Skin Cancer for Primary Care

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Introduction

Skin cancer is the most commonly diagnosed cancer in the United States [1]. The US Surgeon General released a Call to Action to Prevent Skin Cancer in July of 2014, citing the elevated and growing burden of disease [2]. The vast majority of cutaneous neoplasms are basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs), frequently referred to under the umbrella term "non-melanoma skin cancers." Approximately 5.4 million BCCs and SCCs are diagnosed each year (occurring in about 3.3 million Americans). BCCs make up roughly 80% of these tumors [3].

The incidence of non-melanoma skin cancer has continued to rise by 3–8% per year since 1960 in the United States. This pattern is seen in countries worldwide [4]. Death from these cancers is uncommon but occurs in roughly 2000 people each year in the United States [3].

Melanoma, while far less common, is associated with significantly higher mortality. In 2016, an estimated 76, 380 new cases of melanoma will be diagnosed, and 10,130 deaths from melanoma will occur [5]. The incidence of melanoma is expected to continue to increase in the United States [6].

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Common Skin Cancer Mimickers

Most skin lesions that cause concern for patients are benign. Nevi or "moles," seborrheic keratoses, solar lentigines, and cherry angiomas are exceedingly common, particularly as patients age. While these lesions can mimic cutaneous malignancies, in most cases they can be confidently diagnosed based on clinical grounds by their classic morphologic features. A primary care physician familiar with the various presentations of these benign neoplasms can spare a patient the anxiety of awaiting a specialist evaluation and also conserve healthcare dollars. When benignity is in doubt, biopsy or referral to a dermatologist is recommended. A few of the most common benign lesions bear mention.

Seborrheic keratoses (SKs) are typically pink to brown "stuck-on" appearing lesions frequently seen in middle-aged and elderly Caucasian populations (Fig. 1a). They may have a verrucous or mammillated surface (Fig. 1b), and their characteristic keratotic scale gives them a "waxy" appearance (Figs. 2 and 3). SKs arise on both sun-exposed and non-sun-exposed surfaces and, in some families, are inherited in an autosomal dominant manner. Patients frequently describe them as becoming irritated, crusted, or falling off on their own. Seborrheic keratoses are sometimes lightheartedly referred to by dermatologists as "barnacles" due to their widespread prevalence with increasing age. Darker lesions can appear almost black in color and are sometimes mistaken for melanoma.

Solar lentigines are tan to dark-brown macules (Fig. 4a) or small patches (Fig. 4b) that occur on sun-exposed areas. Historically referred to as "liver spots" or "age spots" by patients, these benign neoplasms increase in number with age (Fig. 4c). Unlike ephelides or "freckles" that arise early in life and fade with reduced sun exposure, solar lentigines increase in frequency and darkness with cumulative sun exposure and do not fade in winter months. Solar lentigines on the face can be particularly challenging to differentiate from the lentigo maligna subtype of melanoma in situ. Asymmetric growth or nonuniform darkening can raise suspicion for melanoma, but biopsy is frequently required to definitively rule out malignancy.

There are several common mimickers of basal cell carcinomas, including cherry angiomas, sebaceous hyperplasia, and fibrous papules. Bright red papules known as cherry angiomas frequently arise on the scalp, trunk, and extremities in patients (Fig. 5). These also increase in number with age and are typically asymptomatic. Rarely, they may become traumatized and turn purple or black and bleed, which might prompt patient or clinician concern for malignancy. Sebaceous hyperplasia typically presents on the central face as yellow papules with a central dell and telangiectatic vessels (Fig. 6). Their yellow hue and vessel pattern, which typically spares the center of the lesion, can help differentiate them from BCC. Fibrous papules, also known as angiofibromas, are benign skin-colored bumps often arising on the face, especially the nose (Fig. 7). They feel firm to the touch due to increased fibroplasia of collagen. Fibrous papules tend to have finer telangiectatic vessels than are commonly seen in BCC and rarely grow larger than 3–4 mm.

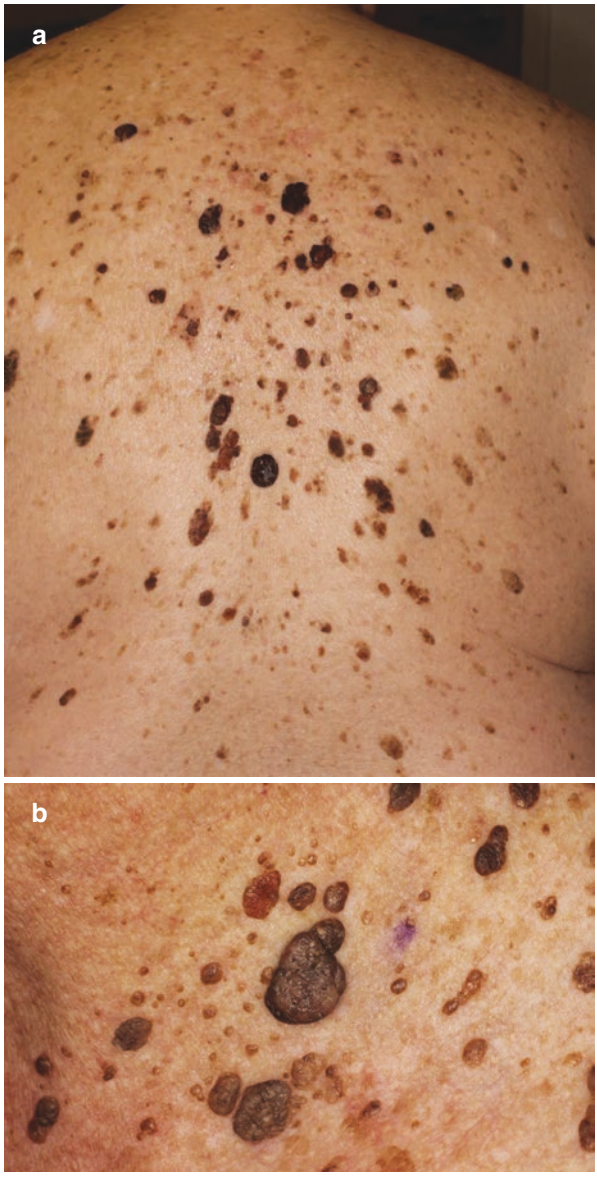

Fig. 1 (**a**) Multiple seborrheic keratosis on the back with a "stuck-on" appearance. (**b**) The surface is characteristically mammillated and waxy in appearance

Differentiating benign nevi or "moles" from malignant melanoma can be a challenge for primary care doctors and dermatologists alike, particularly when nevi are clinically atypical. Nevi can range in color from pink to tan to dark brown (Fig. 8a). Early lesions tend to be flat but gradually become raised with time, only to regress in elderly patients. Moles that present at birth are called congenital nevi. These nevi often have hair growth within them, a reassuring sign (Fig. 8b). The

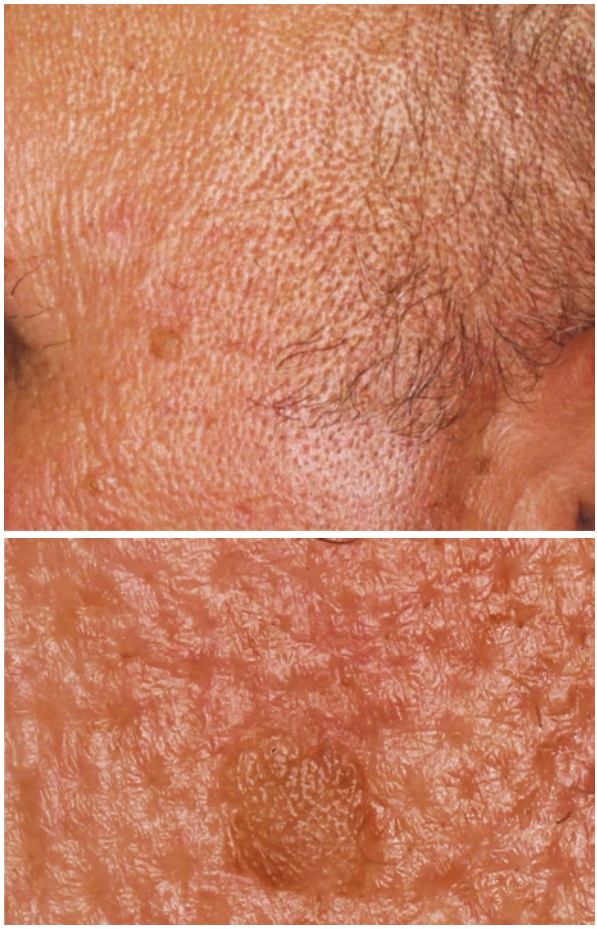

Fig. 2 Note the waxy appearance of this seborrheic keratosis

lifetime risk of melanoma developing in congenital melanocytic nevi is estimated to be up to 10% depending on the size [5]. Those with very large congenital nevi have a higher risk. Those with multiple irregular or large nevi are thought to also have an increased risk of skin cancer. Additional examples of nevi are shown in Fig. 8c–f.

Once the clinician is familiar with the morphology of common, benign lesions, it becomes easier to identify features that warrant higher diagnostic suspicion of malignancy. The "ABCDE" rule for identifying melanoma (A for asymmetry, B for border irregularity, C for color, D for diameter greater than 6 mm, and E for evolution) is an imperfect but easily remembered heuristic for patients and clinicians [7]. One major pitfall of this tool is its low specificity. The ABCDE rule is inclusive of changes frequently seen with other types of skin cancer, as well as numerous benign lesions. Furthermore, not all melanomas exhibit these features. When used by dermatologists, the sensitivity and specificity of a lesion with two of these criteria are

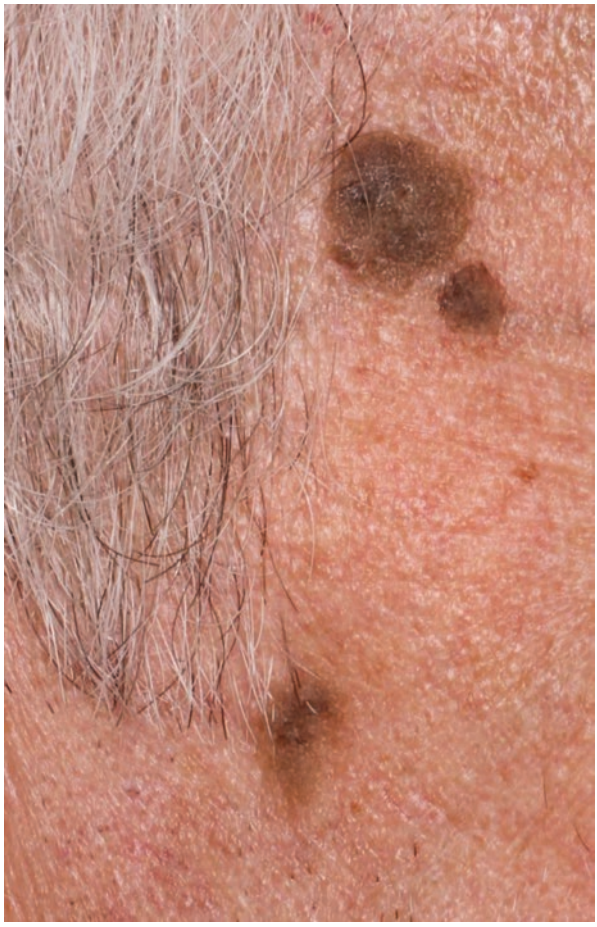

Fig. 3 Classic appearance of a seborrheic keratosis

89.3% and 65.5%, respectively [7]. Another proposed acronym is the "EFG" rule for melanoma, which stands for "evolving, firm, and growing," but this is not widely used or statistically validated.

Patient history can be helpful in identifying evolving lesions. An 8-millimeter diameter mole that has been present for years without change or symptomatic disturbance may be less worrisome than a new or changing 4 millimeter lesion. Recognizing a patient's most common nevus morphology, or "signature nevus" – perhaps oval and pinkish brown in a red-headed patient, for example – can reassure a clinician about a particular lesion's benignity when it fits this pattern or, contrarily, heighten suspicion for malignancy when it does not, the so-called ugly duckling sign (Fig. 9a–b) [7]. Other signs and symptoms such as rapid growth or color change, pain, tenderness, and ulceration are collectively concerning. New ulcerations that have grown or persisted beyond 1–2 months without resolution may warrant biopsy or close follow-up. A family history of

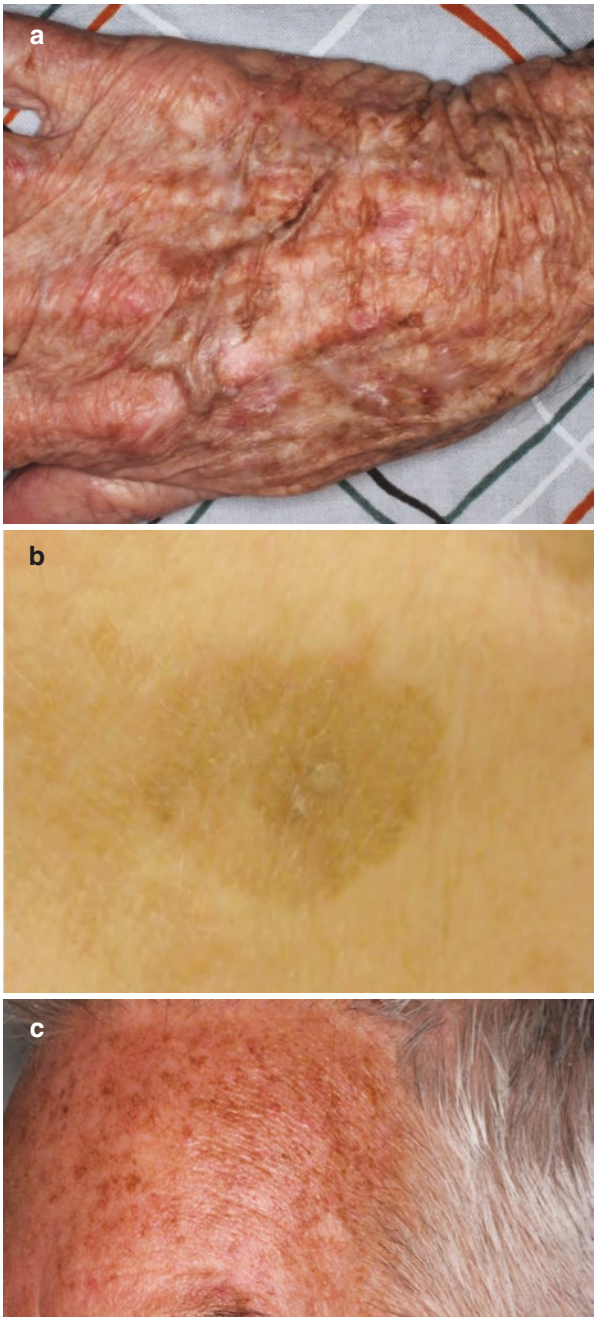

Fig. 4 (**a**) Solar lentigines. Note the light-brown photodistributed macules. (**b**) Larger solar lentigo with scalloped borders. (**c**) Light-brown similar-appearing lentigines

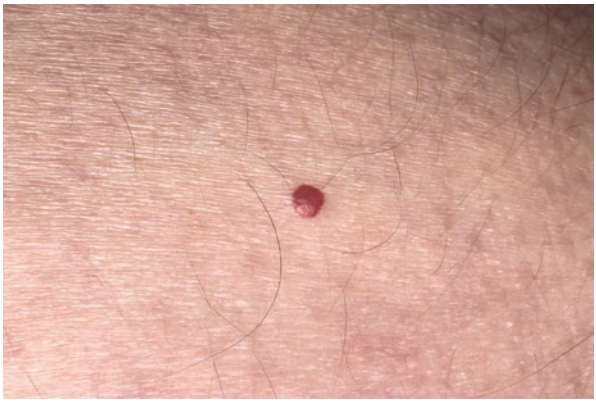

Fig. 5 Cherry angiomas – small, bright pink papule commonly located on the trunk

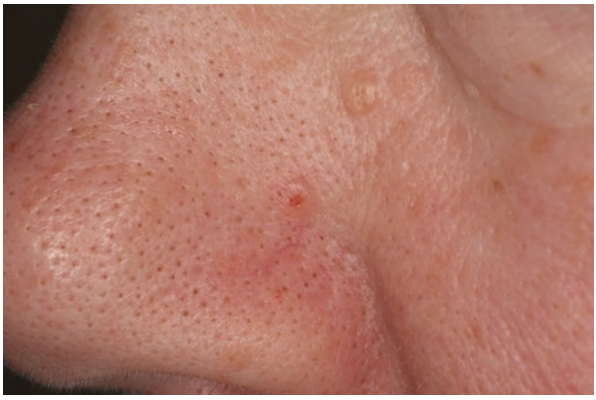

Fig. 6 Compare the superficial yellow papule with a central dell, a sebaceous gland hyperplasia (upper nasal sidewall) to a small BCC (lower nasal sidewall with central ulceration)

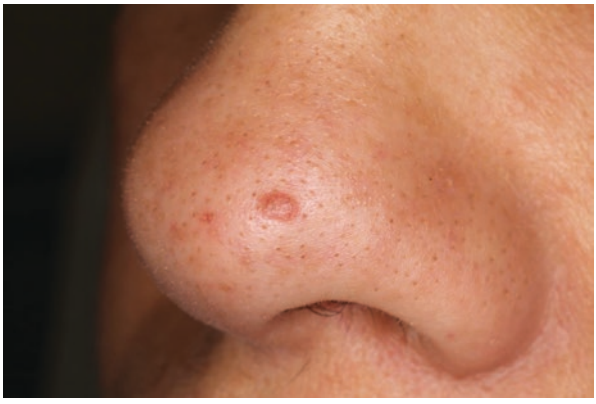

Fig. 7 Fibrous papule

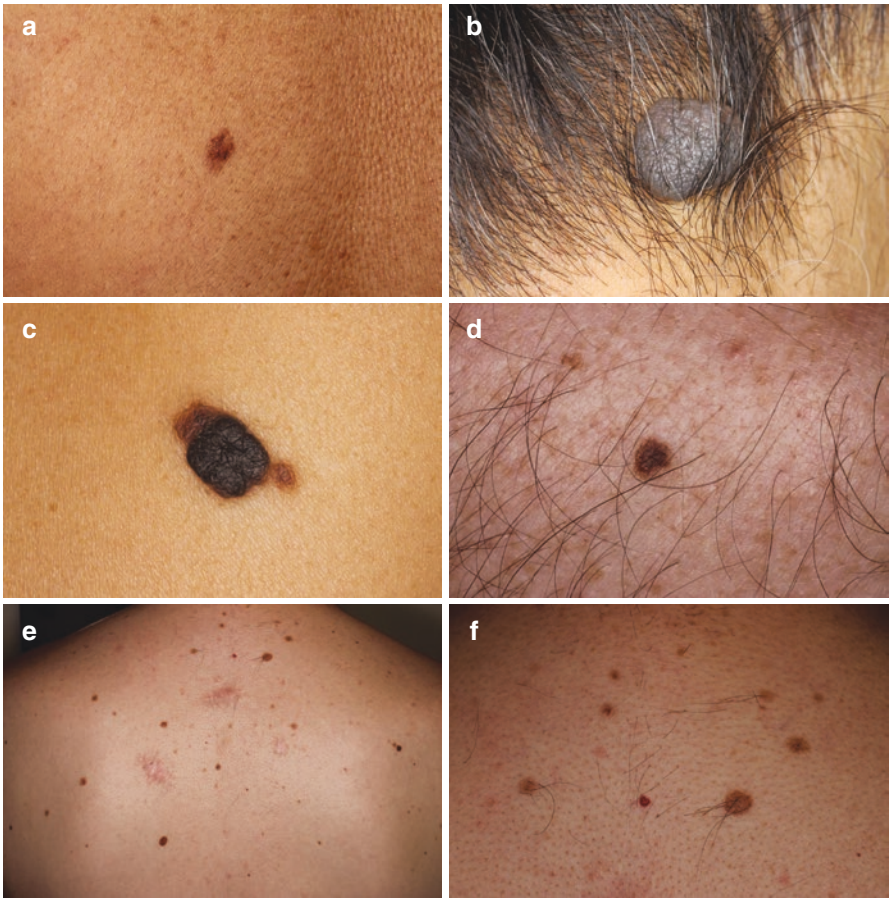

Fig. 8 (**a**) Benign mole. This mole has variation in color but overall has well-defined borders, felt soft, and, according to the patient, was present for years without change. (**b**) This mole, although larger, is soft, well-defined, and without ulceration or pain and has hair growth within, all reassuring signs. (**c**) This nevus, although not perfectly symmetric, is soft, painless, and fairly homogenously pigmented. (**d**) The classic appearance of a congenital pattern nevus. A small, round, well-defined evenly pigmented papule. (**e**) The back of a patient with multiple nevi. Note the scars from prior excisions of nevi which were benign in nature. (**f**) A close-up look at the congenital nevi of this patient. Note the symmetry, similarity in appearance, and homogenous pigmentation of these nevi

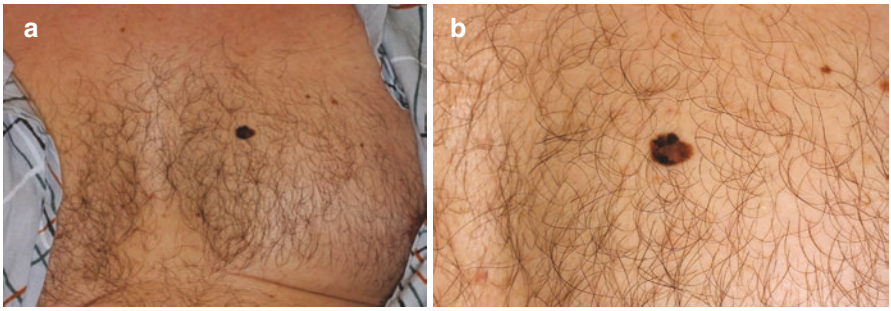

Fig. 9 (**a**) Melanoma in situ, context of the lesion. This lesion catches the eye of the examiner as it stands out from any other growth on the patient's chest, the "ugly duckling sign". (**b**) Melanoma in situ, up close. Note the irregular border, color variegation, asymmetry, and relatively large size of the tumor

melanoma or a high level of patient anxiety about a particular lesion may further lower a clinician's threshold for recommending biopsy.

Non-melanoma Skin Cancer

Non-melanoma skin cancer (NMSC) is associated with environmental, iatrogenic, and patient-related risk factors. Carcinogenesis due to UV radiation is believed to be mediated by direct DNA mutations via covalent bonding between adjacent pyrimidines and the formation of reactive oxygen species. Patients who are predisposed to photosensitivity, such as those with fair skin or red hair and blue eyes and those who always burn (categorized as Fitzpatrick skin type I), are at increased risk. The etiologic impact of human papillomavirus (HPV) has been demonstrated in genital and periungual SCC, as well as non-cutaneous head and neck SCC. Immunosuppressed patients, particularly organ transplant patients, are at high risk of developing SCC and require at least annual surveillance (Fig. 10). SCC risk is increased by 65-fold, or even higher, and BCC risk is increased by ten-fold in this population [8]. Tumors detected in these patients tend to be advanced and exhibit aggressive behavior [9]. A prior history of NMSC confers increased risk of additional skin cancers. Other

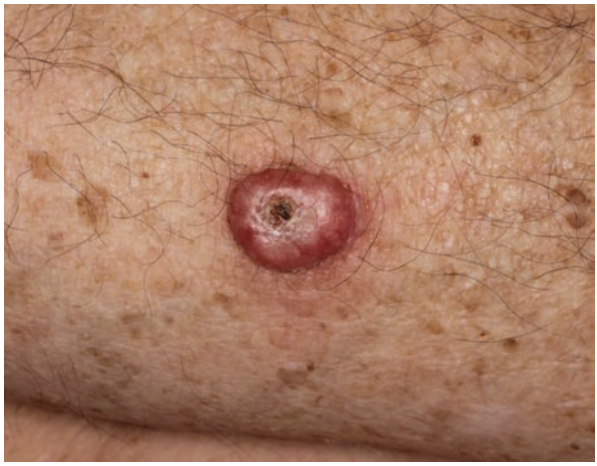

Fig. 10 Squamous cell carcinoma, keratoacanthoma subtype, diagnosed in a renal transplant patient on immunosuppression

risk factors include advanced age, radiation therapy, arsenic exposure, chronic inflammation, ulceration or scarring, and certain genetic mutations or syndromes.

Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common cancer in humans. Its incidence worldwide is increasing by 10% per year. If this trend continues, the prevalence of this tumor will soon equal that of all other cancers combined [10]. BCC accounts for approximately 75–80% of non-melanoma skin cancer cases [3, 9]. While capable of local invasion and destruction, metastatic disease is exceedingly rare, occurring in less than 0.1% of all cases [9].

BCC, like SCC, is an epidermal tumor, but its true cellular origins and pathogenesis are less clear. Although previously thought to arise from the basal layer of the epidermis (hence its name), newer evidence suggests that BCC may originate from immature pluripotent cells of the interfollicular epidermis and outer root sheath of the hair follicle [11]. Cumulative sun exposure is an established risk factor for BCC, but the causal relationship with UV radiation is less clear for BCC than it is with SCC. The majority of BCCs have somatic mutations in the Hedgehog signaling pathway which regulates cell growth and differentiation during embryogenesis [11]. Inherited mutation of the *patched (PTCH)* gene, which encodes for a Hedgehog signaling pathway protein, is the cause of basal cell nevus syndrome, also known as Gorlin syndrome. The defect in syndromic cases is independent of external mutagenic stress, but the somatic *PTCH1* mutation is present in up to 68% of sporadic BCCs [10].

Basal cell carcinomas are divided into several major histologic subtypes: superficial, nodular, micronodular, or infiltrative, morpheaform, and pigmented. A single lesion commonly exhibits more than one histologic pattern. Superficial and nodular

BCCs, and their pigmented variants, are sometimes grouped together under the rubric of "low-risk" tumors. Deep invasion is rare (by definition in the superficial variant), and numerous treatment methods are curative. Nodular BCC is the most common subtype, comprising roughly 50–60% of cases. Nodular BCCs are commonly recognized as pink pearly papules, their "pearly" appearance (Fig. 11) attributed histologically to the mucinous stroma surrounding the aggregations of basaloid cells. These tumors tend to have well-defined, rolled, or indurated borders, with vascularity and translucency as key clues to their clinical diagnosis. Central ulceration may be present, historically referred to as a "rodent" ulcer because it appears to have been gnawed on by a rat (Fig. 12). Pigmented BCCs have irregular globules of pigment throughout the lesion (Fig. 13). A helpful diagnostic feature to the experienced eye, this feature may cause the neoplasm to mimic seborrheic keratosis, melanocytic nevi, or even melanoma.

Superficial BCCs comprise about one-fifth of diagnosed BCCs and occur on sun-exposed areas such as the head, neck, shoulder, and distal extremities [11]. They typically present as extremely thin pink to red telangiectatic papules or small

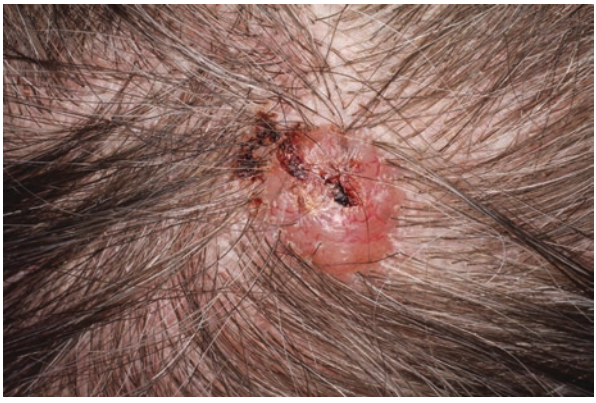

Fig. 11 Shown is the translucent, shiny quality of the surface of a BCC. Note the arborizing tortuous vasculature of this lesion

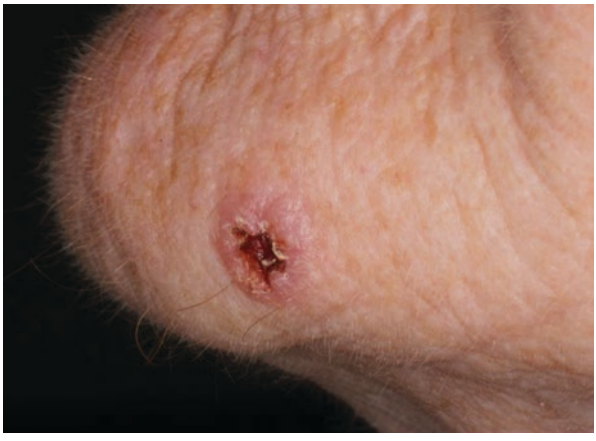

Fig. 12 Classic appearance of a rodent ulcer. Note the "pearly" shine with an almost translucent quality of the surface changes noted on this basal cell carcinoma

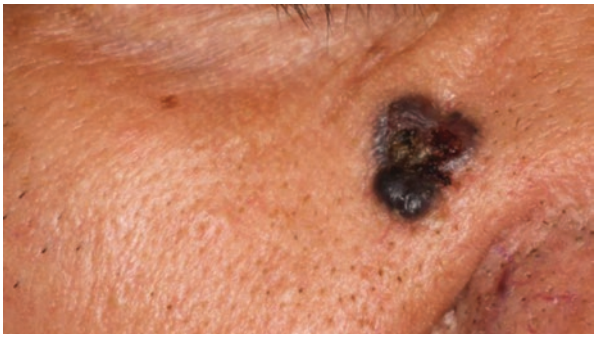

Fig. 13 Pigmented BCC with the characteristic shiny surface

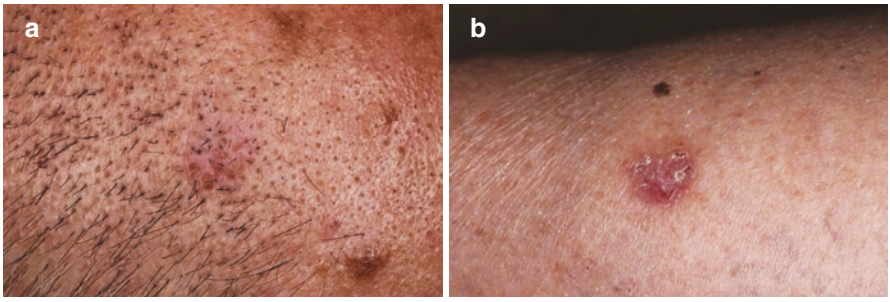

Fig. 14 (**a**) Superficial BCC, noted to appear as a thin pink plaque with keratotic scale. (**b**) Superficial BCC manifesting as a pink to red thin scaling plaque with keratotic scale and telangiectasias

plaques, sometimes with an overlying fine scale (Fig. 14a–b). They may exhibit a pearly or thin rolled border. Like nodular BCCs, they can also be pigmented with specks of blue, gray, brown, or black.

The higher-risk BCC subtypes – infiltrative, micronodular, and morpheaform – exhibit relatively aggressive behavior. Clinically, the micronodular and infiltrative subtypes present in similar fashion as nodular or superficial lesions but are characterized histologically by more deeply invading small islands or strands of basaloid cells. Morpheaform BCCs typically present as slightly depressed, firm, ill-defined pink or skin-colored sclerotic plaques, resembling scars. The morpheaform and infiltrative subtypes tend to have a higher recurrence rate as compared to other subtypes of BCC [12]. They sometimes show perineural invasion, a poor prognostic feature. Another subtype of BCC, the fibroepithelioma of Pinkus, is a skin-colored to pink sessile nodule that favors the trunk, particularly the lower back, and may resemble a skin tag.

Most basal cell carcinomas occur on the head and neck, with the nose being the most common location. Periorbital areas should not be neglected on examination, as BCCs here may be missed without close inspection of the medial canthus (Fig. 15a) and upper and lower lid margins (Fig. 15b). Patients who wear glasses should be asked to remove them prior to examination. Large, arborizing vessels traversing the

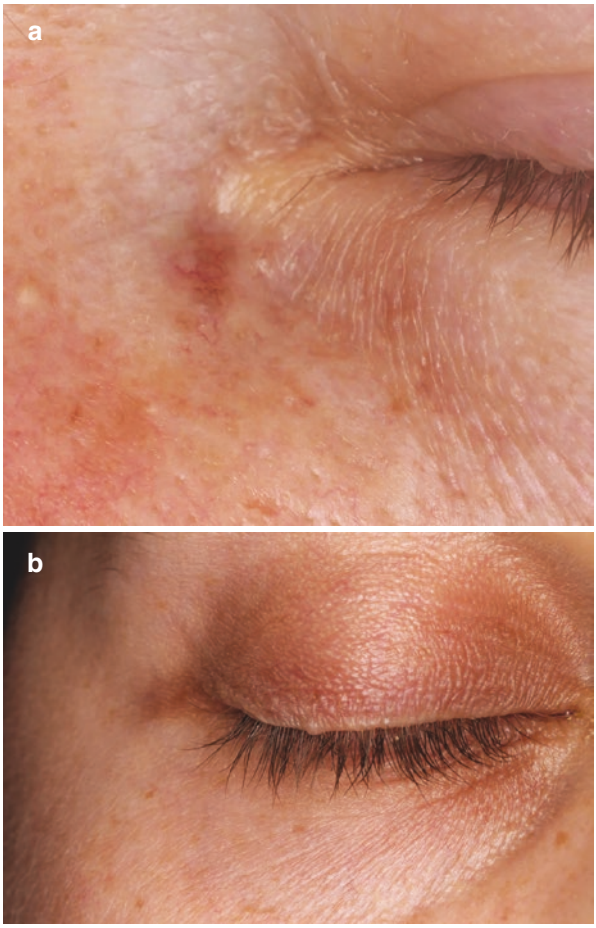

Fig. 15 (**a**) Periocular BCC. Note arborizing telangiectasias on the medial canthus. This required two stages of Mohs micrographic surgery to excise completely. (**b**) Note the small papule which is a subtle BCC on the upper eyelid. The key feature here is the translucent nature of its clinical appearance

lesion is a common clue of malignancy and can help the clinician differentiate BCC from sebaceous hyperplasia or fibrous papules, which are also very common on the face as mentioned earlier. Patient history can be useful to distinguish BCCs from inflammatory or vascular lesions, which may also be pinkish red and papular. A "pimple" or sore that does not heal after 1–2 months warrants closer examination or biopsy to rule out skin cancer.

Actinic Keratoses

Actinic keratoses (AKs), sometimes called solar keratoses or "pre-cancers," are potential precursors of squamous cell carcinoma (SCC). They occur on sun-damaged areas, mainly on the head and neck, upper trunk, and distal extremities, and are typically accompanied by other signs of photoaging, such as lentigines,

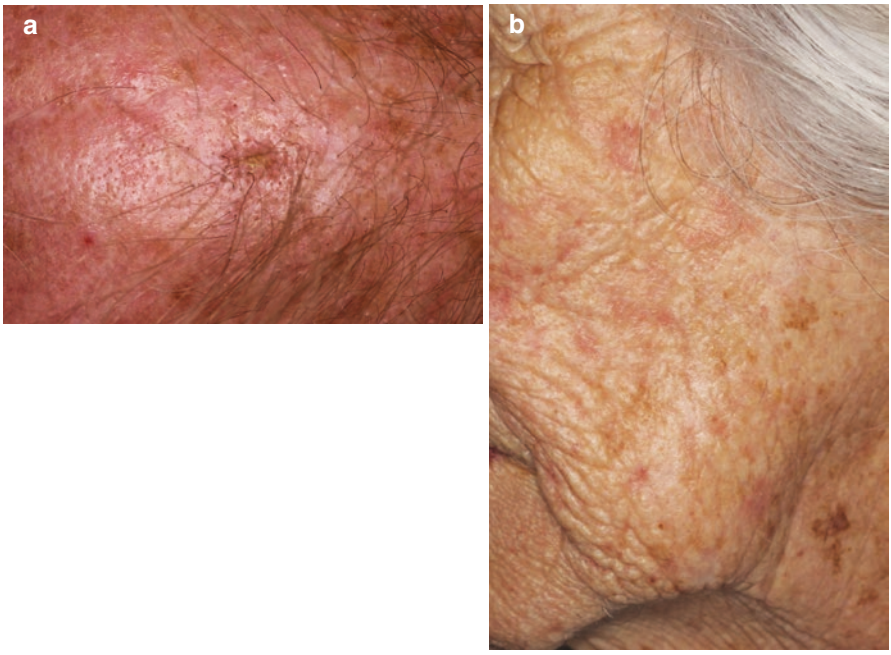

Fig. 16 (**a**) Note the brown keratotic crust overlying erythema. The rough "sandpaper-like" feel of this lesion is characteristic of an actinic keratosis. (**b**) Note multiple pink scaly actinic keratoses on the lateral cheek of this patient

rhytides (wrinkles), mottled pigmentation, and telangiectasias. They are rough or gritty on palpation, sometimes more easily felt than seen. They tend to feature keratotic scale and can range in color from pink to brown (Fig. 16a–b). Erythema may be subtle or absent, and overlying scale can become heaped up or form what is known as a "cutaneous horn." Variants include hyperplastic (typically thicker), pigmented (light to dark brown), lichenoid (pink, inflamed), and atrophic AKs, as well as actinic cheilitis of the vermillion lip. Estimates of an individual lesion's propensity to evolve into SCC vary widely in the literature. One study found that the average number of AKs in affected patients is 7.7, with an accompanying 10% risk of developing SCC over 10 years [13].

Squamous Cell Carcinoma

Studies have demonstrated that SCC arises sequentially after an accumulation of genetic damage. Over 72% of SCCs develop from AKs or areas of actinically damaged skin, referred to as underlying "field cancerization" [14]. The most common mutations found in SCC affect the p53 tumor suppressor gene; others include *WNT*, *Ras*, *p16INK4*, *NF-kB*, and *c-Myc* [9, 15]. Tenderness may be a sign of

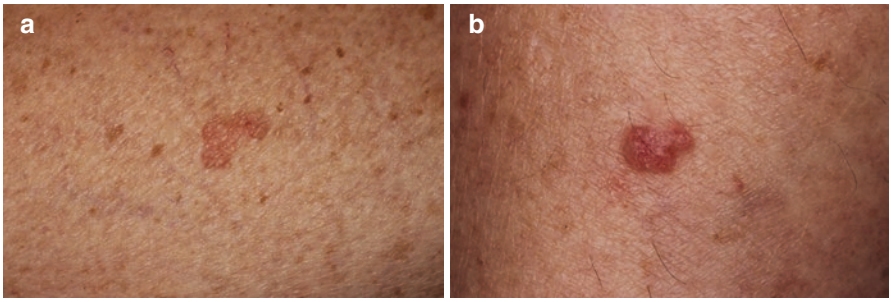

Fig. 17 (**a**) This squamous cell carcinoma in situ resembles a pink small plaque of psoriasis or eczema. (**b**) Bowen's disease showing a single pink plaque with keratotic scale

progression from AK to SCC, although pain or paresthesias are frequently absent in cutaneous malignancies. Squamous cell carcinoma in situ or Bowen's disease, the most superficial form of SCC, may present similarly to AK but tends to have a thicker and more erythematous papular or plaque component underlying the gritty scale. It may resemble a single plaque of psoriasis or eczema (Fig. 17a–b). Invasive SCC lesions may be exophytic or verrucous and can ulcerate (Fig. 18a) or form a firm keratotic scale-crust (Fig. 18b). Like AK, a cutaneous horn may develop from SCC (Fig. 19a) although horns can arise from warts (Fig. 19b), seborrheic keratoses, and other benign growths as well. Lesions are described on both sun-exposed and non-sun-exposed skin. Human papilloma virus has been implicated in the development of genital and periungual SCC. A "wart" in either region that has not resolved with conservative treatment should raise suspicion for malignancy.

Keratoacanthoma is a subtype of SCC characterized by a rapid, eruptive growth pattern. The typical presentation is a dome-shaped papule or nodule with a central crateriform invagination or dell that may grow to become several centimeters in diameter over a period of weeks (Fig. 20a–b). A subset of lesions will then regress spontaneously, which has led to debate over the true malignant potential of KAs. However, due to their rapid growth and ability to invade and distort the skin, they usually are treated in the same manner as other types of SCC.

SCC is associated with a low but significant rate of metastasis, of approximately 3–5% [16]. A small subset of tumors is believed to be responsible for most of the SCC-associated morbidity and mortality. Various clinical criteria have been proposed for identifying this "high-risk" group, including diameter greater than 2 cm, location on the ear, lip, temple, or anogenital region, rapid growth, recurrence after treatment, patient immunosuppression, associated neurologic symptoms, and tumors arising in areas of prior radiation therapy or chronic inflammation. High-risk histologic features include poor cellular differentiation, perineural, lymphatic, or vascular invasion, and invasion beyond the subcutaneous fat [17, 18]. Tumors that meet "high-risk" criteria have metastasis rates up to 30% [19].

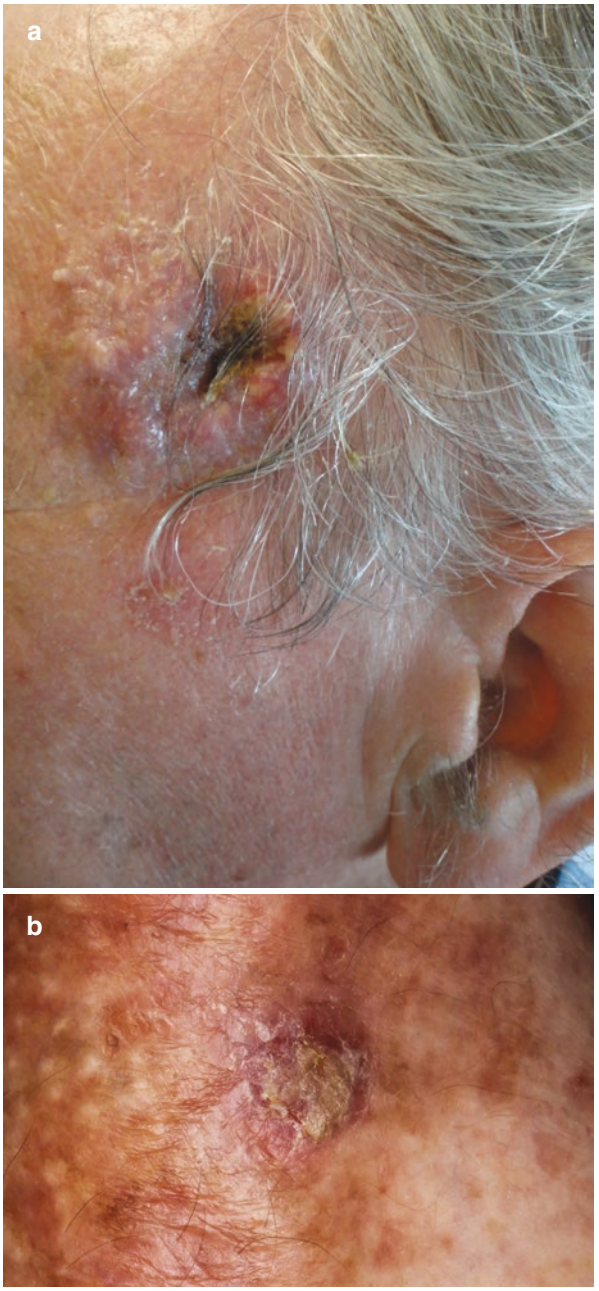

Fig. 18 (**a**) Note large ulceration of this squamous cell carcinoma. (**b**) A squamous cell carcinoma with keratotic crust and erythema at its base on the background of sun-damaged skin

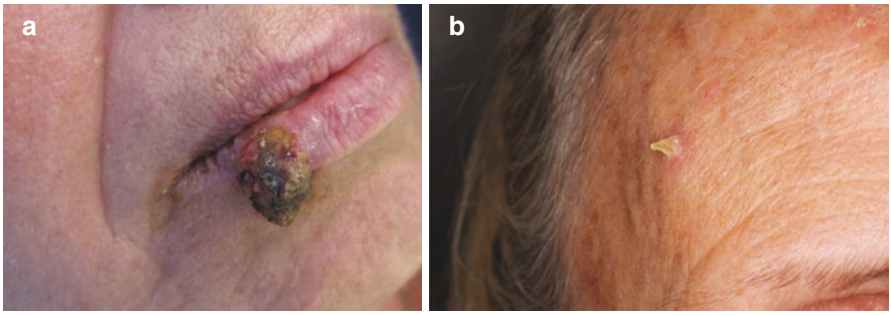

Fig. 19 (**a**) See the cutaneous horn-like verrucous appearance of this SCC. (**b**) A classic appearance of a cutaneous horn. The final diagnosis of this lesion was confirmed to be a wart, although a biopsy was performed in this case to rule out squamous cell carcinoma

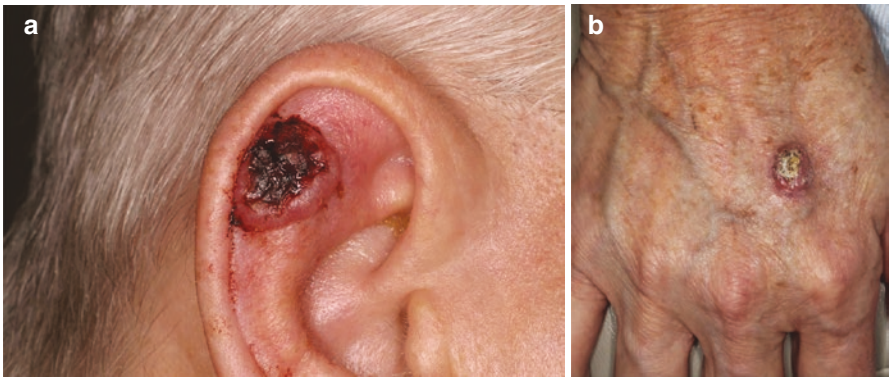

Fig. 20 Keratoacanthoma. Classic dome-shaped nodules with central crateriform ulceration in the center. The ulceration may show either hemorrhagic (**a**) or keratotic (**b**) crust or both

Diagnosis and Treatment of NMSCs

The US Preventive Services Task Force (USPSTF) has concluded that there is insufficient evidence to assess the risks and benefits of visual skin examination by clinicians [1, 20]. The Task Force's inability to recommend visual screenings reflects the paucity of methodologically rigorous studies of the impact of clinician screening on skin cancer morbidity and mortality. Dermatologists most frequently perform full-body visual skin exams. PCPs play a large and important role in detecting cutaneous malignancies during intentional skin-focused exams, as well as during incidental

detection when evaluating other organ systems. A survey of US physicians in 2005 reported that 81% of dermatologists, 60% of primary care physicians, and 56% of internists reported performing a full-body skin cancer screening examination on their adult patients [21]. Studies of non-melanoma skin cancer detection are lacking, but PCPs have been shown to be moderately accurate in diagnosing melanoma, with a sensitivity of 42–100% and a specificity of 70–98% [1]. Most of this data is based on clinician examination of skin lesion images rather than live patient assessment. A meta-analysis of 32 studies was performed to compare the accuracy of dermatologists and primary care physicians in identifying melanoma. For diagnostic accuracy, dermatologists showed a sensitivity of 0.81–1.00, as compared to 0.42–1.00 for PCPs [22]. This study was unable to show differences in diagnostic, biopsy, or referral accuracy between dermatologists and PCPs. Detection of skin cancers at earlier stages allows for improved outcomes; further research is needed on the role of the clinician's full-body skin examination on skin cancer prevention, detection, and outcome.

Biopsy Techniques

Highly suspicious skin lesions should be biopsied or referred to a specialist for further evaluation to rule out malignancy. Shave biopsy is the most common method used by dermatologists to acquire a specimen for histopathologic analysis. After injection of local anesthesia – usually 1% lidocaine with epinephrine for added hemostasis – the clinician uses a scalpel or straight-edged blade to remove all or a portion of an exophytic lesion's surface, leaving a wound that is flush with the surrounding epidermis. A "scoop" shave can be performed to obtain greater depth, but the clinician typically does not attempt to penetrate beneath the dermis. Hemostasis is achieved with application of aluminum chloride solution, electrodesiccation, and/or a pressure dressing. If a deeper specimen is desired, a punch biopsy may be used to include subcutaneous fat as well. The cylindrical cutting edge of a punch biopsy tool resembles a tiny (2–8 mm) "cookie-cutter," which is twisted while applying downward pressure to reach the subcutaneous fat. The freed tissue is then removed with forceps, and the small cylindrical wound heals by secondary intent or by closure with a suture. If suspicion is high for melanoma, where accurate depth assessment is essential to guide treatment and prognosis, and prompt treatment may theoretically reduce mortality, an excisional biopsy of the entire clinically apparent lesion or an incisional biopsy of a portion of a lesion can be obtained with a scalpel or punch biopsy and closed with sutures. If the clinician identifies classic features of a non-melanoma skin cancer, a curette used to scrape, sample, or debulk a tumor can be both diagnostic and therapeutic, particularly when combined with electrodesiccation. The curette method does not allow for histological confirmation of cure and is never recommended if melanoma is a consideration.

Surgical Treatment

Destructive Modalities

A number of techniques are effective in treating low-risk forms of NMSC. Electrodesiccation and curettage (ED&C) is a long-employed method that can be applied to smaller, well-defined, and/or superficial NMSCs in less cosmetically sensitive or functionally important areas [19]. A systematic review of primary BCC treated by ED&C over a 40-year period showed a 5-year recurrence rate of 7.7%, comparable to all other physical modalities excepting Mohs micrographic surgery (MMS) [23]. Recurrence rates are higher for more invasive forms of BCC and high-risk SCC, making this an unsuitable option for treatment of these lesions. Healing time following ED&C is typically longer than that of sutured wounds. Scarring may be less optimal, particularly in hair-bearing areas. Despite its shortcomings, ED&C is a less expensive, less invasive, and less time-consuming alternative to traditional surgical excision with similar cure rates in low-risk NMSC. Careful patient and tumor selection is important in choosing this route of treatment, as there is no histologic confirmation of cure.

Cryosurgery utilizes liquid nitrogen to destroy tumor cells through freezing. Most commonly used to treat pre-cancerous actinic keratoses, cryosurgery is also applied to low-risk NMSC subtypes, particularly in the elderly or poor surgical candidates. The systematic review of primary BCC treatment mentioned above showed a 7.5% 5-year recurrence rate following cryosurgery [21]. Like ED&C, cryosurgery is not recommended for invasive or high-risk NMSC in younger patients due to significantly higher recurrence rates. Another drawback is the high degree of operator-dependent variability in outcomes, which reflects differences in tumor selection, duration of treatment, and number of freeze-thaw cycles. Pain, erythema, and blistering are potential transient side effects, but hypopigmentation, a result of melanocytes' increased sensitivity to freezing, can be permanent. Hypopigmentation is almost guaranteed in dark-skinned individuals.

Wide Local Excision

Traditional wide local excision (WLE) of non-melanoma skin cancers typically includes a 3–5 mm margin of normal skin around the clinically visible tumor. If the clinician intends to suture the surgical wound, triangular-shaped "dog ears" must be excised on either side to create a linear scar that will contour to the surrounding skin. Alternatively, the clinician can design a fusiform or "football-shaped" excision initially, with the skin cancer and margin of normal skin at the center and tapered ends on either side (Fig. 21). The surgical specimen is typically excised at the level of the mid-subcutaneous fat. It's then placed in formalin, embedded in paraffin, and cut into vertical sections for margin examination by a pathologist. Standard excision

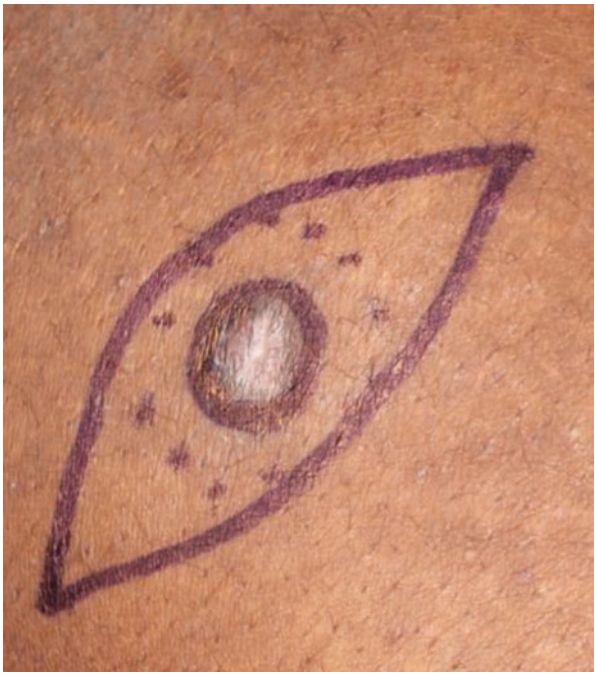

Fig. 21 Fusiform design of an excision

with a predetermined margin of normal skin as outlined above has shown to provide 5-year cure rates of approximately 98% for BCC and 92% for SCC [24–26].

While the NCCN guidelines for BCC advocate for 4 millimeter margins with postoperative margin evaluation, the margin taken ultimately depends on the definition of a tumor's borders, its anatomical location, and histologic subtype, among other factors. For low-risk squamous cell carcinoma, NCCN guidelines advocate 4–6 millimeter margins with postoperative margin evaluations [17]. Wider excisions and Mohs micrographic surgery are recommended for high-risk SCC.

Mohs Micrographic Surgery

Mohs micrographic surgery (MMS) is a tissue-sparing technique that achieves the highest cure rates for non-melanoma skin cancer. Developed in the 1940s by Frederic Mohs, a general surgeon at the University of Wisconsin, the technique has evolved to employ real-time frozen sectioning and histopathologic analysis of excised tissue. MMS has a 5-year cure rate of 99% for untreated BCC and 97% for SCC [23, 24]. For locally recurrent tumors, repeat treatment by surgical excision has been reported to have a local recurrence rate of 23.3% as compared to 10% by MMS for SCC [24]. For high-risk SCC, the 5-year cure rate for traditional surgical excision is 77%, as compared to 90–94% for MMS [27]. Higher MMS cure rates are due not only to intraoperative margin assessment but also to the unique method by

which tissue specimens are processed, which allows for assessment of 100% of the peripheral and deep tissue margins, as compared to less than 1% of the margin examined by traditional vertical sectioning [19]. Should the tumor extend to the margin of tissue excised after the first "stage" or "layer," the Mohs surgeon then excises additional tissue only in the area of margin positivity. Frozen sectioning and histopathologic analysis is then performed on the new specimen. This process is repeated until clear margins are achieved.

Complete, real-time margin assessment allows the Mohs surgeon to excise tumors with narrower margins than traditional WLE, thereby sparing more healthy tissue. This is extremely important in cosmetically sensitive areas such as the face and in areas of limited tissue volume and laxity such as the hands, feet, and genitalia. It also allows the Mohs surgeon to confidently reconstruct wounds with local skin flaps or grafts, which significantly rearrange tissue and would complicate re-excision after failed WLE. Application of MMS to a wider variety of cutaneous malignancies, including dermatofibrosarcoma protuberans (DFSP), Merkel cell carcinoma, and melanoma, has shown promising results, in many cases exceeding cure rates associated with WLE.

Nonsurgical Treatment Modalities

Topical Treatments

Some early, superficial forms of NMSC may be treated by patients at home with serial application of topical creams. Imiquimod is a topical immunomodulator that binds to the T-cell surface toll-like receptor 7, thereby stimulating a robust local immune response that destroys the tumor cells. It is FDA-approved for the treatment of warts, actinic keratoses, and superficial BCC in immunocompetent patients. The 5-year clinical clearance rate with imiquimod monotherapy for biopsy-confirmed superficial BCCs is about 80% [11]. 5-Fluorouracil (5-FU), a pyrimidine analog antimetabolite that directly targets rapidly dividing tumor cells, has been a mainstay of systemic chemotherapy regimens for many years. Its topical formulation, available in several concentrations, is also FDA-approved for the treatment of actinic keratoses and superficial BCC. One study of nonsurgical treatment modalities found tumor-free survival at 3 years posttreatment was 68.2% for fluorouracil versus 79.7% for imiquimod [28]. A third agent, ingenol mebutate, was approved in 2012 for treatment of actinic keratosis only. It has the advantage of a shorter, 3-day course, as compared to 4–6 weeks of daily application of 5-FU or imiquimod. While none of the topical agents are FDA-approved for SCC, in practice they are often used to treat in situ disease. The most common side effect is application site inflammation and irritation, which can be so severe as to be treatment-limiting. Another drawback of topical therapies, as with all nonsurgical modalities, is the lack of histologic confirmation of cure, a particular concern when a superficial biopsy may underestimate the true depth of tumor invasion.

Photodynamic therapy (PDT) involves application of a topical photosensitizer precursor, either 5-aminolevulinic acid (5-ALA) or methyl aminolevulinic acid (MAL), prior to exposure to a visible light source. Tumor cells preferentially convert the topical agent to protoporphyrin IX, a photoactive compound that leads to cytotoxic free radical formation when stimulated by blue or red light. Natural light or "daytime" PDT, which obviates the need for an artificial light source, is gaining in popularity, though its effectiveness is not yet proven. 5-ALA, the only agent available in the United States, is FDA-approved for treatment of actinic keratosis but, like the other topical agents, is often used to treat superficial NMSC. It is particularly useful in patients with larger areas of field cancerization. Most studies of PDT efficacy are limited by short follow-up periods, but few with 5-year follow-up data show superficial or in situ NMSC cure rates similar to destructive modalities like cryotherapy [29]. Thicker tumors are more resistant to treatment due to the limitations of topical agent and visible light penetration. PDT is not recommended for high-risk BCC or SCC.

Radiation

Radiation therapy is a moderately effective NMSC treatment option for patients who are deemed poor surgical candidates due to advanced age or medical comorbidities. It may also function as an adjunctive therapy or for palliative care for symptomatic relief of incurable cancers. A meta-analysis of radiotherapy treatment of BCC found an overall 5-year cure rate of 91.3%. A similar study showed a 5-year cure rate of approximately 90% for SCC [23, 24]. However, cure rates are lower for larger lesions. Areas of the head and neck tolerate radiation better than skin on the trunk and extremities [30]. Early side effects of radiation include headache, nausea, vomiting, skin irritation, hair loss, and fatigue. Late reactions can occur years after treatment and include telangiectasias, epidermal atrophy, and altered pigmentation. Late soft tissue and cartilage necrosis is rare, and the risk is reduced with smaller doses [31].

Systemic Treatment

Systemic therapy is typically reserved for locally advanced, unresectable, or metastatic NMSC. Vismodegib is an oral medication that targets a protein involved in the Hedgehog signaling pathway, commonly mutated in BCC. A two-cohort nonrandomized study revealed a 30% response rate in metastatic BCC and a 43% response rate in patients with locally advanced BCC [32]. Vismodegib is also sometimes used to treat basal cell nevus syndrome, in which patients can develop hundreds of BCCs. Unfortunately, in addition to its limited efficacy, the drug is often poorly tolerated. Side effects include painful muscle spasms, loss of taste, gastrointestinal discomfort, fatigue, alopecia, and hyponatremia [33]. Newer, related formulations are plagued by similar problems. Still, for a small group of unfortunate patients, this family of medicines represents a tumor-specific treatment option where none existed before.

Treatment of locally advanced or inoperable SCC typically involves radiation therapy with or without chemotherapy. Cisplatin with or without 5-fluorouracil, although rarely curative, is the mainstay of systemic treatment of metastatic SCC. More recently, cetuximab, a monoclonal antibody that inhibits the epidermal growth factor receptor, has shown some promise as mono- or adjuvant therapy with radiation or surgery for treatment of locally advanced SCC [34]. Immune checkpoint inhibitors are also being studied as a future treatment option.

Follow-Up of NMSCs

According to NCCN guidelines, lifetime biannual to annual follow-up visits with a clinician are recommended after diagnosis and treatment of a NMSC. These visits serve as opportunities both to evaluate for recurrence and screen for new cutaneous malignancies. High-risk patients, in particular organ transplant recipients, may require more frequent screening, while the extremely elderly may warrant less frequent visits. One meta-analysis reported that the risk of developing a second NMSC within 3 years of the first is 18% for SCC and 44% of BCC [35]. A separate prospective study reported that after a diagnosis of a single BCC or SCC, the 5-year risk of developing an additional non-melanoma skin cancer was 50% overall, 41% for BCC, and 31% for SCC [36]. The risk of future NMSC increases with the diagnosis of additional NMSC. For many patients then, a new NMSC is not a question of "if" but "when." The vast body of literature suggests that earlier detection and treatment leads to higher cure rates and less tumor- and treatment-related morbidity.

Melanoma

The incidence of cutaneous melanoma has risen rapidly over the past 30 years, and rates continue to climb, particularly in patients 50 and older [5]. The annual incidence rate is 25/100,000 in non-Hispanic whites, 4/100,000 in Hispanics, and 1/100,000 in blacks. Below age 50, incidence rates are higher in women, but rates in men double and triple as compared to women by age 65 and 80, respectively. The lifetime risk for a diagnosis of melanoma is 1.94% for males and 1.30% for females [1].

Melanoma accounts for only 1–5% of skin cancer diagnoses but is associated with at least 75% of skin cancer deaths [1]. Although incidence has steadily increased, overall mortality rates are stable since the 1980s. This is likely due to a disproportionate increase in early diagnosis of in situ or superficial tumors, when surgical cure rates are highest. The 5- and 10-year survival rate is 98% for localized melanoma (84% of cases) and declines to 63% and 17% for regional and distant metastatic disease, respectively [2]. Tumor thickness, known as Breslow depth, and sentinel lymph node status are the most important prognostic factors.

Patient risk factors for melanoma include age, male sex (in patients over 50 years of age), skin type (red or blonde hair, lightly colored skin with multiple freckles, blue or hazel eyes), sun sensitivity, multiple dysplastic nevi (5 or more), a total nevi count greater than 100 or the presence of atypical nevi, and a personal or family history of melanoma and a history of NMSC [20]. The number of known genetic mutations that confer increased risk of melanoma is steadily climbing. One of the most well-described mutations occurs in the tumor suppressor gene *CDKN2A*. An autosomal dominant mutation in *CDKN2A* causes familial atypical multiple mole melanoma syndrome (FAMMM), which is associated with multiple clinically atypical nevi (often totaling more than 50) and an increased risk of melanoma [37]. Studies have shown that an increased number of dysplastic nevi is associated with a 6.4-fold increase in the risk of melanoma [20]. Environmental factors such as ultraviolet radiation exposure, sunburns, and artificial tanning bed use are thought to increase the risk of melanoma [20, 38]. However, it is important to note that melanoma can occur in any race on both sun-exposed and non-sun-exposed surfaces.

The World Health Organization (WHO) recognizes four major melanoma subtypes: superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM), nodular melanoma (NM), and acral lentiginous melanoma (ALM). In practice, however, many melanomas do not fit neatly into a single category.

Superficial spreading melanoma (SSM), the most common subtype, is characterized by an initial, radial growth pattern. It classically presents as a pigmented macule or thin papule or plaque, most commonly on the trunk in men and the legs in women. SSM may have jagged, irregular borders and color variegation from

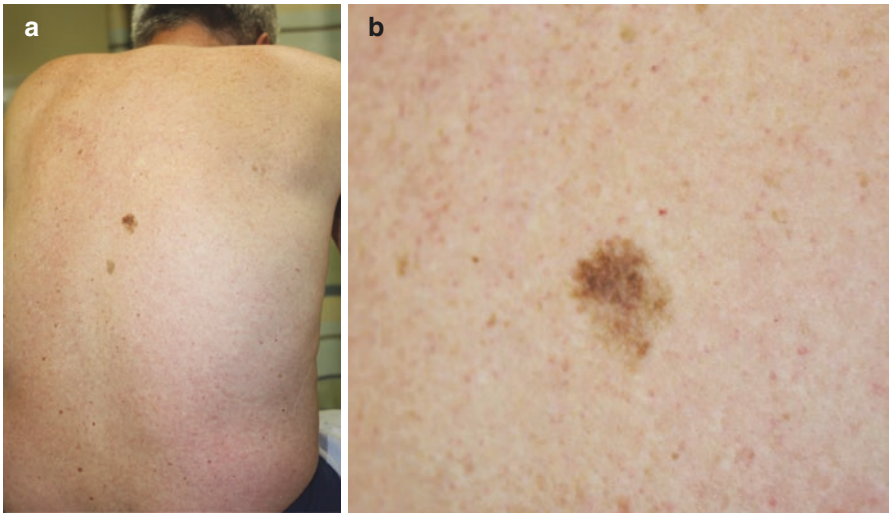

Fig. 22 (**a**) Melanoma in situ presenting on the back of this male patient. Notice the uneven pigmentation and variation in color that stands out in this "ugly duckling". (**b**) Close-up of lesion above. Melanoma in situ. A lack of homogenous pigment and the presence of irregular borders are shown here

brown to gray or black (Fig. 22a–b). With time, SSM may become firmer and thicker as it enters a vertical growth phase. Histologically, atypical melanocytes form and are poorly nested, become confluent along the basal layer of the epidermis, and exhibit "pagetoid" or upward scatter within the epidermis.

Lentigo maligna melanoma (LMM) most commonly affects older patients in the seventh decade of life. It typically presents as a slowly growing, irregularly shaped, light-brown to black macule or patch on sun-damaged facial skin. Lesions can range from a few millimeters to several centimeters in diameter, and borders are frequently ill-defined (Fig. 23). LMM may blend with contiguous benign solar lentigines and surrounding dyspigmented, sun-damaged skin, complicating diagnosis and treatment [39]. Multiple biopsies, which should be interpreted by an experienced dermatopathologist, are frequently required to make a diagnosis. Histologically, LMM shows a proliferation of solitary melanocytes along the basal layer of the epidermis. These subtypes also have a higher propensity to involve skin appendages such as sweat glands and hair follicles.

Nodular melanoma (NM) is characterized by an earlier, more aggressive vertical growth pattern than other subtypes (Fig. 24). It is thought to arise de novo, appears more papular to nodular, and is often firm and surrounded by erythematous induration. It ranges in color from blue to black and can appear ulcerated or hemorrhagic. The incidence of thicker melanomas has remained stable. In recent decades the incidence of in situ and thinner melanomas continues to increase. Although physicians are diagnosing melanomas early, melanoma mortality has not been impacted by this diagnostic trend.

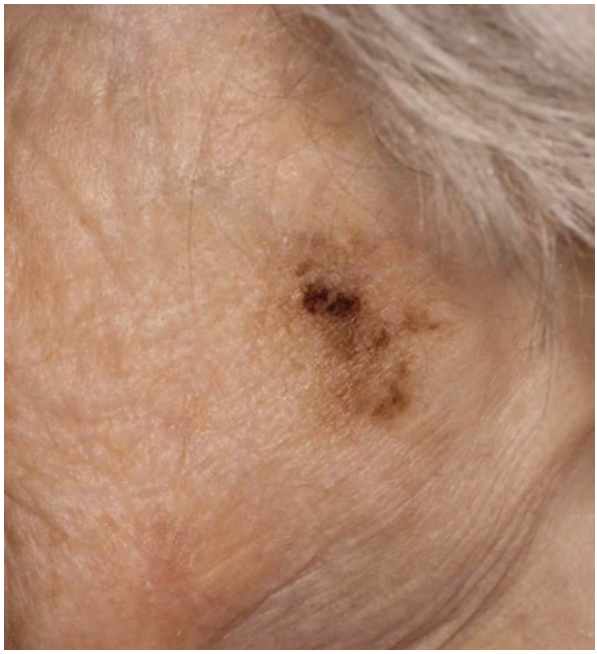

Fig. 23 Lentigo maligna melanoma. This demonstrates the irregular pigmentation and poorly defined borders of a lentigo maligna melanoma

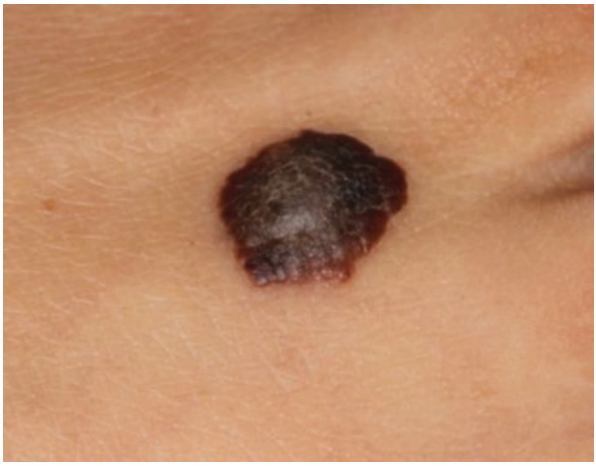

Fig. 24 Nodular melanoma. Note the thickness of this lesion

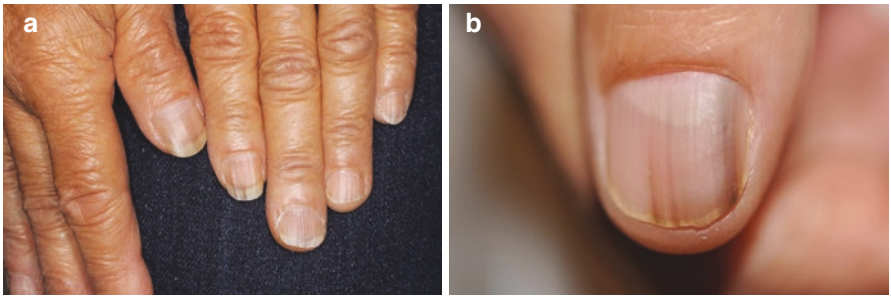

Fig. 25 (**a**) Longitudinal melanonychia is seen in multiple nails, a benign variant seen in more darkly pigmented individuals. (**b**) Note the thicker band of pigmentation and the subtle yet present finding of a Hutchinson's sign on the proximal nail fold. These findings were newly present on a single nail in a Hispanic patient. Nail matrix and nail bed biopsy revealed an invasive melanoma

Acral lentiginous melanoma (ALM) affects the palms, soles, or nail unit. Although a rare variant overall when compared to SSM or LMM, ALM is the most common type of melanoma diagnosed in black and Asian patients [40]. Lesions on the palms and soles typically present as irregularly shaped macules or patches with color variegation from pink to light brown to black. Nail unit disease most commonly presents as pigmented streaks in the nail plate, known as longitudinal melanonychia, with or without discoloration of the proximal nail fold, classically termed Hutchinson's sign. Of note, pigmented longitudinal bands are a normal variant in people with skin of color (Fig. 25a). These are typically light brown and present on multiple nails. A solitary, unusually dark or irregularly shaped band or a thicker band should raise suspicion for melanoma (Fig. 25b). Historically, ALM has been associated with poor prognosis, but this is most likely due to delays in diagnosis and adequate treatment.

Any of the above subtypes may present rarely as an "amelanotic" melanoma, which lacks visible pigment. These lesions are often mistaken for benign moles,

warts, or squamous cell carcinomas. Another rare variant that may lack pigment is desmoplastic melanoma, which typically presents as a firm skin-colored plaque that may be mistaken for scar tissue both clinically and histologically. Mucosal melanomas are extremely rare but may present as pigmented macules or patches on the conjunctiva, in the oral cavity, or on the genitals. Uveal melanoma in its early stages is only detectable by fundoscopic exam and is beyond the scope of this text.

Local signs and symptoms that should raise concern for melanoma are similar to those of other cutaneous malignancies. New, growing, ulcerating, painful, or spontaneously bleeding skin lesions should be evaluated in a timely manner. The "ABCDE" rule, discussed in more detail above, is a fairly sensitive, but non-specific heuristic to aid patients and clinicians in identifying lesions that warrant increased scrutiny. The "ugly duckling" rule, also discussed above, reminds clinicians to pay special attention to pigmented lesions that do not fit an individual patient's common mole pattern. As with SCC, clinical examination of regional lymph nodes near a highly suspicious lesion can be invaluable for identifying metastatic disease and evaluating for recurrence.

Pregnant women frequently seek evaluation for changing moles. One study of 389 pregnant patients found that over 10% of patients reported changes in their moles, most frequently noted during the first trimester. However, no changes in histology were noted on biopsied lesions when compared to a control group [41]. The current consensus is that a suspicious pigmented lesion in a pregnant patient should be treated exactly as it would in a non-pregnant patient. Biopsy or referral to a specialist should not be delayed due to pregnancy. The potential role of estrogen or other hormones in melanoma development is still under investigation, but recent large studies have shown that melanoma prognosis is not significantly affected by pregnancy, nor is there an absolute contraindication to hormonal contraception in females previously diagnosed with melanoma.

Diagnosis and Treatment of Melanoma

Biopsy

Biopsy of a pigmented lesion serves two main purposes: to confirm or exclude a diagnosis of melanoma and to allow for pathologic staging of the tumor, which will in turn guide surgical treatment. The most important prognostic feature is tumor thickness or Breslow depth, but mitotic rate and the presence or absence of ulceration are also included in the seventh edition of the American Joint Committee on Cancer's (AJCC) staging system [42].

A biopsy may sample only part of the lesion ("incisional") or encompass the entire clinically apparent lesion with a small margin of normal skin ("excisional"). In cases of small (less than 1 cm) lesions when suspicion for melanoma is high, an excisional biopsy is recommended with 1–3 mm margins to obtain the entire tumor and accurately assess Breslow depth. Incisional biopsies are typically per-

formed for larger lesions or those in cosmetically or functionally important areas. A punch biopsy tool can be useful both for excisional biopsies of small lesions and to perform several small incisional biopsies within a large lesion concerning for LMM. Shave biopsies are typically reserved for cases where the index of suspicion is low, or the clinician feels confident that adequate depth of the lesion can be obtained. Whatever method is used, the pathologist should be made aware whether a specimen represents the entire clinically apparent tumor or only a sample.

The National Comprehensive Cancer Network (NCCN) does not recommend routine imaging or laboratory tests upon diagnosis of localized melanoma, except to evaluate specific signs or symptoms [38]. Patients with a clinically positive lymph node should have a nodal biopsy and baseline imaging.

Surgical Treatment

Treatment of melanoma is based on AJCC clinical staging criteria and NCCN guidelines [43]. Despite recent advances in medical management of metastatic melanoma, the mainstay of treatment for all stages remains surgical excision when feasible, with margin size dependent upon pathologic stage. Historically, melanoma was excised with aggressive margins of 4 or 5 centimeters or more. However, over time, studies demonstrated that significantly narrower margins did not adversely affect survival [32]. With some notable exceptions, recent studies have confirmed margin recommendations based on expert consensus opinion which have been in place for several decades. For invasive melanoma ≤1.0 mm thick, excision of an additional 1 cm of normal skin around the clinically apparent tumor or biopsy scar is recommended. A 1–2 cm margin is recommended for tumors 1.01–2 mm thick, and a 2 cm margin is recommended for all tumors >2 mm thick. The appropriate excision margin for MIS remains controversial. In general, a 0.5–1.0 cm margin is taken based on expert opinion. Recent literature suggests that a 0.5 centimeter margin may be inadequate for the lentigo maligna subtype most commonly found on the head and neck of elderly patients [44, 45]. Mohs micrographic surgery, aided by immunohistochemical staining, is increasingly being used to treat these ill-defined tumors that in some cases may require >1 cm margins.

The role of sentinel lymph node biopsy (SLNB) in the diagnosis and treatment of melanoma is an area of even greater controversy. Detection of melanoma cells in the lymph nodes draining the primary tumor site is the strongest predictor of overall survival. However, the largest prospective, randomized trial to date of SLNB with or without subsequent complete lymphadenectomy did not show any overall improvement in disease-specific survival [46]. Post-hoc subgroup analysis suggested possible benefits in patients with intermediate-thickness melanoma, but the significance of these findings remains controversial [38]. In general, SLNB is not recommended for tumors ≤0.75 mm in thickness due to an extremely low positivity rate. The

NCCN recommends *consideration* of SLNB for prognostic and staging purposes in patients with tumors 0.76–1.0 mm in thickness with other concerning histologic features or clinical factors, as well as for patients with Stage Ib and II disease. NCCN guidelines also state that patients with known lymph node involvement (Stage III) should be offered a complete lymph node dissection, with the caveat again that a disease-specific survival benefit has not been proven. Lymph node dissection, like all surgical procedures, is not without risk of morbidity. A newly developed genetic expression profile has shown early promise as a non-invasive prognostic indicator and continues to be investigated for its role in determining prognosis and management.

Nonsurgical Treatment

As stated above, surgery is the cornerstone of melanoma treatment. However, topical imiquimod has shown some utility in treating MIS or very thin melanomas arising in elderly patients or other poor surgical candidates. It is also sometimes used as adjuvant treatment for positive peripheral margins in these tumors after incomplete surgical excision. All treatment is off-label, and regimens and outcome data vary widely, but a recent meta-analysis put histologic and clinical clearance rates at 76% and 78%, respectively [47].

Medical and radiation oncologists typically determine adjuvant therapies such as radiation, chemotherapy, and immunotherapy. Historically, cytokine-based immunotherapy such as interferon-α2b played a major role in adjuvant treatment of locally advanced or metastatic disease. The last decade has seen the development of new, more targeted molecular therapies for melanoma. Trials of BRAF kinase inhibitors, anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibodies, MEK inhibitors, and programmed death receptor signaling PD-L1 antibodies, both alone and in combination, have shown promising, if modest, improvements in survival [48].

Treatment Follow-Up

The NCCN recommends at least annual skin exams for life after the diagnosis of melanoma, with more frequent exams in the first 2–5 years due to an increased risk of recurrence or a new primary tumor during this period. Clinical lymph node examination should be performed at each visit, and patients should be educated about how to perform self-examination. A thorough review of systems should also be performed, with particular focus on those organ systems most commonly affected by melanoma metastases (liver, lungs, bones, brain). Routine follow-up imaging or laboratory evaluation is not recommended for asymptomatic patients with a history of cutaneous melanoma, but can be helpful in monitoring patients with proven metastatic disease.

Other Rare Cutaneous Malignancies

Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is a rare neuroendocrine tumor of the skin with an aggressive clinical course. About 1500 cases of MCC are diagnosed in the United States each year, and the incidence is rising [2]. It most commonly affects sun-exposed areas, especially the head and neck, on Caucasian patients 70 and older [49]. MCC is believed to arise from neural cells that function as mechanoreceptors within the basal layer of the epidermis. The majority of cases are associated with a novel polyomavirus, known as the Merkel cell polyomavirus (MCPyV), although an exact causative mechanism remains to be fully elucidated [49]. The clinical appearance of primary MCC varies, but tumors are often firm red to purple non-tender papules or nodules (Fig. 26). They can be rock-hard to the touch and may exhibit rapid growth. The head and neck account for almost half of all cases. Eyelids are frequently affected.

The overall 5-year survival for node-negative disease is 64%. This figure drops precipitously to 39% in regional nodal disease and 18% in metastatic disease [50]. Patients who are immunocompromised have an even worse prognosis. Diagnosis requires histological confirmation, and NCCN staging is influenced by tumor diameter, depth of invasion, and lymph node or distant metastasis [51]. Wide local excision with 1–3 cm margins, Mohs micrographic surgery, or other margin-controlled techniques are recommended for local disease. SLNB is recommended for all patients, even those with clinically negative nodes. A positive SLNB is typically followed by complete nodal basin excision and radiation. Adjuvant radiation treatment appears to reduce recurrence of locoregional disease but may not affect overall survival. Platinum-based chemotherapy, with or without etoposide, is generally reserved for widely metastatic disease. Immunotherapies directly targeting the MCPyV or aimed to boost host immune response are currently under investigation [50].

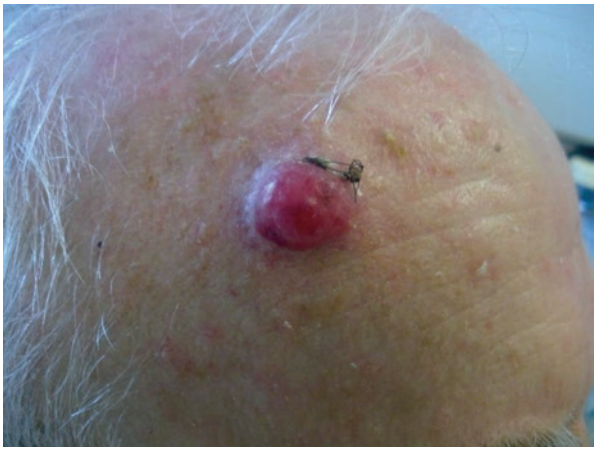

Fig. 26 Merkel cell carcinoma. This neoplasm is red pink due to its vascularity and exophytic and felt firm to palpation

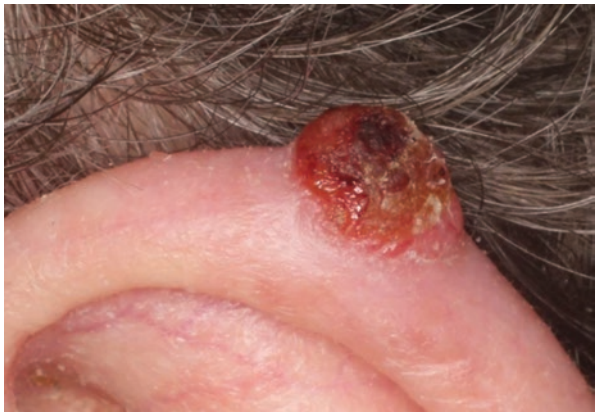

Fig. 27 Sebaceous carcinoma on the helix of the ear

Sebaceous Carcinoma

Sebaceous carcinoma is a rare adnexal neoplasm that tends to occur in areas of high sebaceous gland density. A painless, pink to red or yellowish nodule on the eyelid is the classically described presentation, but other sebaceous areas on the face, scalp, and neck can be affected as well (Fig. 27). The primary lesion, which may also be papular or plaque-like, can resemble a common chalazion, molluscum contagiosum, hemangioma, or keratoacanthoma-type squamous cell carcinoma. A "chalazion" that does not resolve with several weeks of local wound care or antibiotics should raise clinician suspicion for malignancy. Histopathology confirms the diagnosis [52]. A history of extraocular sebaceous carcinoma or multiple sebaceous carcinomas should prompt screening for Muir-Torre syndrome, an autosomal dominant inherited condition associated with increased risk of gastrointestinal and genitourinary malignancies, among others [53].

Cutaneous Metastasis

Roughly 1–2% of all internal malignancies will metastasize to the skin [54]. Cutaneous metastases represent an uncommon occurrence that indicates advanced disease state and portends a poor prognosis. Carcinomas of the lung, colon, and breast are the most likely visceral malignancies to metastasize to the skin. However, melanoma is the most common overall [55]. The scalp, chest, and abdomen are frequently affected. Cutaneous metastases can present as one or multiple nonspecific erythematous, vascular nodules (Fig. 28). The patient may describe bleeding, ulceration, or rapid growth. The first step in managing a suspected cutaneous metastasis is to confirm the cell of origin via biopsy. Treatment aims at identifying and targeting the underlying malignancy, although surgical excision of symptomatic or cosmetically disfiguring metastases may be warranted.

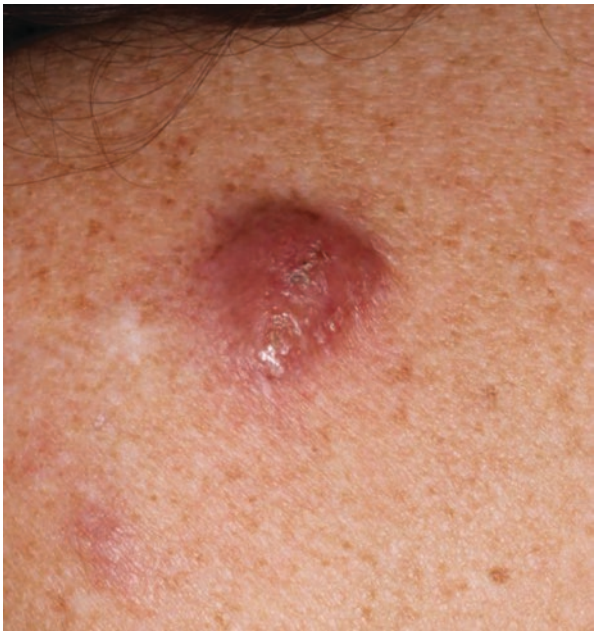

Fig. 28 Cutaneous metastasis. This patient had metastatic breast cancer with a cutaneous metastasis on her upper back

Primary Cutaneous Lymphoma

Primary cutaneous lymphomas are a heterogeneous group of T- and B-cell lymphomas [56]. Mycosis fungoides (MF) and Sézary syndrome (SS) comprise 53% of cutaneous lymphomas and are collectively referred to as cutaneous T-cell lymphomas (CTCL). Early-stage MF typically affects patient in their 50s and 60s and classically presents as well-defined patches and plaques, often with overlying scale, on non-sun-exposed areas (Fig. 29). Plaques may evolve slowly into tumors as the disease progresses. However, MF commonly exhibits clinically indolent behavior and may be managed for years in a manner similar to other chronic papulosquamous diseases such as eczema and psoriasis. Sézary syndrome, a more aggressive leukemic variant, is characterized by circulating neoplastic T cells and erythroderma with or without lymphadenopathy. It can be associated with severe, diffuse pruritus. Although SS often arises de novo over a short time period, some cases have been reported to follow longstanding MF [56].

Primary cutaneous B-cell lymphomas (PCBCL) are less common than CTCL and comprise roughly 20–25% of all primary cutaneous lymphomas [57]. PCBCL also encompasses a heterogeneous group of diseases that are categorized based on histology, immunophenotyping, and prognosis. PCBCL may present as one or multiple patches, plaques, nodules, or firm tumors. In most cases, the disease remains localized to the skin. In general, PCBCL has a more indolent clinical course and favorable prognosis as compared to nodal disease [58].

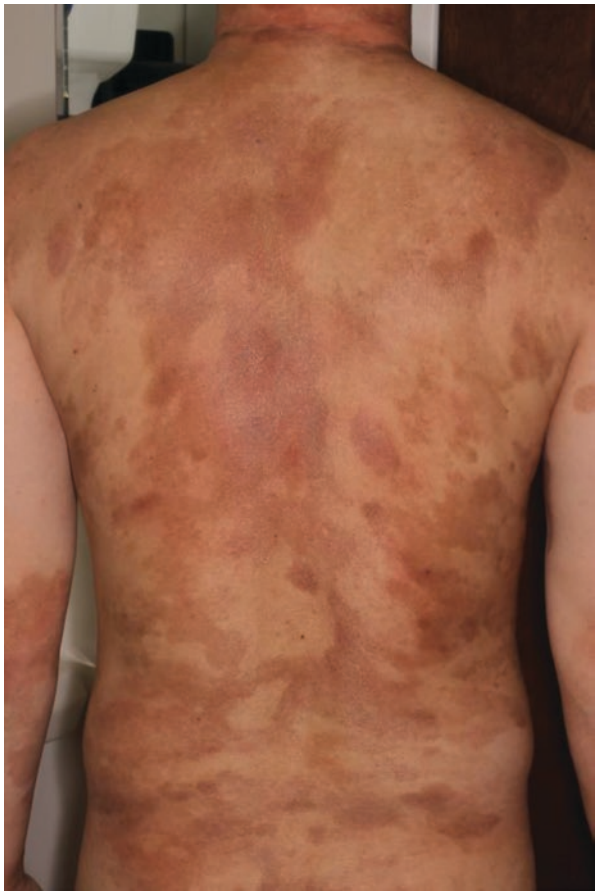

Fig. 29 Mycosis fungoides manifesting as asymmetric erythematous plaques

Proper diagnosis, classification, and staging of primary cutaneous lymphomas often require a battery of tissue- and blood-based tests, imaging studies, and lymph node sampling. Patients should be referred to a cutaneous lymphoma specialist for disease management and surveillance.

Dermatofibrosarcoma Protuberans (DFSP)

DFSP is a low-grade soft tissue malignancy that typically arises in younger patients aged 24–50 years. It most commonly occurs on the trunk, with a predilection for the shoulder or pelvic region, but may also present on the head and neck. It appears as a painless, slowly enlarging skin-colored to pink or red subcutaneous nodule or plaque (Fig. 30a–b). Lesions are often firm to the touch and feel adherent to underlying structures. The diagnosis is made based on histology and immunohistochemistry.

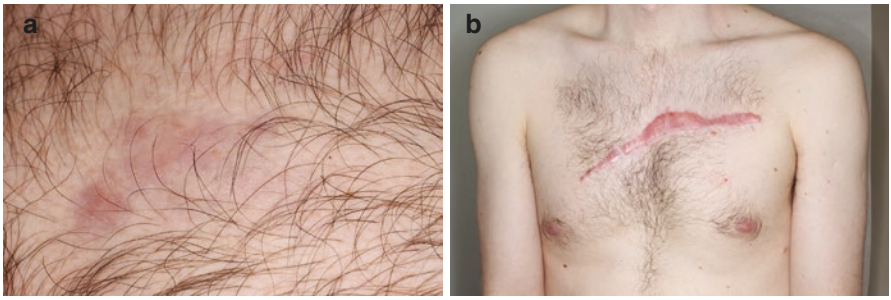

Fig. 30 Dermatofibroma sarcoma protuberans. (**a**) This shows an ill-defined sclerotic firm pink plaque. As these lesions progress, they can become more raised and nodular in appearance as described in more classical cases. (**b**) A large scar results from the reconstruction required after excision by Mohs micrographic surgery

DFSP has a tendency to recur after treatment, but the rate of distant metastasis is very low [59]. The standard of treatment is wide local excision to the underlying fascia or Mohs micrographic surgery. The chromosomal translocation t(17;22) q(22;q13), also found in chronic myeloid leukemia, is thought to play a pathogenic role in a majority of cases. Imatinib maculate targets the platelet-derived growth factor receptor activated by the translocation and is FDA-approved for patients with unresectable recurrent, or metastatic DFSP.

Angiosarcoma

Angiosarcomas are rare, aggressive tumors of vascular or lymphatic origin. Early lesions can be very subtle, initially resembling a bruise, but they tend to progress to nodules or tumors which ulcerate and hemorrhage. Angiosarcoma most commonly presents on the face or scalp in elderly men [60]. Most cases are sporadic, but disease presenting in non-head and neck locations is often associated with chronic lymphedema or a history of radiation, with peak incidence 5–10 years after radiation [61]. Treatment entails surgical resection and adjuvant radiation; recurrence is high.

Mammary and Extramammary Paget's Disease

Mammary Paget's disease most commonly presents in postmenopausal women in conjunction with an underlying intraductal breast carcinoma. It typically appears as a scaly pink to red plaque involving the nipple. Mammary Paget's disease often mimics an eczematous dermatitis, which can lead to delays in diagnosis. Patients classically provide a history of "eczema" of the nipple or breast

that has not responded to topical corticosteroids of increasing strength. Benign dermatitides of the nipple are fairly common, but a clinician should always ensure that a patient is up-to-date on age-appropriate mammography screening, particularly when the presentation is unilateral. Needless to say, a biopsy-proven diagnosis of mammary Paget's necessitates further investigation for underlying malignancy.

Extramammary Paget's disease is frequently divided into two subtypes: primary and secondary. Primary extramammary Paget's, the more common form, is an intraepithelial adenocarcinoma that arises de novo in apocrine gland-bearing skin such as the vulva, perianal region, scrotum, penis, or axillae. Surgical excision or Mohs micrographic surgery is the standard of care, but recurrence is common. Secondary disease is thought to represent contiguous spread of an underlying malignancy, typically localized to the same anatomic region [62, 63].

Patient Education

Comprehensive patient education includes skin cancer prevention and detection strategies and applies to all patients, regardless of age or skin type. Although melanoma and NMSC are far more common in whites, darker-skinned patients tend to present at more advanced stages with poorer prognosis [64]. The American Academy of Dermatology recommends year-round, everyday application of a broad-spectrum (UVA- and UVB-blocking), water-resistant sunscreen with an SPF of at least 30 for all skin types. A sufficiently thick layer should be applied to all uncovered skin 15 minutes prior to sun exposure and reapplied every 2 hours while outdoors thereafter (or every hour if swimming or sweating). Sun protective clothing and avoidance of peak sun hours between 10 am and 2 pm further reduce carcinogenic UV exposure. Tree or cloud shade is not sufficiently protective. Fair skin, severe or blistering sunburns, and prolonged chronic sun exposure are all associated with increased risk of skin cancer [20]. Tanning bed use has been associated with both melanoma and NMSC and should be strongly discouraged.

Conclusion and Future Directions

As our population ages, the incidence of skin cancer and its associated healthcare costs are projected to increase. Improved patient education, prevention, early detection, and treatment strategies are all needed to counter these trends. With the shift toward an accountable care organization model, primary care doctors and specialists alike will be expected to contain costs while improving quality and access to care. Technology, in the form of electronic medical records, telemedicine, and other nascent or as yet unconceived innovations, will play an increasingly important role

in this process. Developments in genetics and targeted molecular-based therapies are beginning to change the diagnosis and treatment of melanoma, still one of the deadliest human cancers. As our basic understanding of tumor biology grows, so too will our ability to alleviate the significant toll skin cancer takes on our patients' lives.

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