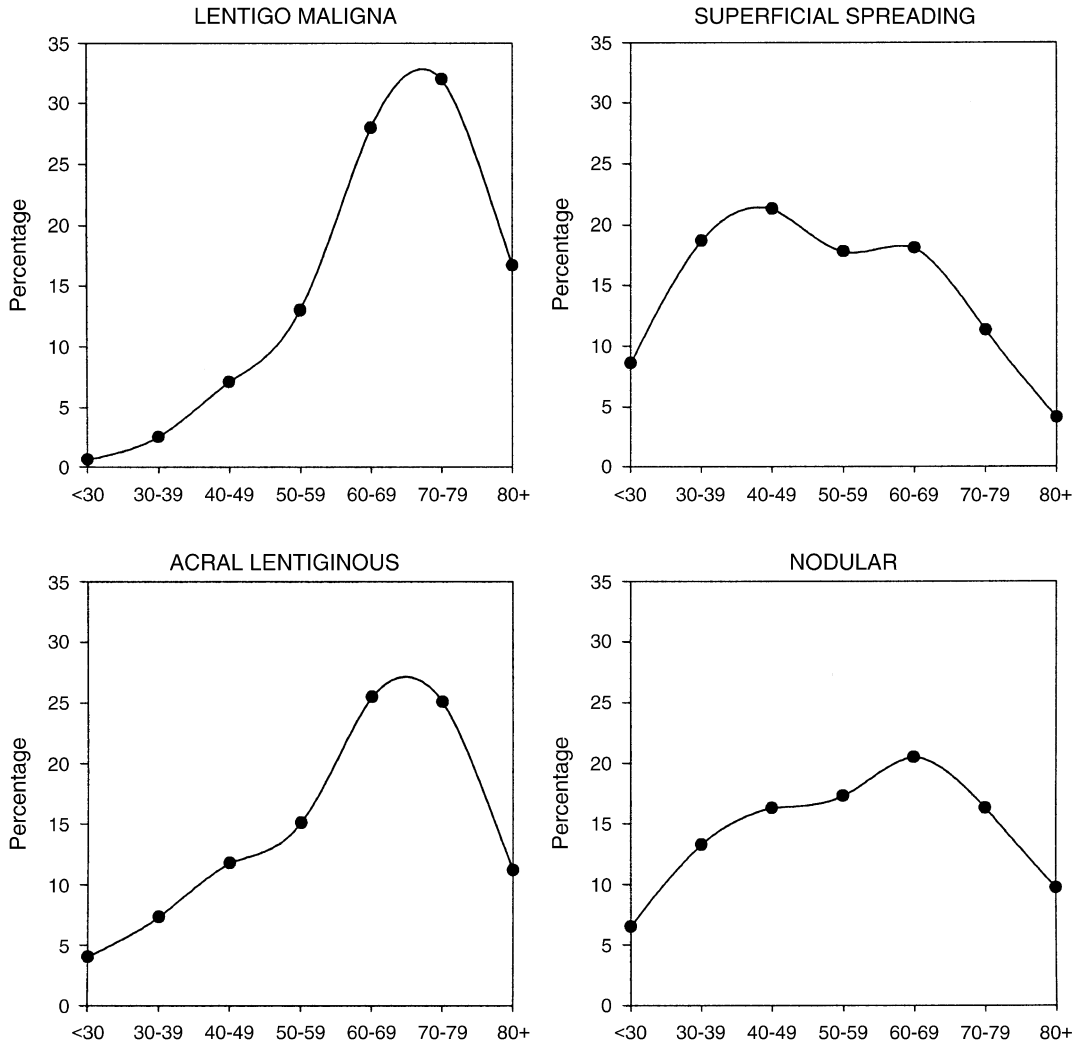

Fig. 8 Average age at diagnosis for the most common subtypes of melanoma – superficial spreading and nodular – is at least 10 years younger than for the other two subtypes

829 nevi from 23 patients found that 52% of the patients displayed a dominant dermoscopic pattern in their nevi (Hofmann-Wellenhof et al. 2001). The authors suggested that it is familiarity with the numerous benign lesions on the skin that largely permits clinicians to accurately recognize melanoma.

Nodular melanoma (NM) (Fig. 9) occurs more commonly on chronically sun-damaged skin, such as the head and neck of older individuals, and is less frequently associated with large numbers of nevi compared to SSM (Chamberlain et al. 2003; Warycha et al. 2008). NM more commonly arises de novo, rather than in association with a nevus, highlighting the importance of awareness of new lesions. NM tends to have more rapid (Pan et al. 2017). They tend to have more rapid growth kinetics than SSM (Liu et al. 2006; Martorell-Calatayud et al. 2011; Tejera-Vaquerizo et al. 2010), and consequences of diagnostic delay are therefore greater. NM is often thick at diagnosis and contributes disproportionately to melanoma deaths (Mar et al. 2013a; Shaikh et al. 2012). Diagnostic accuracy

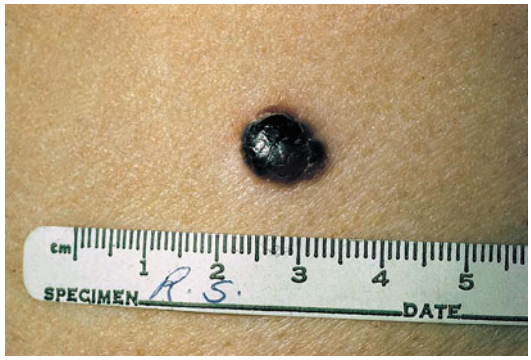

Fig. 9 Nodular melanoma. (Courtesy of American Cancer Society, New England Division)

for NM is poorer than for the more common SSM as they more frequently lack pigment and tend not conform to the *ABCD* criteria, but instead are *e*levated, *f*irm, and growing (EFG criteria) (Lin et al. 2014; Mar et al. 2017). A large dermoscopic study found that 37.3% of NM were hypomelanotic or amelanotic compared to 8.5% of invasive non-NM (Menzies et al. 2013). However, the often striking color and shiny surface may permit detection when the lesion is small.

Lentigo maligna melanoma [LMM] (Fig. 10) occurs on chronically sun-exposed skin in elderly individuals (Cohen 1995). More than 75% of patients diagnosed with LMM are older than 60; these melanomas most commonly occur on the skin of the face but can also occur on other sites that are chronically exposed to UV radiation. The intraepidermal precursor of LMM (i.e., melanoma in situ) is known as lentigo maligna or Hutchinson's freckle, and it usually grows slowly for up to 15 or more years before invasion develops. The rate of transformation of lentigo maligna to invasive melanoma has been estimated to be 5%, and the recurrence rate with standard excision is 8–20% (McKenna et al. 2006). Once invasion occurs, however, the prognosis is dependent on tumor depth, as is the case for other melanoma subtypes (Koh et al. 1984). Lentigo maligna can be difficult to distinguish clinically from solar lentigo and lichen planus-like keratosis. Areas of fine reticulate black pigmentation arising in the background of a solar lentigo can be an early sign of evolving lentigo maligna. Partial incisional biopsies of these often large

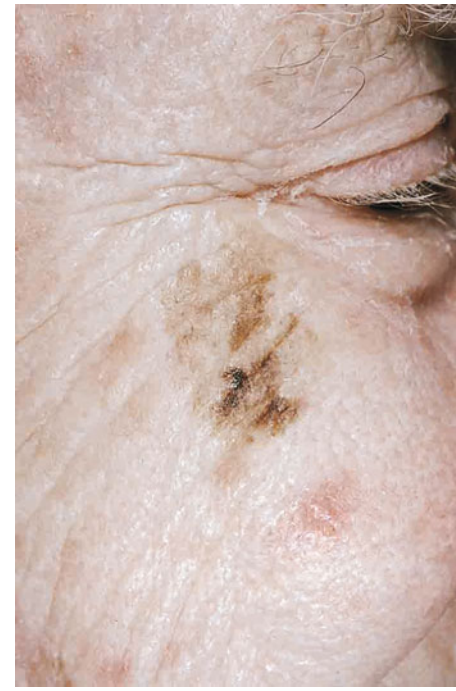

Fig. 10 Lentigo maligna melanoma

macular facial lesions, even in the hands of experienced clinicians, are susceptible to sampling error (Somach et al. 1996). In addition, the clinical borders of these lesions are often indistinct. Wood's lamp examination (UV-A spectrum 320–340 nm) can help to define the clinical margins in some cases. Left untreated or partially treated, LMM can progress to a vertical growth phase and metastasize (Albert et al. 1990). The vertical growth phase of LMM can be associated with a desmoplastic component. The development of an amelanotic papule or nodule near a suspected or previously treated lentigo maligna should raise suspicion of a possible desmoplastic vertical growth phase.

Acral lentiginous melanoma (ALM) presents in two distinct clinical subtypes – melanoma of the palms and soles and subungual melanoma. Although the histogenic type of melanoma differs by race, the proportional predominance of ALM in blacks and Asians reflects the paucity of the other types of melanomas in nonwhites rather than a reflection of increased risk of ALM (Stevens et al. 1990). On the other hand, benign pigmented

lesions in the mucosa, acral sites, and nail beds are more common in blacks than in Caucasians (Leyden et al. 1972; Marchetti et al. 2015; Palicka and Rhodes 2010). Hence awareness of ALM in darkly pigmented races must be tempered by knowledge of the highly prevalent benign pigmented lesions that occur at these anatomic sites in these same individuals. ALM typically is diagnosed at a relatively advanced stage compared with other types of melanomas (Phan et al. 2007). This relates to many factors, including the following: the lesions occur in areas that are not amenable to casual observation; they often are ignored because of a misconception that melanomas only occur in sun-exposed sites or that melanomas do not occur in darkly pigmented individuals; they can mimic many other benign processes; and they occur at surgically sensitive sites that do not readily lend themselves to biopsy. Plantar and subungual melanomas exhibit a higher rate of diagnostic error relative to melanomas at other anatomic sites (Ng et al. 2010). Thus, awareness of the varied atypical presentations of acral melanoma may be important for making a proper diagnosis and improving the outcome. Lesions that mimic ALM include the common wart or callus, fungal disorders, foreign bodies, crusty lesions, conditions affecting the sweat glands, blisters, nonhealing wounds, moles, keratoacanthomas, subungual hematomas, onychomycosis, ingrown toenails, and defective or infected toenails (Rosen 2006; Serarslan et al. 2004; Soon et al. 2003). In 1 hospital-based series of 53 cases of plantar or lower extremity subungual melanoma, 18 were initially misdiagnosed, and 50% (n = 9) of the misdiagnosed cases were clinically amelanotic (Soon et al. 2003).

Palmar-plantar melanoma: The initial macular component of palmar-plantar melanomas (Fig. 11) can be masked by the thickened stratum corneum at these sites (Arrington et al. 1977; Saida 2000). When evaluating such lesions, swabbing the skin surface with mineral oil or alcohol often will be dramatically helpful in delineating the extent of the lesion. Many of these lesions become somewhat verrucous in appearance, leading to a misdiagnosis of warts. Several studies

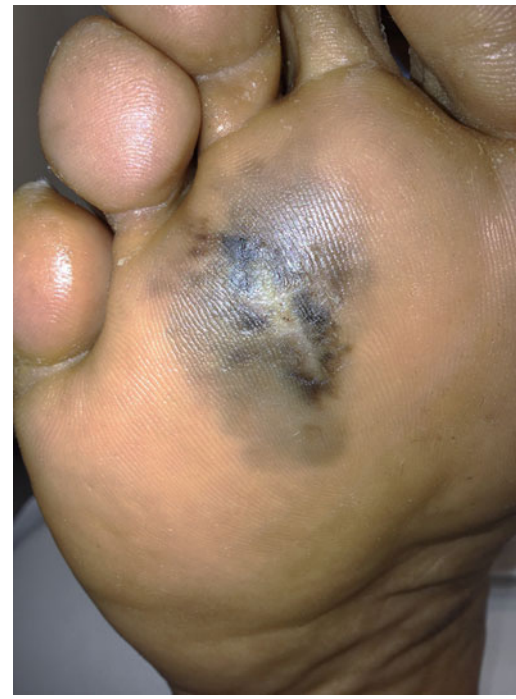

Fig. 11 Acral lentiginous melanoma on the sole

have shown that acquired acral lesions more than 7 mm in diameter have a higher probability of being melanoma, regardless of other morphologic criteria (Braun et al. 2007b; Saida 2000; Saida et al. 1993; Saida et al. 1990). A low threshold for biopsy is critical in making the diagnosis of melanoma. Interestingly, it should be noted that plantar melanoma is the most prevalent type of melanoma in Japanese populations (Saida 2000).

Subungual melanoma: A subungual melanoma arises in the nail matrix or paronychium/hyponychium with subsequent extension onto the nail bed. It most commonly appears as an isolated, changing, acquired pigmented nail band of the great toe or thumb in older individuals during the fourth to sixth decades of life (Fig. 12). Clinical distinction between melanoma and a benign pigmented nail band (e.g., subungual hematoma, fungal infection, lentigo, nevus) can be quite difficult and often relies on the clinical context as much as the morphology of the lesion. Use of dermoscopy can facilitate the examination of pigmented nail bands (Braun et al. 2007a). Multiple pigmented nail bands are common in dark-

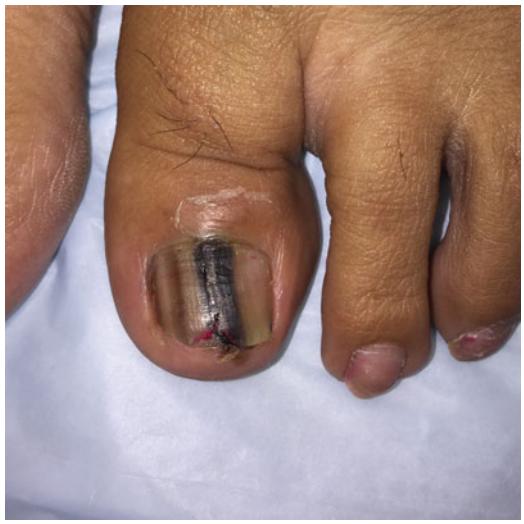

Fig. 12 Subungual melanoma with pigment on the hyponychium (Hutchinson's sign). This melanoma has a Breslow thickness of 1.3 mm and metastasized to the patient's regional lymph nodes

skinned individuals with increasing age (Haneke and Baran 2001; Leyden et al. 1972; Molina and Sanchez 1995). Morphologic features of a pigmented nail band that are cause for concern include an irregular edge; variegate pigmentation; variability in the thickness, color, spacing, and width of bands; nail dystrophy; and a band width greater than 3 mm (Braun et al. 2007a). Adequate biopsy of a pigmented nail band requires knowledge of nail anatomy and an appreciation that pigmentation of the nail plate and nail bed often arises from lesional cells restricted to the nail matrix. Hence a biopsy that fails to include the nail matrix can lead to misdiagnosis (Braun et al. 2007a).

Subungual hematomas caused by trauma are common events that require distinction from subungual melanoma. Although the etiologic role of trauma in subungual melanoma has been debated, many patients who are first seen with subungual melanomas of the great toes and thumbs report a history of antecedent trauma. Accordingly, a history of trauma in itself does not exclude a diagnosis of melanoma because subungual melanoma may be associated with hemorrhage. The failure of a presumed subungual hematoma to clear proximally over a course of months should precipitate a biopsy. A suggestive but not pathognomonic feature of subungual melanoma is Hutchinson's sign. This is the extension of brown-black pigmentation onto the nail fold or hyponychium, and it is seen in more advanced stages. It is important to distinguish true Hutchinson's sign from pseudo-Hutchinson's sign. The latter is the visibility of pigment through the nail fold rather than pigmentation of the nail fold itself. It is also important to note that there are other sources of pigment of the nail folds and hyponychium that can be readily confused with Hutchinson's sign. These include pigmentation of the nail fold in dark-skinned people, Laugier-Hunziker syndrome, Peutz-Jeghers syndrome, radiation therapy, minocycline, zidovudine, and nevoid melanosis (Baran et al. 2018; Baran and Kechijian 1996). The differential diagnosis of a subungual lesion should also include tumor metastasis to the nail unit, especially from primary lung and genitourinary malignancies, not only in oncology patients but also in individuals who were previously cancer-free (Cohen 2001).

Mucosal melanoma: Although it is rare, melanoma can occur on any mucosal surface. Its pattern of distribution does not follow that of other types of melanomas that develop on sun-exposed sites. Thus, the risk factors and behaviors associated with other types of melanomas, including increased sun exposure, do not apply to mucosal lesions. Indeed, mucosal melanomas show a markedly different genomic landscape compared to cutaneous melanomas, with a drastically lower mutational burden that is characterized by structural variants and mutated genes previously thought to be characteristic of uveal melanoma (*GNAQ*, *SF3B1*) (Hayward et al. 2017).

Rates of mucosal melanoma are approximately two times higher in whites compared with blacks (McLaughlin et al. 2005). Mucosal melanoma (Fig. 13) occurs most commonly in the head and neck followed by the female genital tract, the anorectal mucosa, and the urinary tract (see chapter ▶ "Mucosal Melanoma") (Patrick et al. 2007; Rogers and Gibson 1997). Although mucosal melanomas typically occur in occult anatomic locations, appropriate visual inspection during routine dental and gynecologic examinations

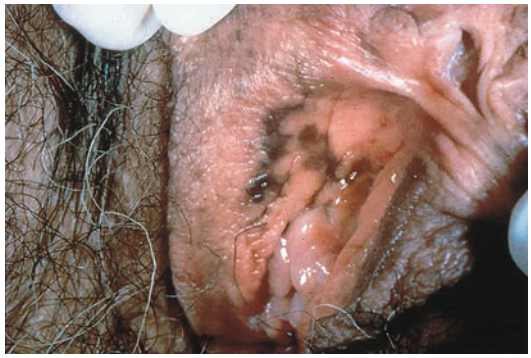

Fig. 13 Mucosal melanoma involving the vulva and vagina

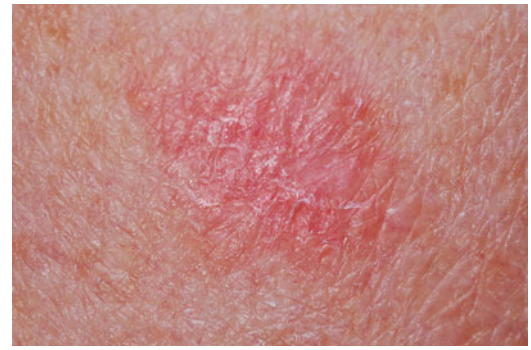

Fig. 14 Amelanotic melanoma

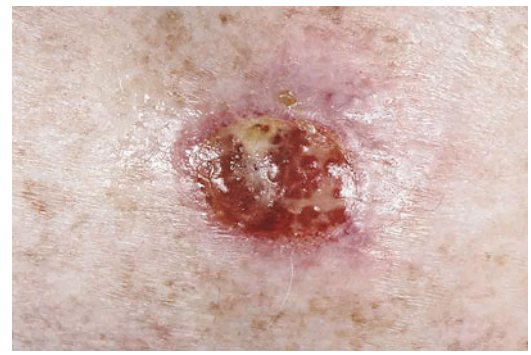

Fig. 15 This 5-cm-wide, advanced amelanotic melanoma had a Breslow thickness greater than 8 mm

permits the detection of some of these lesions. Pap smears performed at the time of routine gynecologic examination also can detect some cases. Unfortunately, many of these lesions come to clinical attention as a mass or site of bleeding. Primarily because of the more advanced stage at presentation, mucosal melanomas are associated with a high rate of locoregional recurrence and poor overall survival (Tacastacas et al. 2014; Vyas et al. 2016). The differential diagnosis of mucosal melanoma includes melanosis, nevi, and amalgam tattoos.

Variant clinical presentations Several variant presentations of melanoma are worth mentioning. These include amelanotic melanoma, desmoplastic melanoma, spitzoid melanoma, verrucous melanoma, polypoid melanoma, and collision tumors.

Amelanotic melanoma: Any of the four main types of melanoma can occur as an amelanotic variant (Menzies et al. 2008). While over 40% of NM, ALM, and desmoplastic melanomas have been reported to be hypomelanotic or amelanotic, this is less common for SSM and LMM subtypes (Chamberlain et al. 2003; Liu et al. 2006; Phan et al. 2010). Amelanotic melanomas (Figs. 14 and 15) can be completely devoid of clinically apparent pigmentation and therefore are often mistaken for benign lesions or simply overlooked (Lin et al. 2014; Mar et al. 2017). Amelanotic lentigo maligna can be easily mistaken for an eczematous patch. Amelanotic nodular melanomas are usually biopsied because of a clinical suspicion of basal cell carcinoma or pyogenic granuloma. On the mucosa, amelanotic melanomas are typically diagnosed as a mass or ulcerated lesion of unknown etiology. Due to their diagnostic difficulty, amelanotic melanomas are identified at more advanced stages, which is associated with worse survival at the population level compared to pigmented melanoma (Thomas et al. 2014). Dermoscopy can significantly help in the identification of amelanotic melanoma, which often reveals a polymorphous vascular pattern with or without shiny white structures (Menzies et al. 2008).

Desmoplastic melanoma: As noted earlier, desmoplastic melanoma (DM) is a variant of the vertical growth phase most commonly seen in association with lentigo maligna melanoma (Bruijn et al. 1992). Desmoplastic melanoma can occur with or without a radial growth phase, and further classification of desmoplastic melanoma

into pure (pDM, >90% desmoplastic component) and combined (cDM, 10–90% desmoplastic component) subtypes has been proposed based on the observation that these may differ in their clinical behavior (Busam et al. 2004; Scolyer and Thompson 2005). Pure DM has been shown to arise predominantly on the head and neck, tends to be thicker, and more commonly exhibits neurotropism compared to cDM (Murali et al. 2010).

Desmoplastic melanoma often first appears as a firm nondescript papule, plaque, nodule, or subcutaneous nodule (Fig. 16). Dermoscopic features may be subtle, and they can be mistaken clinically for scar tissue or dermatofibroma. Desmoplastic melanomas have a higher rate of local recurrence (6–15%) than non-desmoplastic subtypes (<5%) (Chen et al. 2008; Posther et al. 2006). Local recurrence appears to be more strongly related to inadequate surgical margins than the presence of neurotropism (Chen et al. 2008; Varey et al. 2017). Desmoplastic melanoma differs from other melanomas in its clinical course. Although it is associated with a higher tendency for local recurrence, metastasis to regional lymph nodes is less common (Busam 2005; Cummins et al. 2007). A systematic review of 16 studies showed a significantly lower rate of sentinel node positivity for pDM (5.4%) compared to cDM (13.8%) (Dunne et al. 2017), and although several studies have shown an improved prognosis with pDM (Busam et al. 2004; Hawkins et al. 2005; Maurichi et al. 2010), others have not (Murali et al. 2010).

Spitzoid melanoma: The clinical, histologic, and molecular distinctions between Spitz nevus and spitzoid melanoma (Fig. 17) can at times be difficult (Busam and Pulitzer 2008; Lallas et al. 2015; Luo et al. 2011a; Luo et al. 2011b; Wiesner et al. 2016). Accordingly, some spitzoid tumors may be classified as having uncertain malignant potential. In these cases, the clinical context, such as the patient's age and history of stability of the lesion, may influence the diagnostic process. Location can also be helpful in distinguishing Spitz nevi from malignant melanoma. Among excised lesions on the thigh, Spitz nevi outnumber melanomas 8:1 in patients less than 40 years of age whereas on the trunk melanomas are over 7 times more frequent than Spitz nevi in people over 40 years of age (Schmoeckel et al. 2007). Given the diagnostic difficulty and case reports documenting the occurrence of metastasis and death from lesions originally classified as Spitz nevi, it is the opinion of many dermatologists that all spitzoid neoplasms should be completely excised, particularly in adolescents and adults (Bron et al. 2005; Costa et al. 2017; Gelbard et al. 2002). While sentinel node biopsy provides prognostic information for melanoma, a positive sentinel node in atypical spitzoid tumors is not predictive of outcome (Lallas et al. 2014; McCormack et al. 2014).

Rare subtypes of melanoma include *verrucous melanoma*, *polypoid melanoma*, and *nevoid*

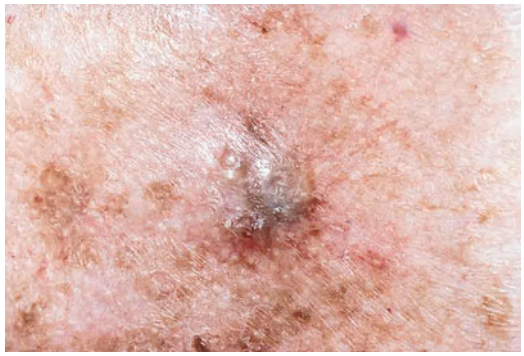

Fig. 16 Desmoplastic melanoma. This is an example of an ill-defined, erythematous, and firm nodule. This melanoma had a Breslow thickness of 2.8 mm

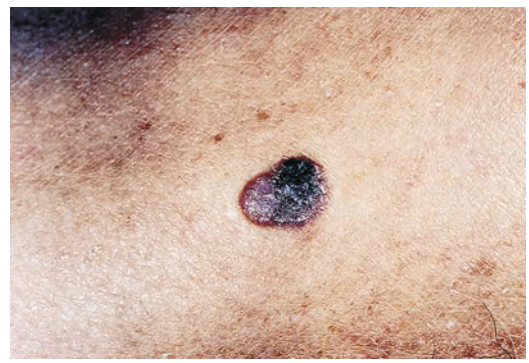

Fig. 17 Verrucous melanoma. This lesion is easily mistaken for an irritated seborrheic keratosis

melanoma. Verrucous melanoma may mimic seborrheic keratosis, verruca, or a compound or congenital nevus (Fig. 18) (Carrera et al. 2017; Chamberlain and Ng 2009). Polypoid melanomas are thought to be a variant of NM associated with more aggressive clinical behavior (Manci et al. 1981). Nevoid melanomas are melanomas in which the melanoma cells have a nevus-like morphology. These melanomas can clinically resemble superficial spreading melanoma or nodular melanoma. However, they can also manifest a clinical morphology resembling a nevus. These nevus-like nevoid melanomas are often raised, sessile, and mamillated lesions that display a polymorphous vessel pattern on dermoscopy.

Collision tumors: As dictated by chance, melanoma can occur in contiguity with a benign or malignant skin lesion. One such collision tumor that has been reported is a melanoma arising within a seborrheic keratosis (Zabel et al. 2000). This should be kept in mind when evaluating clinically complex lesions. The identification of seemingly pathognomonic signs of a benign lesion, such as pseudo-horn cysts of seborrheic keratoses in one part of a lesion, should not preclude biopsy if another portion of the same lesion reveals features of melanoma. In addition, as melanoma has been reported to colonize basal cell carcinoma (BCC), empiric treatment of BCC without a diagnostic procedure is not recommended (Mancebo et al. 2015).

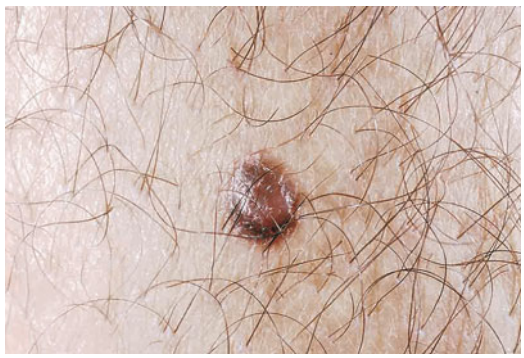

Fig. 18 Spitzoid melanoma. Clinically this lesion can resemble a nodular melanoma. Histologically, it has features in common with Spitz nevi

Aids to Diagnosis

The timely diagnosis and treatment of melanoma during the earliest stages of its evolution are crucial to patient survival. Despite extensive research investigating the varied presentations and physical characteristics of melanoma, clinical diagnostic accuracy remains suboptimal. A meta-analysis examining the performance of physicians in a clinical setting (i.e., not an image-based reader study) estimated a sensitivity for melanoma of approximately 70% using naked eye examination alone (Vestergaard et al. 2008). The diagnostic accuracy for primary care providers tends to be even lower (Argenziano et al. 2006). These poor performance statistics for visual examination coupled with increased awareness of a rising incidence of melanoma has led to an appropriately high index of suspicion and biopsy of lesions in which melanoma enters the differential diagnosis; as a result, in non-specialized centers, as many as 29 unnecessary biopsies of nevi are performed for every melanoma diagnosed (Argenziano et al. 2012). Attempts to improve diagnostic accuracy for melanoma have included the development of innovative noninvasive techniques such as dermoscopy, photography, computerized image analysis systems, reflectance confocal scanning laser microscopy (RCM), electrical impedance spectroscopy, and adhesive patch molecular assays. Although many of these techniques hold great promise, physical examination with simple visual inspection remains today's cornerstone in the early detection of melanoma. Two well-established aids in the visual diagnosis of melanoma that have entered clinical practice over the past decades – photography and dermoscopy – will now be discussed. Newer and evolving technologies will be discussed later in this chapter. Use of dermoscopy initially gained significant popularity in Europe and Australia with appreciably slower uptake in the United States; however, by 2013, 80.7% of US dermatologists reported the use of dermoscopy, and 97.8% of dermatologists with 5 years or less in practice used dermoscopy (Murzaku et al. 2014). There has also been noticeable uptake of dermoscopy by non-dermatologists in the United States who examine the skin

(e.g., family physicians, internists, and plastic surgeons), with 15% reporting having ever used dermoscopy in a 2015–2016 survey (Morris et al. 2017). Total body photography for melanoma surveillance in high-risk individuals is also no longer relegated primarily to specialized centers.

Clinical Photography

Photographs have been used in various ways to facilitate the accurate diagnosis of melanoma. In their simplest use, photographs can be used to document the location of a biopsy site to reduce the likelihood of future wrong site treatment (Zhang et al. 2016). Closeup photography has been used to monitor individual lesions for change. This can be helpful when the suspicion of melanoma is low and/or biopsy is problematic. Total body photography entails obtaining a baseline set of 20–50 photographs representing the entire cutaneous surface. Traditionally, various poses and techniques have been proposed and used for this purpose (Fig. 19). Digital or printed photographs are used during routine patient skin self-examinations and physician follow-up examinations to facilitate identification of new or changing lesions. Computerized systems to facilitate the acquisition and archiving of these images have become commercially available, improving workflows and integration into clinical practice. These systems also permit easy acquisition and archiving of large numbers of closeup images that may further aid in follow-up comparisons. Recently, three-dimensional (3-D) stereophotogrammetry-based total body photography has become available in dermatology clinics (Rayner et al. 2018; VECTRA WB360 3D Whole Body Imaging System), reducing image acquisition and examination times and allowing more consistent "en face" visualization of lesions.

Total body photography has been used primarily in patients with high numbers of nevi and/or atypical nevi to improve sensitivity and specificity of skin examinations for a high-risk population that presents a significant challenge to naked eye examination. Clinics that use total body

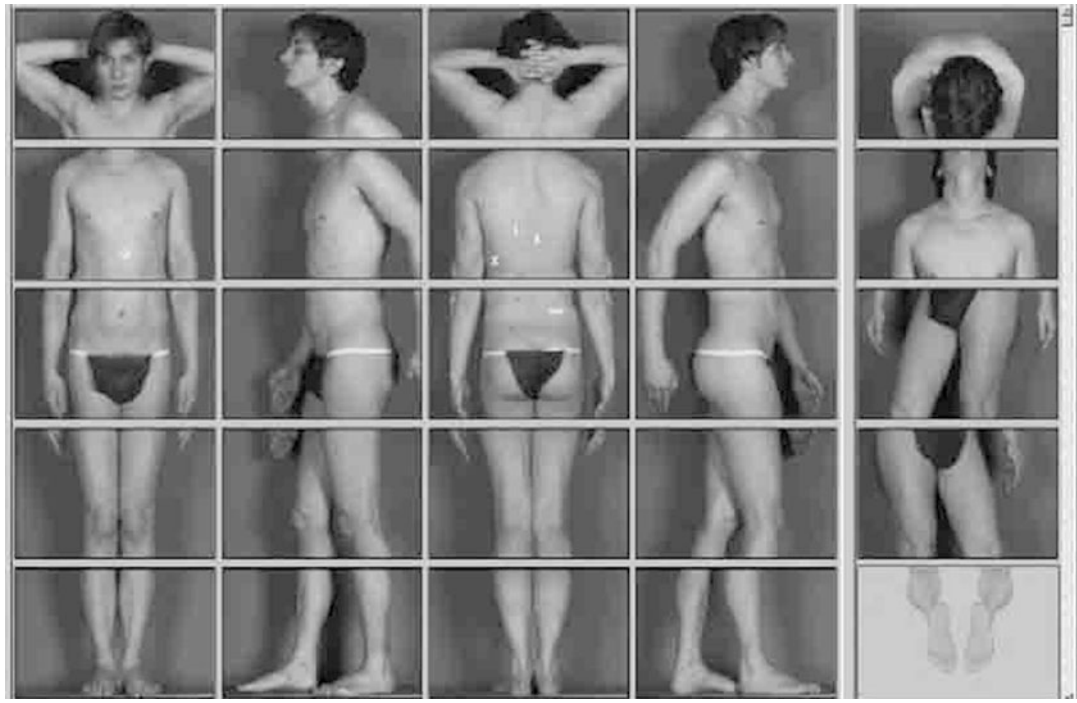

Fig. 19 Total body photography

photography have confirmed that a significant number of melanomas are recognized solely based on changes noted in comparison to baseline photographs (Feit et al. 2004; Goodson et al. 2010; Kelly et al. 1997; Rhodes 1998). Proponents of this technique also claim that, over the long term, the availability of the photographs reduces the number of biopsies and/or excisions performed on dysplastic nevi (Truong et al. 2016). In contemporary practice at high-risk centers, total body photography is used in a complementary fashion with other noninvasive diagnostic techniques, such as dermoscopy and RCM. Retrospective and prospective series of patients who are at extremely high risk for melanoma and monitored at academic centers have underscored the diagnostic value of total body photography for melanoma, with up to 40% of melanomas being detected solely via comparison to baseline total body photography images (Moloney et al. 2014; Salerni et al. 2012).

Increasingly patients are assuming greater responsibility in monitoring their body for suspicious skin lesions and are using smartphone-based applications (apps) to improve their ability to perform skin self-examinations. Dozens of increasingly sophisticated dermatologic apps are available that provide information on skin cancer recognition, permit users to capture images of individual lesions of concern for monitoring, and allow users to digitally catalogue their moles and mark and record lesions on 3-D models for ongoing surveillance (Chao et al. 2017). Although appropriate concerns have been raised regarding the lack of (a) established clinical efficacy for these apps, (b) quality standards and regulatory oversight of apps to ensure patient safety and minimize harm, and (c) image encryption, confidentiality, and security (Marek et al. 2016), dermatologic apps nonetheless offer a unique approach to enhance the secondary prevention of melanoma.

Dermoscopy

Dermoscopy (epiluminescence microscopy, dermatoscopy, skin surface microscopy) is a noninvasive technique that uses a handheld instrument (Fig. 20) to permit the visualization of colors, structures, and patterns in skin lesions that are imperceptible to the naked eye. Although primarily used by physicians, the recent availability of inexpensive dermoscopy attachments for smartphones (Fig. 21) has led to investigations into patient-performed mobile teledermoscopy (Horsham et al. 2016; Manahan et al. 2015; Wu et al. 2015). This section discusses the most salient points relevant to the clinical presentations of melanoma as an exhaustive review of the application of this technology to melanoma diagnosis is provided in chapter ▶ "Dermoscopy/Confocal Microscopy for Melanoma Diagnosis."

Three meta-analyses have found that dermoscopy has higher diagnostic accuracy for melanoma over naked eye examination alone, with the biggest improvement noted with regard to sensitivity (Bafounta et al. 2001; Kittler et al.

Fig. 20 Examples of dermatoscopes

Fig. 21 Examples of dermoscopy smartphone attachments

2002; Vestergaard et al. 2008). Studies limited to family physicians and/or non-experts have shown similar results, with dermoscopy consistently having a higher sensitivity than naked eye examination (Herschorn 2012). Further evidence suggests that dermoscopy reduces unnecessary biopsies of benign skin lesions. A prospective randomized trial of the addition of dermoscopy to naked eye examination found a 42% decrease in patients referred for skin biopsy ($P = 0.01$) (Carli et al. 2004a), and a retrospective study demonstrated that the benign/malignant ratio of excised melanocytic lesions significantly decreased in dermatologists who adopted dermoscopy (18:1 to 4.3:1, $P = 0.037$), with no change in dermatologists who continued with naked eye examination alone (11.8:1 to 14.4:1) (Carli et al. 2004b). In aggregate, there is compelling evidence for the use of dermoscopy in evaluating skin lesions during total body examinations; a systematic review of clinical practice guidelines for identification, screening, and follow-up of individuals at high risk of primary cutaneous melanoma concluded that there is a high level of evidence (Oxford level of evidence 1–2) to recommend the training and utilization of dermoscopy by clinicians routinely examining pigmented skin lesions (Watts et al. 2015).

Nevertheless, use of dermoscopy has been criticized by some for not clearly being associated with improved patient outcomes and for requiring considerable training. Despite its utility, a reassuring dermoscopic evaluation should not override a strong clinical suspicion of melanoma; similarly, a lesion with an innocuous clinical appearance but concerning dermoscopic examination should prompt consideration for biopsy. Expertise in dermoscopy interpretation is crucial because although expert dermoscopists demonstrate an increased sensitivity for diagnosing melanoma, studies of physicians with no formal training in dermoscopy have shown mixed results. An early meta-analysis found a decrease of approximately 10% in sensitivity for diagnosing melanoma among untrained or less-experienced users (Kittler et al. 2002). However, primary care physicians in Spain and Italy randomized to dermoscopy training during a 1-day skin cancer course more accurately triaged lesions suggestive of skin cancer over a 16-month trial than those physicians randomized to clinical examination training alone, with a notable difference in sensitivity (79.2% vs. 54.1%, $p = 0.002$) and negative predictive value (98.1% vs. 95.8%, $p = 0.004$) (Argenziano et al. 2006).

Melanomas often exhibit a dermoscopic pattern that deviates from well-recognized benign nevus patterns, demonstrates asymmetry of dermoscopic colors and structures, and displays a dermoscopic architecture that is disordered. Most melanomas will also contain at least one of the following structures: atypical network, angulated lines, streaks, atypical dots and/or globules, negative network, off-center pigmented blotch, blue-white veil, scar-like depigmentation, peppering, atypical vascular structures, shiny white lines, or peripheral tan structureless area (Fig. 22). Although most melanomas display at least some degree of asymmetry of pattern, color, and structure, there exists a subset of early melanomas that are challenging to recognize. Fortunately, most of these early melanomas can be correctly identified by carefully observing their growth characteristics over time (see below).

Numerous structured approaches have been created to facilitate the recognition of melanoma

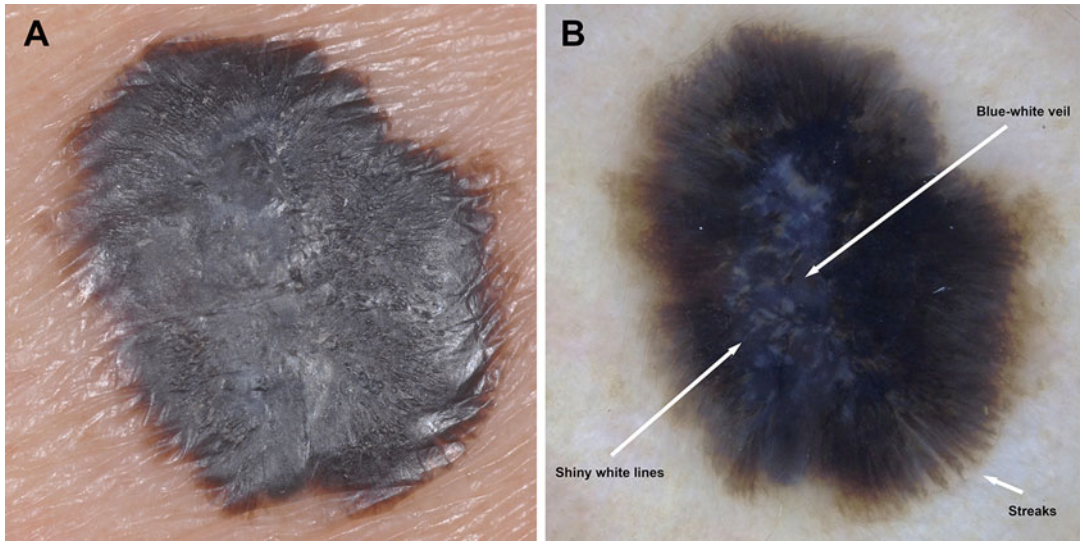

Fig. 22 (**a**) Clinical image of a melanoma. (**b**) Dermoscopy image of the same melanoma. (Note that with dermoscopy one can visualize colors and structures that are not perceptible with naked eye examination)

using dermoscopy, including the ABCD rule of dermoscopy, Menzies method, CASH algorithm, TADA, and the 7- and 3-point checklists, among others (Carrera et al. 2016). Less-experienced dermoscopists may attain a higher diagnostic accuracy and sensitivity for melanoma detection using a structured algorithm, although no single algorithm has emerged as a valid, reliable, and easy-to-learn method that is superior to the rest. In contrast, experts of dermoscopy tend to reach a diagnosis without use of structured analytical criteria, a diagnostic process that can be referred to as pattern analysis.

Early detection of melanomas that do not yet show dermoscopic features of malignancy may be possible with the aid of sequential dermoscopic imaging. This technique has also been shown to reduce unnecessary biopsies of benign lesions compared to the use of dermoscopy alone (Tromme et al. 2012). For example, 55% and 65% of featureless incipient melanomas were detected by specific signs (asymmetrical enlargement and/or architectural change) at follow-up intervals of 4.5–8.0 months and 8.0+ months, respectively (Kittler et al. 2006). Prospective observational studies of high-risk cohorts have found that 34–40% of melanomas are detected exclusively based on dermoscopic changes identified over time (Haenssle et al. 2006; Moloney et al. 2014). However, even the expert application of dermoscopy and the use of short-term follow-up do not yield perfect diagnostic accuracy for melanoma. Hence, the development of additional diagnostic aids is discussed in the following sections.

Reflectance Confocal Scanning Laser Microscopy (RCM)

RCM is a noninvasive imaging technique that allows in vivo examination of the epidermis and papillary dermis at a resolution approaching histologic detail. RCM works by tightly focusing a low-power laser light source on a specific point in the skin and detecting only the light reflected from the focal point through a pinhole-sized spatial filter. This beam is then scanned horizontally over a two-dimensional grid to obtain a horizontal subsurface microscopic section. RCM has primarily been studied as a second-level diagnostic test in combination with clinical and dermoscopic examination and has been demonstrated to improve diagnostic accuracy and to reduce unnecessary biopsies of ultimately benign melanocytic neoplasms (Guitera et al. 2009; Pellacani et al. 2014).

It has also shown significant potential in the preoperative and intraoperative assessment of melanoma margins (Flores et al. 2015; Hibler et al. 2015, 2017; Menge et al. 2016; Yelamos et al. 2017) and in the monitoring of the histologic response of lentigo maligna melanoma to nonsurgical treatments (Alarcon et al. 2014). Significant limitations that have prevented more widespread adoption of RCM in dermatology clinics outside of imaging-oriented academic centers include the cost of the device, the specialized training and expertise required for accurate image interpretation, and the lengthy acquisition times needed for lesion imaging. Recent developments of automated, computer vision-based video mosaicking hold significant promise to decrease acquisition times for imaging tissue in vivo (Kose et al. 2017), and the development of smartphone-based confocal microscopy may permit more widespread adoption of this technology in the future (Freeman et al. 2018). ▶ "Dermoscopy/Confocal Microscopy for Melanoma Diagnosis" chapter provides a more comprehensive review of the application of RCM to melanoma diagnosis.

Image Analysis for Diagnosis

Advances in computer technology, digital imaging, and software programming (i.e., deep learning based on convolutional neural networks), in combination with the availability of larger and more diverse datasets of validated dermatologic images (ISIC Archive), have led to dramatic improvements in automated lesion segmentation, attribute detection (e.g., dermoscopic melanoma-specific features), and disease classification using dermatological images (Gutman et al. 2016). Neural network-based analysis of clinical and dermoscopic images has shown dermatologist-level performance in the discrimination of benign and malignant melanocytic lesions in multiples studies (Esteva et al. 2017; Haenssle et al. 2018; Han et al. 2018; Marchetti et al. 2018; Yu et al. 2018). If results from these artificial, proof-of-concept studies are validated in rigorous clinical studies, computerized assessment of lesions may significantly expand the availability of accurate melanoma diagnosis to settings outside the dermatology clinic. However, datasets used in these studies have been significantly limited in their design and do not include the full spectrum of human populations and benign mimickers of melanoma. Furthermore, there remains a paucity of data on the impact of AI-based dermatological systems on diagnostic accuracy, clinical decision-making, and patient outcomes. Questions regarding the "black box" of artificial intelligence as it relates to melanoma diagnosis have also been raised, as at least one neural network-based algorithm has been shown to lack generalizability to external images, particularly with regard to diagnostic sensitivity, and to be susceptible to perturbations in image zoom, contrast/brightness settings, and image rotation (Navarrete-Dechent et al. 2018).

Aside from the capture and analysis of individual lesions, digital imaging also has been used to document the presence or absence of nevi within defined body sectors (total body photographs). Such a method, if refined and reliable, would be of potential benefit in following patients with multiple nevi. Finally, attempts are also being made to create automated systems for whole-body three-dimensional skin imaging that can detect new or changing lesions (Korotkov et al. 2015).

Other Techniques: Multispectral Imaging, Electrical Impedance Spectroscopy, Adhesive Patch Molecular Assays, Optical Coherence Tomography, and Ultrasound Imaging

Multispectral Imaging

The knowledge that light of different wavelengths penetrates the skin to different depths led investigators to evaluate pigmented lesions under specific wavelengths of light ranging from infrared to near ultraviolet. Sequences of images taken at different wavelengths of light are called *multispectral images*. Spectral images at wavelengths ranging from 400 to 1000 nm can provide more information on the distribution of collagen, melanin content, and blood vessel distribution within skin lesions. A commercially available handheld

spectrophotometric skin imaging device produces five digital images that a user can evaluate for relevant features (SIAscopy 2018). However, studies have shown that use of the device in evaluating pigmented lesions does not aid dermatologists in distinguishing melanoma from benign lesions (Haniffa et al. 2007) and does not improve the appropriateness of referrals of suspicious pigmented lesions by primary care physicians to dermatologists (Walter et al. 2012).

A fully automated computer vision system that used 15 spectral bands between 483 nm (blue) and 951 nm (near infrared) was reported to achieve a sensitivity of 98.4% in a sample of 1831 pigmented lesions biopsied to rule out melanoma (Monheit et al. 2011); the poor specificity of the device, however, limited its clinical utility, and it is no longer commercially available.

Electrical Impedance Spectroscopy

Different classes of skin lesions have been shown to have unique electrical properties based on differences in their intra- and extracellular environments, cell types, shapes, sizes, and cellular membrane compositions. These data have suggested that measurement of the overall resistance within a lesion with alternating electrical currents of various frequencies (1 kHz–2.5 MHz) may yield diagnostically relevant data. Indeed, an automated device with 5 electrode bars that measure electrical impedance spectra across 10 permutations has been shown in a multicenter, prospective study of 1951 patients with 2416 lesions to have a sensitivity of 96.6% (256 of 265 melanomas) and a specificity of 34.4% for the diagnosis of cutaneous melanoma (Malvehy et al. 2014) (Nevisense, Scibase, Stockholm, Sweden). The device has also been investigated as an adjunct in the examination of suspicious melanocytic lesions that are selected to undergo close dermoscopic monitoring and shown to potentially reduce the number of lesions that require follow-up by 46.9% (95% CI 39.0–54.9) (Rocha et al. 2017).

Adhesive Patch Molecular Assays

The inherent challenges associated with the histopathological diagnosis of melanoma using routine hematoxylin and eosin staining of tissue sections led to efforts to create ancillary molecular-based diagnostic techniques, such as fluorescence in situ hybridization, comparative genomic hybridization, and messenger RNA expression profiling (Clarke et al. 2017). These molecular assays, however, relied on surgically obtained lesional tissue specimens. The development of custom adhesive films to sample RNA from the stratum corneum has led to noninvasive gene expression assays for classification of pigmented skin lesions. A 2-gene classification method based on LINC00518 and preferentially expressed antigen in melanoma (PRAME) gene expression obtained via analysis of adhesive patch biopsy was shown to have a sensitivity of 91% and specificity of 69% for melanoma diagnosis (Gerami et al. 2017) and is commercially available (Pigmented Lesion Assay (PLA), DermTech, La Jolla, California). A reader study using 45 dermatologists and 60 clinical and dermoscopic images of atypical pigmented lesions found that the results of the 2-gene classification assay led to an increase in the diagnostic accuracy of the dermatologists for melanoma; sensitivity increased from 95.0% to 98.6% ($p = 0.01$), and specificity increased from 32.1% to 56.9% ($p < 0.001$) (Ferris et al. 2017a).

Optical Coherence Tomography

Optical coherence tomography uses low-level coherent super-luminescent diodes at a wavelength of approximately 1300 nm. Optical coherence tomography provides two-dimensional, cross-sectional, and en face images of the skin with a scan length of a few millimeters, a resolution of 3–15 μm, and a detection depth of 0.4–2.00 mm. This level of resolution enables visualization of the gross architecture of the epidermis and superficial dermis. Similar to ultrasonography and MRI, optical coherence tomography may be helpful in determining the Breslow thickness or the melanoma volume. Dynamic optical coherence tomography allows visualization of cutaneous microvasculature. The application of optical coherence tomography to melanoma diagnosis is limited by the resolution afforded by this imaging modality and the optical properties of melanin; however, it appears to hold greater promise for the diagnosis of keratinocyte carcinoma (Olsen et al. 2018b).

Ultrasound Imaging

Both 20 MHz ultrasound and more recently higher-frequency (50–100 MHz) ultrasound have been used to examine melanocytic lesions. The newer 50–100 MHz scanners have an axial resolution of 10 μm, as opposed to the 80 μm achieved with the 20 MHz scanners, and the lateral resolution is less than 30 μm, compared with 200 μm for the lower frequency scanners. The interpretation of sonographic images such as borders of lesions, echogenicity, and vascular patterns with duplex color sonography requires formal training. The wide variety of diagnostic information provided by ultrasound imaging underlines its essential position in certified skin cancer centers. Melanomas generally appear as echolucent areas on ultrasound images. Although ultrasound imaging cannot be used to make a diagnosis of melanoma (Maj et al. 2015), it may be of use in determining the in vivo maximum melanoma thickness, volume, vascularity, and staging via mapping of lymph node and subcutaneous metastases (Guitera et al. 2008; Meyer et al. 2014). Ultrasound imaging can, at times, overestimate tumor thickness because of the presence of lymphocytic infiltrates and/or nevus remnants. It can also underestimate thickness if single or small clusters of melanoma cells are in the deeper dermis. Combined information obtained from ultrasonography and dermoscopy is being evaluated to better predict the in vivo melanoma thickness.

Continued development of technologies for noninvasive imaging of the skin likely will lead to enhanced diagnostic accuracy of pigmented skin lesions. This will, in turn, lead to the avoidance of unnecessary excision of benign lesions and improved early detection of curable melanomas.

Evolving Paradigms in the Visual Assessment of Skin Lesions

Technological advances in automated diagnosis have prompted a critical analysis of the visual and cognitive elements of the clinician's assessment of pigmented lesions. Observational strategies used by experts in the evaluation of pigmented lesions include analytical reasoning, comparative recognition, differential recognition, and pattern analysis (gestalt), in addition to patient-derived anamnestic data (Gachon et al. 2005; Marghoob and Scope 2009). It has been demonstrated that the process of observation is subjective and the act of interpreting observational findings, or rather perception, is even more subjective and varies according to person, time, and place. This is supported by the finding that examination of photographic or dermoscopic images in the absence of face-to-face contact with the patient leads to mismanagement of approximately 30% of difficult melanomas (Carli et al. 2005).

There has been significantly more research on radiologist methods of analyzing radiographs compared with dermatologists' means of interpreting skin lesions. These studies have distinguished two types of visual examinations: scanning and focusing. Scanning involves rapid eye movement with high activation of the rods and cones, whereas focusing uses the macula and fovea, areas with the highest concentration of photoreceptors, and requires deliberate saccadic suppression. Studies have shown that experts display longer intervals of saccadic eye movements (scanning) than non-experts and rapidly focus on regions of interest that ultimately prove to the key to making the diagnosis (Krupinski et al. 2006). The cognitive counterpart of saccadic vision might be the way experts quickly scan their mental knowledge bank and draw on various types of knowledge to "form an overall opinion of the image that lies before them." Experts also spend less time dwelling on particular areas (Krupinski 2005). Dermoscopy is especially dependent on the clinician's ability to focus on primary morphology and discern subtleties within an otherwise benign-appearing lesion (Zalaudek 2006).

In trying to answer the question of why many second melanomas are found within 2 months of the diagnosis of the first melanoma, Carli et al. succinctly commented, "Concern about the first lesion (the thickest in most cases) probably rendered the second one less evident to both patients and clinician, until the first follow-up examination after excision of the first lesion" (Carli et al. 2002). This phenomenon has been observed in the field of radiology as well and has been *defined* as

satisfaction of search by researchers in that field. Satisfaction of search refers to the phenomenon of missing a finding because another abnormality has been identified (Berbaum et al. 2007; Berlin 2014). Research with the use of gaze tracking has shown that unreported lesions actually are examined but are then disregarded perhaps because the search has been satisfied by another area of interest (Kundel 2006). A related concept referred to as *anchoring bias* describes a shortcut in a person's thought process that bypasses multiple diagnoses and latches, even arbitrarily, onto one that seems to be the most compelling (Braga et al. 2008). One interpretation might gain dominance over others because of the conspicuity of the relevant visual finding. However, this can be modified with the use of different imaging techniques and computer software (Revesz 1985; Revesz and Kundel 1977). For example, polarized and non-polarized light dermoscopy have mechanical differences that provide complementary conspicuity information. This enables certain features to be more prominent than others, altering the way an image is perceived and, more important, diagnosed (Braun et al. 2011). Experts use various analytical reasoning strategies simultaneously in an interactive fashion. Deliberative analytical reasoning, as exemplified by many of the algorithms or scoring methods in dermoscopy, is the primary strategy when a case is complex or ill defined, the clinical findings are unusual, or the physician has had little clinical experience with the particular disease entity (Bowen 2006). The method of pattern analysis, in contrast, relies on non-analytical reasoning. It is more intuitive than logical, not easily replicable, and difficult to learn. A critical element of becoming an expert is accruing the experience that enables one to recognize patterns effortlessly and to also recognize when the findings do not fit a pattern at all (Norman 2006).

The *moles breed true* or *ugly duckling* concepts of melanoma emphasize that an "outlier" lesion that looks different from the others should be suspect; in other words, these concepts refer to intra-patient comparative analysis of skin lesions. These concepts have been joined by the *beauty and the beast sign*, which holds that, in the expert's eyes, a benign lesion is usually beautiful, whereas a malignant one is ugly (Marghoob et al. 2007). These diagnostic attributes emphasize that melanomas are usually morphologic outliers that lack the symmetry of structure, pattern, and color typically associated with benign lesions. Indeed, the *ugly duckling sign* has been shown to be of major importance to the effectiveness of the diagnosis of melanoma in the clinical setting; one study found that compared to lesion-focused analysis, intra-patient comparative analysis in the clinical setting has superior specificity and reduces the number of nevi considered for biopsy (Gaudy-Marqueste et al. 2017). As we improve our understanding of the visual and cognitive elements of diagnosing melanoma, we will be better able to teach both humans and machines how to accurately detect early melanomas.

Cross-References

- ▶ Acquired Precursor Lesions and Phenotypic Markers of Increased Risk for Cutaneous Melanoma
- ▶ Acral Lentiginous Melanoma
- ▶ Biopsy of Suspected Melanoma
- ▶ Classification and Histopathology of Melanoma
- ▶ Clinical Epidemiology of Melanoma
- ▶ Clinical Genetics and Risk Assessment of Melanoma
- ▶ Dermoscopy/Confocal Microscopy for Melanoma Diagnosis
- ▶ Lentigo Maligna Melanoma
- ▶ Melanoma in Children and Teenagers
- ▶ Melanoma Prevention and Screening
- ▶ Molecular Pathology and Genomics of Melanoma
- ▶ Mucosal Melanoma

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