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SCC is a malignant tumour of keratinising cells of the epider - mis or its appendages. It arises from the stratum basalis of the epidermis and expresses cytokeratins 1 and 10. Epidemiology Four BCCs occur for every SCC, which is the second most common form of skin cancer. It is strongly related to cumu - lative sun exposure and damage, especially in white-skinned individuals living nearer the equator. In the northern hemi - sphere it a ff ects the elderly , whereas it is not uncommon in sun-damaged, middle-aged white people in the souther n hemisphere. Everywhere, it is more common in men than in women. SCC is also associa ted with chronic inflammation (chronic sinus tracts, pre-existing scars, osteomyelitis, burns, vaccination points) and immunosuppression. When a SCC appears in a scar it is known as a Marjolin’s ulcer.

(a, b)

Squamous cell carcinoma /uni25CF /uni25CF /uni25CF IR causes SCC, as do chemical carcinogens (arsenicals, tar) and infection with HPV subtypes 5 and 16. There is also evidence that current and previous tobacco use doubles the relative risk of SCC. In the past, actinic (solar) keratoses (AKs), i.e. cutaneous horns and keratoacanthomas, were considered to be prema lignant lesions leading to SCC. Current thinking is to classify these lesions on a continuum of lesions, some of which can impro ve, as with other squamous cell tumours suc h as cervical intraepithelial neoplasia. AKs are areas of permanent sun damage in which there is dyskeratosis, partial-thickness cellular atypia and subep idermal inflammation, but an intact basement membrane (Figure 45.31). They ‘wax and wane’ macroscopically between macular and papular, with and without keratinous surfaces. Most improve after moisturisation and remain as erythema tous macules; however, up to 20% form SCC. When an AK has a keratinous surface with a height greater than its base diameter, it is termed a keratin horn; 10% will have an underlying SCC (Figure 45.32). Keratoacanthomas are rapidly growing, nodular tumour exhibiting symmetry around a central keratin-filled crater. John T Bowen , 1857–1941, Professor of Dermatology , Harvard University Medical School, Boston, MA, USA, described this condition in 1912. August Queyrat , 1856–1933, dermatologist, Paris, France, described this condition in 1911. - Current thinking is that, rather than being separate pre - malignant entities, they are better considered as self-healing - SCCs and, as such, are often reported by pathologists as ‘keratoacanthoma-like SCCs’ (Figure 45.33). Keratoacantho - mas are twice as common in men as in women and are usually found on the face or limbs of chronically sun-damaged 50- to - 70-year-old white-skinned individuals. T hey may be caused by HPV in a hair follicle during the growth phase and are also associated with smoking and chemical carcinogen exposure. Excision is recommended, rather than observation, as the dif - ferential diagnosis includes anaplastic SCC and the excision s scar is often better than that which remains after

resolution. in situ and often develops as Bowen’s disease is SCC full-thickness dysplasia in hypertrophic AKs (Figure 45.34). SCC in situ usually presents as a slowly enlarging erythematous scaly plaque and may occur anywhere on the mucocutaneous surface of the body . On the glans penis, it is called erythroplasia of Queyrat (Figure 45.35). Topical therapy with 5-fluorouracil or imiquimod is an e ff ective treatment. Alternatives include surgical excision with a 4-mm margin or Mohs’ micrographic surgery for larger or recurrent lesions.

Associated with UVR, chronic in /f_l ammation, immunosuppression and chemical carcinogens High- and low-risk SCC Metastasis in 2% of low-risk and up to 30% of high-risk cases Figure 45.31 Actinic keratosis (courtesy of St John’s Institute for Dermatology, London, UK). Figure 45.32 Cutaneous horn (courtesy of St John’s Institute for Dermatology, London, UK). Figure 45.33 Keratoacanthoma (courtesy of St John’s Institute for Dermatology, London, UK).

Macroscopic The appearance of SCC may vary from smooth nodular, verrucous, papillomatous to ulcerating lesions. All ulcerate eventually as they grow . The ulcers have a characteristic everted edge and are surrounded by inflamed, indurated skin. Di ff erential diagnoses of SCC include: AK; BCC; pyoderma gangrenosum; warts; and lichen simplex chronicus (Figure 45.36). Albert Compton Broders , 1885–1964, American pathologist, MN, USA, and Chairman of the Department of Surgical Patholog MN, USA; for 1 year in 1935 Professor of Surgical Pathology and Director of Cancer Research, University of V graded rectal cancer in the USA in a similar manner to the one that Cuthbert Dukes used to classify it in the UK. A combination of Broders’ grading and Dukes’ classification gave a more accurate prognosis for rectal carcinoma than either method alone. Microscopic Characteristic irregular masses of squamous epithelium are noted to proliferate and invade the dermis from the basal layer. The tumour stains positive for cytokeratins 1 and 10. SCC can be graded histologically according to Broders’ grading, which describes the proportion of dedi ff erentiated cells in the tumour. Table 45.1 presents tumour classification and staging. Prognosis There are several independent prognostic variables for SCC: /uni25CF Depth: the deeper the lesion, the worse the prognosis. For SCC <2 /uni00A0 mm, metastasis is highly unlikely; if SCC >6 /uni00A0 mm, 15% will have metastasised. y, M a y o Clinic, Rochester, irginia, Charlottesville, V A, USA. Broders also

Figure 45.34 Bowen’s disease – squamous cell carcinoma in situ (courtesy of St John’s Institute for Dermatology, London, UK). TABLE 45.1 Tumour–node–metastasis (TNM) classi /f_i cation and staging of squamous cell carcinoma. Size Nodes NX TX Nodal involvement cannot be Primary tumour cannot be assessed assessed T0 N0 No evidence of primary tumour No regional nodes N1 Tis Spread to 1 ipsilateral nearby node In situ (con /f_i ned to full-thickness that is <3 /uni00A0 cm in diameter epidermal) disease T1 N2a Primary <2 /uni00A0 cm Spread to 1 ipsilateral nearby node that is 3–6 /uni00A0 cm in diameter T2 N2b Primary >2 /uni00A0 cm Spread to >1 ipsilateral nearby nodes but none >6 /uni00A0 cm in diameter T3 N2c Primary invasion of a facial bone Spread to contralateral node(s) but none are >6 /uni00A0 cm in diameter N3 T4 Spread to any node >6 /uni00A0 cm in Invasion of muscle, base of skull diameter or other bones Figure 45.35 Erythroplasia of Queyrat – squamous cell carcinoma in situ on the glans penis; also called Paget’s disease of the penis (courtesy of St John’s Institute for Dermatology, London, UK). Metastases Stages M0 Stage 0 No metastatic disease Tis, N0, M0 M1 Stage I Metastatic disease present T1, N0, M0 Stage II T2, N0, M0 Stage III T3, N0, M0 or T1–T3, N1, M0 Stage IV T1–T3, N2, M0 or any disease that is N3, or T4 or M1

/uni25CF Surface size: lesions >2 /uni00A0 cm have a worse prognosis than smaller ones. /uni25CF Histological grade: the higher the Broders' grade, the worse the prognosis. /uni25CF Microscopic invasion of lymphovascular spaces or nerve tissue carries a high risk of metastatic disease. Therefore, as well as information on pathological pattern, cellular morphology and Broders' grade, any histopathology report for SCC should include the depth of invasion, the pres ence of perineural or lymphovascular invasion and the deep and peripheral margin clearance. /uni25CF Site: SCCs on the lips and ears have higher local recur rence rates than lesions elsewhere, and tumours at the extremities fare worse than those on the trunk. /uni25CF Aetiology: SCCs that arise in burn scars, osteomyelitis skin sinuses, chronic ulcers and areas of skin that have been irradiated have a higher metastatic potential. /uni25CF Immunosuppression: SCCs will invade further in those with impaired immune response. The overall rate of metastasis varies between 2% and 30% for SCC (usually to regional nodes) with a local recurrence rate of 20%. Management SCC is a heterogeneous tumour with a malignant potential that varies between subtypes. Management must address the tumour's tendency for lymphatic metastasis and the possibility of in-transit metastasis. Surgical excision is the only means of providing accurate information on histology and clearance. The margins for pri - mary excision should be tailored to surface size in the first instance. This should ideally be assessed using surgical loupe - magnification. A 4-mm clearance margin should be achieved and a 1-cm clearance if the SCC measures <2 /uni00A0 cm across, margin if the SCC measures >2 /uni00A0 cm; 95% of local recurrence and regional metastases occur within 5 years, thus follow-up - beyond this period is not indicated. Cutaneous malignant melanoma Melanoma is a cancer of melanocytes and can, therefore, arise in skin, mucosa, retina and the leptomeninges. Epidemiology Observational data suggest that cutaneous melanoma is caused by exposure to UVR, but this general observation, which is a generally reliable fact, may hide some of the nuanced variables that contribute to melanoma formation.

(c) Figure 45.36 (a) A squamous cell carcinoma (SCC) on the face. /uni00A0 (c) SCC arising on the dorsum of the hand in a renal transplant recipient on immunosuppressive therapy. who worked outside on a farm. ((a–c) courtesy of Mr AR Greenbaum; (d) (b) A recurrent SCC arising in a previously skin-grafted area of the scalp. (d) SCC arising on the lip of a smoker (d) courtesy of St John's Institute for Dermatology, London, UK.)

recreational activity in the sun and emigration among white- skinned people not suited to sun exposure. Although it accounts for less than 5% of skin malignancy (and 1.6% of all malignancy worldwide), it is responsible for over 75% of skin malignancy-related deaths. It is the commonest cancer in young adults (20–39 years) and the most likely cause of cancer-related death. Distribution between the sexes varies around the world and reflects occupational and recreational exposure to sunlight. Likewise, geographical distribution reflects e xposure of white- skinned individuals to sunlight: Australia and New Zealand, countries with a predominantly white-skinned, immigrant population, have an incidence of 33.6 per 100 /uni00A0 000. Five per cent of all patients with malignant melanoma will develop a second primary melanoma; 7% of malignant melanomas pres ent as occult metastasis from an unknown primary . What is less clear within data on cutaneous melanoma is the contribution by variables such as serum vitamin D levels and vitamin receptor genotypes, because thinner melanomas and low er recurrence rates have been linked to higher serum vitamin D levels, and why some forms of melanoma seem more attributable to cumulative sun exposure (superficial spreading) than others (nodular). Studies exploring whether there may be benefit from a degree of sun exposure that avoids 'sunbathing' and burning and

whether sun-related vitamin D production in skin, rather than supplemental vitamin D, is beneficial are ongoing, but our best information still bases sun avoidance at the centre of melanoma prevention. Pathophysiology Cumulative UV exposure favours the development of lentigo maligna melanoma (LMM) and later onset of disease, whereas ‘flash fry’ exposure, typical of rapidly acquired holiday tans, favours the other morphological variants and early onset of disease. A small proportion of malignant melanoma is genetically mediated and develops at an earlier age. People at most risk of developing malignant melanoma include: those with genetic syndromes; those with a past history of malignant melanoma or with a first-degree rela tive who has malignant melanoma; those who have more than 30 sun-acquired naevi or a history of five significant sunburns before the age of 16; fair-skinned/ red-haired people living close to the equator; anyone with excessive UVR exposure (environmental or salon-delivered); Summary box 45.4 Malignant melanoma /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF Alexander Breslow , 1928–1980, pathologist, George Washington University , Washington, DC, USA, first reported in 1970 that the prognosis depends upon the thickness of the tumour. nant melanoma incidence 20- to 30-fold). Male gender and solitary living are both associated with thicker melanomas at diagnosis. In women, higher socioeconomic status is positively correlated with developing melanoma. Macroscopic Only 10–20% of malignant melanomas form in pre-existing naevi, with the remainder arising de novo in previously normally pigmented skin. The most likely naevi to form malignant mela - noma are atypical naevi, atypical junctional lentiginous naevi (usually facial) and giant pigmented congenital naevi. Macroscopic features in a pre-existing naevus that suggest malignant change are listed in Summary box 45.5 . There are four common macroscopic variants of malig - nant melanoma and several other notable, but rarer, forms, - as follows. This is the most common presentation (70%); usually arises in a pre-existing naevus after several years of slow c hange, followed by rapid g rowth in the months before presentation (Figure 45.37) . Nodularity within SSM heralds the onset of the vertical growth phase. NM accounts for 15% of all malignant melanoma and tends to be more aggressive than SSM, with a shorter clinical onset. These lesions often arise de novo in skin and are more common in men than in women, often presenting in middle age and usually on the trunk, head or neck (Figure 45.38) . They typically appear as blue/black papules, 1–2 /uni00A0 cm in diameter, and because they lack the hori - zontal growth phase they tend to be sharply demarcated. Up to 5% are amelanotic.

Rising incidence Genetic and acquired risk factors Super /f_i cial spreading form the most common Breslow thickness is the most important prognostic indicator Sentinel node biopsy (SNB) is useful for staging Super /f_i cial spreading melanoma (SSM). Nodular melanoma (NM). Figure 45.37 Super /f_i cial spreading melanoma (courtesy of St John’s Institute for Dermatology, London, UK).

LMM was previously also known as Hutchinson’s melanotic freckle. This variant presents as a slow-growing, variegated brown macule on the face, neck or hands of the elderly (Figure 45.39) . They are positively correlated with prolonged, intense sun exposure and a ff ect women more than men. They account for between 5% and 10% of malignant melanomas. LMMs are thought to have less metastatic potential than other variants as they take longer to enter a vertical growth phase. Nonetheless, when they have entered the vertical growth phase their metasta tic potential is the same as any other mel anoma. ALM a ff ects the soles and palms. It is rare in white-skinned individuals (2–8% of malignant melanoma) but more common in Afro-Caribbean, Hispanic and Asian populations (35–60%). It usually presents as a flat, irregular macule in later life; 25% are

amelanotic and may mimic a fungal infection or py ogenic granuloma. Sir Jonathan Hutchinson , 1828–1913, surgeon, St Bartholomew’s Hospital, London, UK. Malignant melanomas under the fingernail are usually SSM rather than ALM. For finger- or toenail lesions it is vital to biopsy the nail matrix rather than just the pigment on the nail plate. A classical feature of a subungual melanoma is Hutchin - son’s sign: nail fold pigmentation that widens progressively to produce a triangular pigmented macule with associated nail dystrophy . The di ff erential diagnosis is ‘benign racial melanon - ychia’, which produces a linear dark streak under a nail in a - individual. Malignancy is unlikely if the nail fold dark-skinned is uninvolved (Figure 45.40). /uni25CF Amelanotic melanoma may present as a flesh-coloured skin lesion; as a metastasis from an unknown skin primary; or in the gastrointestinal tract, with obstruction or intus - susception.

Figure 45.38 Nodular melanoma (courtesy of St John’s Institute for Dermatology, London, UK). Lentigo maligna melanoma. Acral lentiginous melanoma (ALM). (a) Figure 45.40 (a) Acral lentiginous melanoma on the sole of the foot. Note the swelling proximal to the nailfold. (c) Benign racial melanonychia. (Institute for Dermatology, London, UK.) Figure 45.39 Lentigo maligna melanoma

(courtesy of St John’s Insti

tute for Dermatology, London, UK). Miscellaneous (b) (c) (b) Subungual melanoma – probably a super /f_i cial spreading melanoma. (a) courtesy of Mr AR Greenbaum; (b, c) courtesy of St John’s

neck region. It has a propensity for perineural infiltration and often recurs locally if not widely excised. It may be amelanotic clinically . Summary box 45.5 Macroscopic features in naevi suggestive of malignant melanoma /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF Microscopic Malignant change occurs in the melanocytes in the basal epidermis, while in situ atypical melanocytes are limited to the dermoepidermal junction and show no evidence of dermal involvement. During the horizontal growth phase, cells spread along the dermoepidermal junction; although they may breach the dermis, their migration is predominantly radial. During the vertical growth phase, the dermis may be invaded. The greater the depth of invasion, the greater the metastatic potential of the tumour. Management History and clinical examination should be directed at discov ering the primary lesion and identification of local, regional or distant spread. An excision biopsy with a 2- to 3-mm margin of skin and a cu ff of subdermal fat is acceptable. Incision biopsy is occasion ally indicated: for instance, in large lesions on the face where an excision biopsy of the whole lesion would be disfiguring. In experienced hands, observation and review every 2 /uni00A0 months may avoid biopsies in equivocal cases, but serial clin ical and dermoscopic photography by a clinician with exper tise in dermoscopy is mandatory when observ ation is chosen, rather than excision biopsy for definitive histopathological diagnosis. Dermoscopy coupled to computers with learning capability may soon outperform clinicians in melanoma diag nosis to the point where screening becomes m uch easier. Biopsy and pathological examination provide the first step towards staging melanoma. The Breslow thickness of a mel anoma (measured to the nearest 0.1 /uni00A0 mm from the granular layer to the base of the tumour) is the most important prog nostic indica tor in the absence of lymph node metastases. The American Joint Committee on Cancer (AJCC) staging system takes lymph node involvement, distant metastases and evidence-based prognostic factors into account; these can then be used to guide optimum care and inclusion in researc studies for adjuvant or other treatments where applicable. The detail of the AJCC melanoma staging system has become too specialised for the ambit of this text; most spe cialists look up its detail as they assign a stage to a patient (Table 45.2). Guidelines for staging are controversial. The author suggests that investigations should be directed towards detecting occult disease, so as to upstage patients and treat them accurately and appropriately , the only cure for malignant melanoma currently being appropriate surgery . Thus, o ff ering SNB to patients with T2a disease and greater is critical and investigations for T3a disease and greater should be directed to individual clinical presentation. Local treatment The treatment for melanoma is surgery . Lentigo maligna (melanoma in situ) should be excised completely in most clin - ical situations because of the risk of it entering the vertical growth phase to become LMM. A complete excision requires no further treatment. For melanoma in situ a wide excision of 5 /uni00A0 mm is su ffi cient; for melanoma <1 /uni00A0 mm deep, a 1-cm margin is su ffi cient; and for deeper lesions, a 2-cm only margin is recommended, as there is no evidence that wider margins make a di ff erence. Regional lymph nodes The likelihood of metastatic spread to regional lymph nodes is proportional to the Breslow thickness of the melanoma. Management of regional lymph nodes has been a contentious topic for well over a century . Some advocated simultaneous elective lymph node clearance at the

time of wide excision of the primary melanoma. Others favoured a therapeutic lymphadenectomy if regional metastases became clinically evident. Ideally , one would like to be able to select for treatment - those patients with the highest risk of metastatic spread. SNB, an investigation based on the fact that lymphatic metastases proceed in an orderly fashion and can be predicted by mapping the lymphatic drainage from a primary tumour to the first or - ‘sentinel’ node in the regional lymphatic basin, o ff ered that potential, but prospective controlled studies have shown no survival benefit from lymphadenectomy after positive SNB involving micrometastasis <0.2 /uni00A0 mm in a single node. This may - be because most patients have been treated by removing the - sentinel node, which was the only node involved at that stage. However, completion lymphadenectomy after positive SNB remains, on current evidence, the optimum method for regional control, if patients accept the morbidity associated - with regional lymphadenectomy . Adjuvant therapy - When mutation locks BRAF protein signalling to ‘on’, it a ff ects the mitogen-activated protein kinase (MAPK) cellular - pathway , promoting initiation, malignant transformation, tumour progression and metastasis in the 50% of malignant melanomas with BRAF V600 mutations. Targeted therapy in stage IV melanoma using dabrafenib or vemurafenib, which block BRAF action, has shown promising results with h metastatic melanoma. Trametinib has a di ff erent action on the MAPK pathway: stopping cell growth and promoting apoptosis. Combined use with dabrafenib to counter acquired - tumour resistance via MAPK pathway reactivation shows promising results in stage IV disease. Also, the selective immune

Change in size Shape Colour Thickness (elevation/nodularity or ulceration) Satellite lesions (pigment spreading into surrounding area) Tingling/itching/serosanguineous discharge (usually late signs)

checkpoint inhibitors ipilimumab and nivolumab demonstrate benefit in metastatic or unresectable melanoma. Over the last 5 years, five randomised prospective trials of adjuvant therapy have reported findings in the treatment of patients with stage II to IV disease. While all five trials showed a significant impro vement in relapse-free survival, only two of the trials were mature enough to report on overall survival. Prognosis The Breslow thickness of the primary tumour o ff ers the best correlation with survival in stage I disease. The higher the mitotic index, the poorer the prognosis of the primary tumour. This has greater significance than the presence or absence of ulceration. The presence of lymph node metastases is the single most important prognostic index in melanoma, outweighing both tumour and host factors. The number of a ff ected nodes and the presence of extranodal extension are also significant outcome predictors. Once regional nodes are clinically involved, 70–85% of patients will have occult distant metastases. Merkel cell (dermal mechanoreceptor) tumour This is an aggressive malignant tumour of Merkel cells and usually a ff ects the elderly . It is four times more common in Haig H Kasabach , 1898–1943, radiologist, Presbyterian Hospital, New Y ork, NY , USA. Katharine K Merritt , 1886–1986, pediatrician, Babies Hospital, Columbia University College of Physicians and Surgeons, New Y ork, NY , USA. Kasabach and Merritt described the condition as a joint paper in 1940. women than in men (Figure 45.41). Treatment is with wide local excision, aiming for a 25- to 30-mm margin, followed by radiotherapy .

Primary tumour Regional nodes NX TX Patients in whom nodes cannot be assessed Primary tumour cannot be assessed (has (e.g. previous excision) been curettage or has severely regressed) T0 N0 No evidence of primary tumour No node involvement Tis Melanoma in situ N1 a: <0.8 /uni00A0 mm, no ulceration T1 1 node b: 0.8–1.0 /uni00A0 mm, no <1.0 /uni00A0 mm ulceration; or <1.0

/uni00A0 mm with ulceration a: No ulceration N2 T2 b: With ulceration 2 or 3 nodes 1.01–2.0 /uni00A0 mm a: No ulceration N3 T3 b: With ulceration 2.01–4.0 /uni00A0 mm a: No ulceration T4 b: With ulceration

> 4 /uni00A0 mm Clinical staging of melanoma Stage IIa: T2b or T3a, N0, M0 Stage 0: Tis, N0, M0 Stage IIb: T3b or T4a, N0, M0 Stage Ia: T1a, N0, M0 Stage IIc: T4b, N0, M0 Stage Ib: T1b or T2a, N0, M0 LDH, lactate dehydrogenase; MSI denotes the presence of satellite lesions, in-transit lesions or local recurrence. Distant metastases M0 No detected distant metastases M1a a: Micrometastasis (no MSI) Skin, subcutaneous or distant lymph node b: Macrometastasis (no MSI) metastases (normal serum LDH levels) c: MSI present M1b a: Micrometastasis (no MSI) Lung metastases (normal serum LDH b: Macrometastasis (no MSI) levels) c: MSI present M1c a: Micrometastasis, >3 nodes All other visceral metastases or any distant (no MSI) metastases with elevated serum LDH b: Micrometastasis, >3 nodes levels or matted or 1 clinical node (no MSI) c: 1 clinical or occult node with MSI present M1d Brain metastases Stage III: any T, >N1, M0 Stage IV: any T, any N1, M1

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/uni25CF Surface size: lesions >2 /uni00A0 cm have a worse prognosis than smaller ones. /uni25CF Histological grade: the higher the Broders' grade, the worse the prognosis. /uni25CF Microscopic invasion of lymphovascular spaces or nerve tissue carries a high risk of metastatic disease. Therefore, as well as information on pathological pattern, cellular morphology and Broders' grade, any histopathology report for SCC should include the depth of invasion, the pres ence of perineural or lymphovascular invasion and the deep and peripheral margin clearance. /uni25CF Site: SCCs on the lips and ears have higher local recur rence rates than lesions elsewhere, and tumours at the extremities fare worse than those on the trunk. /uni25CF Aetiology: SCCs that arise in burn scars, osteomyelitis skin sinuses, chronic ulcers and areas of skin that have been irradiated have a higher metastatic potential. /uni25CF Immunosuppression: SCCs will invade further in those with impaired immune response. The overall rate of metastasis varies between 2% and 30% for SCC (usually to regional nodes) with a local recurrence rate of 20%. Management SCC is a heterogeneous tumour with a malignant potential that varies between subtypes. Management must address the tumour's tendency for lymphatic metastasis and the possibility of in-transit metastasis. Surgical excision is the only means of providing accurate information on histology and clearance. The margins for pri - mary excision should be tailored to surface size in the first instance. This should ideally be assessed using surgical loupe - magnification. A 4-mm clearance margin should be achieved and a 1-cm clearance if the SCC measures <2 /uni00A0 cm across, margin if the SCC measures >2 /uni00A0 cm; 95% of local recurrence and regional metastases occur within 5 years, thus follow-up - beyond this period is not indicated. Cutaneous malignant melanoma Melanoma is a cancer of melanocytes and can, therefore, arise in skin, mucosa, retina and the leptomeninges. Epidemiology Observational data suggest that cutaneous melanoma is caused by exposure to UVR, but this general observation, which is a generally reliable fact, may hide some of the nuanced variables that contribute to melanoma formation.

(c) Figure 45.36 (a) A squamous cell carcinoma (SCC) on the face. /uni00A0 (c) SCC arising on the dorsum of the hand in a renal transplant recipient on immunosuppressive therapy. who worked outside on a farm. ((a–c) courtesy of Mr AR Greenbaum; (d) (b) A recurrent SCC arising in a previously skin-grafted area of the scalp. (d) SCC arising on the lip of a smoker (d) courtesy of St John's Institute for Dermatology, London, UK.)

recreational activity in the sun and emigration among white- skinned people not suited to sun exposure. Although it accounts for less than 5% of skin malignancy (and 1.6% of all malignancy worldwide), it is responsible for over 75% of skin malignancy-related deaths. It is the commonest

cancer in young adults (20–39 years) and the most likely cause of cancer-related death. Distribution between the sexes varies around the world and reflects occupational and recreational exposure to sunlight. Likewise, geographical distribution reflects e xposure of white- skinned individuals to sunlight: Australia and New Zealand, countries with a predominantly white-skinned, immigrant population, have an incidence of 33.6 per 100 /uni00A0 000. Five per cent of all patients with malignant melanoma will develop a second primary melanoma; 7% of malignant melanomas pres ent as occult metastasis from an unknown primary . What is less clear within data on cutaneous melanoma is the contribution by variables such as serum vitamin D levels and vitamin receptor genotypes, because thinner melanomas and low er recurrence rates have been linked to higher serum vitamin D levels, and why some forms of melanoma seem more attributable to cumulative sun exposure (superficial spreading) than others (nodular). Studies exploring whether there may be benefit from a degree of sun exposure that avoids ‘sunbathing’ and burning and whether sun-related vitamin D production in skin, rather than supplemental vitamin D, is beneficial are ongoing, but our best information still bases sun avoidance at the centre of melanoma prevention. Pathophysiology Cumulative UV exposure favours the development of lentigo maligna melanoma (LMM) and later onset of disease, whereas ‘flash fry’ exposure, typical of rapidly acquired holiday tans, favours the other morphological variants and early onset of disease. A small proportion of malignant melanoma is genetically mediated and develops at an earlier age. People at most risk of developing malignant melanoma include: those with genetic syndromes; those with a past history of malignant melanoma or with a first-degree rela tive who has malignant melanoma; those who have more than 30 sun-acquired naevi or a history of five significant sunburns before the age of 16; fair-skinned/ red-haired people living close to the equator; anyone with excessive UVR exposure (environmental or salon-delivered); Summary box 45.4 Malignant melanoma /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF Alexander Breslow , 1928–1980, pathologist, George Washington University , Washington, DC, USA, first reported in 1970 that the prognosis depends upon the thickness of the tumour. nant melanoma incidence 20- to 30-fold). Male gender and solitary living are both associated with thicker melanomas at diagnosis. In women, higher socioeconomic status is positively correlated with developing melanoma. Macroscopic Only 10–20% of malignant melanomas form in pre-existing naevi, with the remainder arising de novo in previously normally pigmented skin. The most likely naevi to form malignant mela - noma are atypical naevi, atypical junctional lentiginous naevi (usually facial) and giant pigmented congenital naevi. Macroscopic features in a pre-existing naevus that suggest malignant change are listed in Summary box 45.5 . There are four common macroscopic variants of malig - nant melanoma and several other notable, but rarer, forms, - as follows. This is the most common presentation (70%); usually arises in a pre-existing naevus after several years of slow c hange, followed by rapid g rowth in the months before presentation (Figure 45.37) . Nodularity within SSM heralds the onset of the vertical growth phase. NM accounts for 15% of all malignant melanoma and tends to be more aggressive than SSM, with a shorter clinical onset. These lesions often arise de novo in skin and are more common in men than in women, often presenting in middle age and usually on the trunk, head or neck (Figure 45.38) . They typically appear as blue/black papules, 1–2 /uni00A0 cm in diameter, and because they lack the hori - zontal growth phase they tend to be sharply demarcated. Up to 5% are amelanotic.

Rising incidence Genetic and acquired risk factors Super /f_i cial spreading form the most common Breslow thickness is the most important prognostic indicator Sentinel node biopsy (SNB) is useful for staging Super /f_i cial spreading melanoma (SSM). Nodular melanoma (NM). Figure 45.37 Super

/f_i cial spreading melanoma (courtesy of St John’s Institute for Dermatology, London, UK).

LMM was previously also known as Hutchinson’s melanotic freckle. This variant presents as a slow-growing, variegated brown macule on the face, neck or hands of the elderly (Figure 45.39) . They are positively correlated with prolonged, intense sun exposure and a ff ect women more than men. They account for between 5% and 10% of malignant melanomas. LMMs are thought to have less metastatic potential than other variants as they take longer to enter a vertical growth phase. Nonetheless, when they have entered the vertical growth phase their metasta tic potential is the same as any other mel anoma. ALM a ff ects the soles and palms. It is rare in white-skinned individuals (2–8% of malignant melanoma) but more common in Afro-Caribbean, Hispanic and Asian populations (35–60%). It usually presents as a flat, irregular macule in later life; 25% are amelanotic and may mimic a fungal infection or py ogenic granuloma. Sir Jonathan Hutchinson , 1828–1913, surgeon, St Bartholomew’s Hospital, London, UK. Malignant melanomas under the fingernail are usually SSM rather than ALM. For finger- or toenail lesions it is vital to biopsy the nail matrix rather than just the pigment on the nail plate. A classical feature of a subungual melanoma is Hutchin - son’s sign: nail fold pigmentation that widens progressively to produce a triangular pigmented macule with associated nail dystrophy . The di ff erential diagnosis is ‘benign racial melanon - ychia’, which produces a linear dark streak under a nail in a - individual. Malignancy is unlikely if the nail fold dark-skinned is uninvolved (Figure 45.40). /uni25CF Amelanotic melanoma may present as a flesh-coloured skin lesion; as a metastasis from an unknown skin primary; or in the gastrointestinal tract, with obstruction or intus - susception.

Figure 45.38 Nodular melanoma (courtesy of St John’s Institute for Dermatology, London, UK). Lentigo maligna melanoma. Acral lentiginous melanoma (ALM). (a) Figure 45.40 (a) Acral lentiginous melanoma on the sole of the foot. Note the swelling proximal to the

nailfold. (c) Benign racial melanonychia. (Institute for Dermatology, London, UK.) Figure 45.39 Lentigo maligna melanoma (courtesy of St John’s Insti

tute for Dermatology, London, UK). Miscellaneous (b) (c) (b) Subungual melanoma – probably a super /f_i cial spreading melanoma. (a) courtesy of Mr AR Greenbaum; (b, c) courtesy of St John’s

neck region. It has a propensity for perineural infiltration and often recurs locally if not widely excised. It may be amelanotic clinically . Summary box 45.5 Macroscopic features in naevi suggestive of malignant melanoma /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF Microscopic Malignant change occurs in the melanocytes in the basal epidermis, while in situ atypical melanocytes are limited to the dermoepidermal junction and show no evidence of dermal involvement. During the horizontal growth phase, cells spread along the dermoepidermal junction; although they may breach the dermis, their migration is predominantly radial. During the vertical growth phase, the dermis may be invaded. The greater the depth of invasion, the greater the metastatic potential of the tumour. Management History and clinical examination should be directed at discov ering the primary lesion and identification of local, regional or distant spread. An excision biopsy with a 2- to 3-mm margin of skin and a cu ff of subdermal fat is acceptable. Incision biopsy is occasion ally indicated: for instance, in large lesions on the face where an excision biopsy of the whole lesion would be disfiguring. In experienced hands, observation and review every 2 /uni00A0 months may avoid biopsies in equivocal cases, but serial clin ical and dermoscopic photography by a clinician with exper tise in dermoscopy is mandatory when observ ation is chosen, rather than excision biopsy for definitive histopathological diagnosis. Dermoscopy coupled to computers with learning capability may soon outperform clinicians in melanoma diag nosis to the point where screening becomes m uch easier. Biopsy and pathological examination provide the first step towards staging melanoma. The Breslow thickness of a mel anoma (measured to the nearest 0.1 /uni00A0 mm from the granular layer to the base of the tumour) is the most important prog nostic indica tor in the absence of lymph node metastases. The American Joint Committee on Cancer (AJCC) staging system takes lymph node involvement, distant metastases and evidence-based prognostic factors into account; these can then be used to guide optimum care and inclusion in researc studies for adjuvant or other treatments where applicable. The detail of the AJCC melanoma staging system has become too specialised for the ambit of this text; most spe cialists look up its detail as they assign a stage to a patient (Table 45.2). Guidelines for staging are controversial. The author suggests that investigations should be directed towards detecting occult disease, so as to upstage patients and treat them accurately and appropriately , the only cure for

malignant melanoma currently being appropriate surgery . Thus, o ff ering SNB to patients with T2a disease and greater is critical and investigations for T3a disease and greater should be directed to individual clinical presentation. Local treatment The treatment for melanoma is surgery . Lentigo maligna (melanoma in situ) should be excised completely in most clin - ical situations because of the risk of it entering the vertical growth phase to become LMM. A complete excision requires no further treatment. For melanoma in situ a wide excision of 5 /uni00A0 mm is su ffi cient; for melanoma <1 /uni00A0 mm deep, a 1-cm margin is su ffi cient; and for deeper lesions, a 2-cm only margin is recommended, as there is no evidence that wider margins make a di ff erence. Regional lymph nodes The likelihood of metastatic spread to regional lymph nodes is proportional to the Breslow thickness of the melanoma. Management of regional lymph nodes has been a contentious topic for well over a century . Some advocated simultaneous elective lymph node clearance at the time of wide excision of the primary melanoma. Others favoured a therapeutic lymphadenectomy if regional metastases became clinically evident. Ideally , one would like to be able to select for treatment - those patients with the highest risk of metastatic spread. SNB, an investigation based on the fact that lymphatic metastases proceed in an orderly fashion and can be predicted by mapping the lymphatic drainage from a primary tumour to the first or - ‘sentinel’ node in the regional lymphatic basin, o ff ered that potential, but prospective controlled studies have shown no survival benefit from lymphadenectomy after positive SNB involving micrometastasis <0.2 /uni00A0 mm in a single node. This may - be because most patients have been treated by removing the - sentinel node, which was the only node involved at that stage. However, completion lymphadenectomy after positive SNB remains, on current evidence, the optimum method for regional control, if patients accept the morbidity associated - with regional lymphadenectomy . Adjuvant therapy - When mutation locks BRAF protein signalling to ‘on’, it a ff ects the mitogen-activated protein kinase (MAPK) cellular - pathway , promoting initiation, malignant transformation, tumour progression and metastasis in the 50% of malignant melanomas with BRAF V600 mutations. Targeted therapy in stage IV melanoma using dabrafenib or vemurafenib, which block BRAF action, has shown promising results with h metastatic melanoma. Trametinib has a di ff erent action on the MAPK pathway: stopping cell growth and promoting apoptosis. Combined use with dabrafenib to counter acquired - tumour resistance via MAPK pathway reactivation shows promising results in stage IV disease. Also, the selective immune

Change in size Shape Colour Thickness (elevation/nodularity or ulceration) Satellite lesions (pigment spreading into surrounding area) Tingling/itching/serosanguineous discharge (usually late signs)

checkpoint inhibitors ipilimumab and nivolumab demonstrate benefit in metastatic or unresectable melanoma. Over the last 5 years, five randomised prospective trials of adjuvant therapy have reported findings in the treatment of patients with stage II to IV disease. While all five trials showed a significant impro vement in relapse-free survival, only two of the trials were mature enough to report on overall survival. Prognosis The Breslow thickness of the primary tumour o ff ers the best correlation with survival in stage I disease. The higher the mitotic index, the poorer the prognosis of the primary tumour. This has greater significance than the presence or absence of ulceration. The presence of lymph node metastases is the single most important prognostic index in melanoma, outweighing both tumour and host factors. The number of a ff ected nodes and the presence of extranodal extension are also significant outcome predictors. Once regional nodes are clinically involved, 70–85% of patients will have occult distant metastases. Merkel cell (dermal

mechanoreceptor) tumour This is an aggressive malignant tumour of Merkel cells and usually a ff ects the elderly . It is four times more common in Haig H Kasabach , 1898–1943, radiologist, Presbyterian Hospital, New Y ork, NY , USA. Katharine K Merritt , 1886–1986, pediatrician, Babies Hospital, Columbia University College of Physicians and Surgeons, New Y ork, NY , USA. Kasabach and Merritt described the condition as a joint paper in 1940. women than in men (Figure 45.41). Treatment is with wide local excision, aiming for a 25- to 30-mm margin, followed by radiotherapy .

Primary tumour Regional nodes NX TX Patients in whom nodes cannot be assessed Primary tumour cannot be assessed (has (e.g. previous excision) been curettage or has severely regressed) T0 N0 No evidence of primary tumour No node involvement Tis Melanoma in situ N1 a: <0.8 /uni00A0 mm, no ulceration T1 1 node b: 0.8–1.0 /uni00A0 mm, no <1.0 /uni00A0 mm ulceration; or <1.0 /uni00A0 mm with ulceration a: No ulceration N2 T2 b: With ulceration 2 or 3 nodes 1.01–2.0 /uni00A0 mm a: No ulceration N3 T3 b: With ulceration 2.01–4.0 /uni00A0 mm a: No ulceration T4 b: With ulceration

> 4 /uni00A0 mm Clinical staging of melanoma Stage IIa: T2b or T3a, N0, M0 Stage 0: Tis, N0, M0 Stage IIb: T3b or T4a, N0, M0 Stage Ia: T1a, N0, M0 Stage IIc: T4b, N0, M0 Stage Ib: T1b or T2a, N0, M0 LDH, lactate dehydrogenase; MSI denotes the presence of satellite lesions, in-transit lesions or local recurrence. Distant metastases M0 No detected distant metastases M1a a: Micrometastasis (no MSI) Skin, subcutaneous or distant lymph node b: Macrometastasis (no MSI) metastases (normal serum LDH levels) c: MSI present M1b a: Micrometastasis (no MSI) Lung metastases (normal serum LDH b: Macrometastasis (no MSI) levels) c: MSI present M1c a: Micrometastasis, >3 nodes All other visceral metastases or any distant (no MSI) metastases with elevated serum LDH b: Micrometastasis, >3 nodes levels or matted or 1 clinical node (no MSI) c: 1 clinical or occult node with MSI present M1d Brain metastases Stage III: any T, >N1, M0 Stage IV: any T, any N1, M1

Cutaneous squamous cell carcinoma

SCC is a malignant tumour of keratinising cells of the epider - mis or its appendages. It arises from the stratum basalis of the epidermis and expresses cytokeratins 1 and 10. Epidemiology Four BCCs occur for every SCC, which is the second most common form of skin cancer. It is strongly related to cumu - lative sun exposure and damage, especially in white-skinned individuals living nearer the equator. In the northern hemi - sphere it a ff ects the elderly , whereas it is not uncommon in sun-damaged, middle-aged white people in the souther n hemisphere. Everywhere, it is more common in men than in women. SCC is also associa ted with chronic inflammation (chronic sinus tracts, pre-existing scars, osteomyelitis, burns, vaccination points) and immunosuppression. When a SCC appears in a scar it is known as a Marjolin’s ulcer.

(a, b)

Squamous cell carcinoma /uni25CF /uni25CF /uni25CF IR causes SCC, as do chemical carcinogens (arsenicals, tar) and infection with HPV subtypes 5 and 16. There is also evidence that current and previous tobacco use doubles the relative risk of SCC. In the past, actinic (solar) keratoses (AKs), i.e. cutaneous horns and keratoacanthomas, were considered to be prema lignant lesions leading to SCC. Current thinking is to classify these lesions on a continuum of lesions, some of which can impro ve, as with other squamous cell tumours suc h as cervical intraepithelial neoplasia. AKs are areas of permanent sun damage in which there is dyskeratosis, partial-thickness cellular atypia and subep idermal inflammation, but an intact basement membrane (Figure 45.31). They ‘wax and wane’ macroscopically between macular and papular, with and without keratinous surfaces. Most improve after moisturisation and remain as erythema tous macules; however, up to 20% form SCC. When an AK has a keratinous surface with a height greater than its base diameter, it is termed a keratin horn; 10% will have an underlying SCC (Figure 45.32). Keratoacanthomas are rapidly growing, nodular tumour exhibiting symmetry around a central keratin-filled crater. John T Bowen , 1857–1941, Professor of Dermatology , Harvard University Medical School, Boston, MA, USA, described this condition in 1912. August Queyrat , 1856–1933, dermatologist, Paris, France, described this condition in 1911. - Current thinking is that, rather than being separate pre - malignant entities, they are better considered as self-healing - SCCs and, as such, are often reported by pathologists as ‘keratoacanthoma-like SCCs’ (Figure 45.33). Keratoacantho - mas are twice as common in men as in women and are usually found on the face or limbs of chronically sun-damaged 50- to - 70-year-old white-skinned individuals. T hey may be caused by HPV in a hair follicle during the growth phase and are also associated with smoking and chemical carcinogen exposure. Excision is recommended, rather than observation, as the dif - ferential diagnosis includes anaplastic SCC and the excision s scar is often better than that which remains after resolution. in situ and often develops as Bowen’s disease is SCC full-thickness dysplasia in hypertrophic AKs (Figure 45.34). SCC in situ usually presents as a slowly enlarging erythematous scaly plaque and may occur anywhere on the mucocutaneous surface of the body . On the glans penis, it is called erythroplasia of Queyrat (Figure 45.35). Topical therapy with 5-fluorouracil or imiquimod is an e ff ective treatment. Alternatives include surgical excision with a 4-mm margin or Mohs’ micrographic surgery for larger or recurrent lesions.

Associated with UVR, chronic in /f_l ammation, immunosuppression and chemical carcinogens High- and low-risk SCC Metastasis in 2% of low-risk and up to 30% of high-risk cases Figure 45.31 Actinic keratosis (courtesy of St John’s Institute for Dermatology, London, UK). Figure 45.32 Cutaneous horn (courtesy of St John’s Institute for Dermatology, London, UK). Figure 45.33 Keratoacanthoma (courtesy of St John’s Institute for Dermatology, London, UK).

Macroscopic The appearance of SCC may vary from smooth nodular, verrucous, papillomatous to ulcerating lesions. All ulcerate eventually as they grow . The ulcers have a characteristic everted edge and are surrounded by inflamed, indurated skin. Di ff erential diagnoses of SCC include: AK; BCC; pyoderma gangrenosum; warts; and lichen simplex chronicus (Figure 45.36). Albert Compton Broders , 1885–1964, American pathologist, MN, USA, and Chairman of the Department of Surgical Patholog MN, USA; for 1 year in 1935 Professor of Surgical Pathology and Director of Cancer Research, University of V graded rectal cancer in the USA in a similar manner to the one that Cuthbert Dukes used to classify it in the UK. A combination of Broders’ grading and Dukes’ classification gave a more accurate prognosis for rectal carcinoma than either method alone. Microscopic Characteristic irregular masses of squamous epithelium are noted to proliferate and

invade the dermis from the basal layer. The tumour stains positive for cytokeratins 1 and 10. SCC can be graded histologically according to Broders' grading, which describes the proportion of dedi ff erentiated cells in the tumour. Table 45.1 presents tumour classification and staging. Prognosis There are several independent prognostic variables for SCC: /uni25CF Depth: the deeper the lesion, the worse the prognosis. For SCC <2 /uni00A0 mm, metastasis is highly unlikely; if SCC >6 /uni00A0 mm, 15% will have metastasised. y, M a y o Clinic, Rochester, irginia, Charlottesville, V A, USA. Broders also

Figure 45.34 Bowen's disease – squamous cell carcinoma in situ (courtesy of St John's Institute for Dermatology, London, UK). TABLE 45.1 Tumour–node–metastasis (TNM) classi /f_i cation and staging of squamous cell carcinoma. Size Nodes NX TX Nodal involvement cannot be Primary tumour cannot be assessed assessed T0 N0 No evidence of primary tumour No regional nodes N1 Tis Spread to 1 ipsilateral nearby node In situ (con /f_i ned to full-thickness that is <3 /uni00A0 cm in diameter epidermal) disease T1 N2a Primary <2 /uni00A0 cm Spread to 1 ipsilateral nearby node that is 3–6 /uni00A0 cm in diameter T2 N2b Primary >2 /uni00A0 cm Spread to >1 ipsilateral nearby nodes but none >6 /uni00A0 cm in diameter T3 N2c Primary invasion of a facial bone Spread to contralateral node(s) but none are >6 /uni00A0 cm in diameter N3 T4 Spread to any node >6 /uni00A0 cm in Invasion of muscle, base of skull diameter or other bones Figure 45.35 Erythroplasia of Queyrat – squamous cell carcinoma in situ on the glans penis; also called Paget's disease of the penis (courtesy of St John's Institute for Dermatology, London, UK). Metastases Stages M0 Stage 0 No metastatic disease Tis, N0, M0 M1 Stage I Metastatic disease present T1, N0, M0 Stage II T2, N0, M0 Stage III T3, N0, M0 or T1–T3, N1, M0 Stage IV T1–T3, N2, M0 or any disease that is N3, or T4 or M1

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presentation (70%); usually arises in a pre-existing naevus after several years of slow c hange, followed by rapid g rowth in the months before presentation (Figure 45.37) . Nodularity within SSM heralds the onset of the vertical growth phase. NM accounts for 15% of all malignant melanoma and tends to be more aggressive than SSM, with a shorter clinical onset. These lesions often arise de novo in skin and are more common in men than in women, often presenting in middle age and usually on the trunk, head or neck (Figure 45.38) . They typically appear as blue/black papules, 1–2 /uni00A0 cm in diameter, and because they lack the hori - zontal growth phase they tend to be sharply demarcated. Up to 5% are amelanotic.

Rising incidence Genetic and acquired risk factors Super /f_i cial spreading form the most common Breslow thickness is the most important prognostic indicator Sentinel node biopsy (SNB) is useful for staging Super /f_i cial spreading melanoma (SSM). Nodular melanoma (NM). Figure 45.37 Super /f_i cial spreading melanoma (courtesy of St John’s Institute for Dermatology, London, UK).

LMM was previously also known as Hutchinson’s melanotic freckle. This variant presents as a slow-growing, variegated brown macule on the face, neck or hands of the elderly (Figure 45.39) . They are positively correlated with prolonged, intense sun exposure and a ff ect women more than men. They account for between 5% and 10% of malignant melanomas. LMMs are thought to have less metastatic potential than other variants as they take longer to enter a vertical growth phase. Nonetheless, when they have entered the vertical growth phase their metasta tic potential is the same as any other mel anoma. ALM a ff ects the soles and palms. It is rare in white-skinned individuals (2–8% of malignant melanoma) but more common in Afro-Caribbean, Hispanic and Asian populations (35–60%). It usually presents as a flat, irregular macule in later life; 25% are amelanotic and may mimic a fungal infection or py ogenic granuloma. Sir Jonathan Hutchinson , 1828–1913, surgeon, St Bartholomew’s Hospital, London, UK. Malignant melanomas under the fingernail are usually SSM rather than ALM. For finger- or toenail lesions it is vital to biopsy the nail matrix rather than just the pigment on the nail plate. A classical feature of a subungual melanoma is Hutchin - son’s sign: nail fold pigmentation that widens progressively to produce a triangular pigmented macule with associated nail dystrophy . The di ff erential diagnosis is ‘benign racial melanon - ychia’, which produces a linear dark streak under a nail in a - individual. Malignancy is unlikely if the nail fold dark-skinned is uninvolved (Figure 45.40). /uni25CF Amelanotic melanoma may present as a flesh-coloured skin lesion; as a metastasis from an unknown skin primary; or in the gastrointestinal tract, with obstruction or intus - susception.

Figure 45.38 Nodular melanoma (courtesy of St John’s Institute for Dermatology, London, UK). Lentigo maligna melanoma. Acral

lentiginous melanoma (ALM). (a) Figure 45.40 (a) Acral lentiginous melanoma on the sole of the foot. Note the swelling proximal to the nailfold. (c) Benign racial melanonychia. (Institute for Dermatology, London, UK.) Figure 45.39 Lentigo maligna melanoma (courtesy of St John’s Insti

tute for Dermatology, London, UK). Miscellaneous (b) (c) (b) Subungual melanoma – probably a super /f_i cial spreading melanoma. (a) courtesy of Mr AR Greenbaum; (b, c) courtesy of St John’s

neck region. It has a propensity for perineural infiltration and often recurs locally if not widely excised. It may be amelanotic clinically . Summary box 45.5 Macroscopic features in naevi suggestive of malignant melanoma /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF Microscopic Malignant change occurs in the melanocytes in the basal epidermis, while in situ atypical melanocytes are limited to the dermoepidermal junction and show no evidence of dermal involvement. During the horizontal growth phase, cells spread along the dermoepidermal junction; although they may breach the dermis, their migration is predominantly radial. During the vertical growth phase, the dermis may be invaded. The greater the depth of invasion, the greater the metastatic potential of the tumour. Management History and clinical examination should be directed at discov ering the primary lesion and identification of local, regional or distant spread. An excision biopsy with a 2- to 3-mm margin of skin and a cu ff of subdermal fat is acceptable. Incision biopsy is occasion ally indicated: for instance, in large lesions on the face where an excision biopsy of the whole lesion would be disfiguring. In experienced hands, observation and review every 2 /uni00A0 months may avoid biopsies in equivocal cases, but serial clin ical and dermoscopic photography by a clinician with exper tise in dermoscopy is mandatory when observ ation is chosen, rather than excision biopsy for definitive histopathological diagnosis. Dermoscopy coupled to computers with learning capability may soon outperform clinicians in melanoma diag nosis to

the point where screening becomes m uch easier. Biopsy and pathological examination provide the first step towards staging melanoma. The Breslow thickness of a mel anoma (measured to the nearest 0.1 /uni00A0 mm from the granular layer to the base of the tumour) is the most important prog nostic indica tor in the absence of lymph node metastases. The American Joint Committee on Cancer (AJCC) staging system takes lymph node involvement, distant metastases and evidence-based prognostic factors into account; these can then be used to guide optimum care and inclusion in researc studies for adjuvant or other treatments where applicable. The detail of the AJCC melanoma staging system has become too specialised for the ambit of this text; most spe cialists look up its detail as they assign a stage to a patient (Table 45.2). Guidelines for staging are controversial. The author suggests that investigations should be directed towards detecting occult disease, so as to upstage patients and treat them accurately and appropriately , the only cure for malignant melanoma currently being appropriate surgery . Thus, o ff ering SNB to patients with T2a disease and greater is critical and investigations for T3a disease and greater should be directed to individual clinical presentation. Local treatment The treatment for melanoma is surgery . Lentigo maligna (melanoma in situ) should be excised completely in most clin - ical situations because of the risk of it entering the vertical growth phase to become LMM. A complete excision requires no further treatment. For melanoma in situ a wide excision of 5 /uni00A0 mm is su ffi cient; for melanoma <1 /uni00A0 mm deep, a 1-cm margin is su ffi cient; and for deeper lesions, a 2-cm only margin is recommended, as there is no evidence that wider margins make a di ff erence. Regional lymph nodes The likelihood of metastatic spread to regional lymph nodes is proportional to the Breslow thickness of the melanoma. Management of regional lymph nodes has been a contentious topic for well over a century . Some advocated simultaneous elective lymph node clearance at the time of wide excision of the primary melanoma. Others favoured a therapeutic lymphadenectomy if regional metastases became clinically evident. Ideally , one would like to be able to select for treatment - those patients with the highest risk of metastatic spread. SNB, an investigation based on the fact that lymphatic metastases proceed in an orderly fashion and can be predicted by mapping the lymphatic drainage from a primary tumour to the first or - ‘sentinel’ node in the regional lymphatic basin, o ff ered that potential, but prospective controlled studies have shown no survival benefit from lymphadenectomy after positive SNB involving micrometastasis <0.2 /uni00A0 mm in a single node. This may - be because most patients have been treated by removing the - sentinel node, which was the only node involved at that stage. However, completion lymphadenectomy after positive SNB remains, on current evidence, the optimum method for regional control, if patients accept the morbidity associated - with regional lymphadenectomy . Adjuvant therapy - When mutation locks BRAF protein signalling to ‘on’, it a ff ects the mitogen-activated protein kinase (MAPK) cellular - pathway , promoting initiation, malignant transformation, tumour progression and metastasis in the 50% of malignant melanomas with BRAF V600 mutations. Targeted therapy in stage IV melanoma using dabrafenib or vemurafenib, which block BRAF action, has shown promising results with h metastatic melanoma. Trametinib has a di ff erent action on the MAPK pathway: stopping cell growth and promoting apoptosis. Combined use with dabrafenib to counter acquired - tumour resistance via MAPK pathway reactivation shows promising results in stage IV disease. Also, the selective immune

Change in size Shape Colour Thickness (elevation/nodularity or ulceration) Satellite lesions (pigment spreading into surrounding area) Tingling/itching/serosanguineous discharge (usually late signs)

checkpoint inhibitors ipilimumab and nivolumab demonstrate benefit in metastatic or unresectable melanoma. Over the last 5 years, five randomised prospective trials of adjuvant therapy have reported findings in the treatment of patients with stage II to IV disease. While all five trials showed a significant impro vement in relapse-free survival, only two of the trials were mature enough to report on overall survival. Prognosis The Breslow thickness of the primary tumour o ff ers the best correlation with survival in stage I disease. The higher the mitotic index, the poorer the prognosis of the primary tumour. This has greater significance than the presence or absence of ulceration. The presence of lymph node metastases is the single most important prognostic index in melanoma, outweighing both tumour and host factors. The number of a ff ected nodes and the presence of extranodal extension are also significant outcome predictors. Once regional nodes are clinically involved, 70–85% of patients will have occult distant metastases. Merkel cell (dermal mechanoreceptor) tumour This is an aggressive malignant tumour of Merkel cells and usually a ff ects the elderly . It is four times more common in Haig H Kasabach , 1898–1943, radiologist, Presbyterian Hospital, New Y ork, NY , USA. Katharine K Merritt , 1886–1986, pediatrician, Babies Hospital, Columbia University College of Physicians and Surgeons, New Y ork, NY , USA. Kasabach and Merritt described the condition as a joint paper in 1940. women than in men (Figure 45.41). Treatment is with wide local excision, aiming for a 25- to 30-mm margin, followed by radiotherapy .

Primary tumour Regional nodes NX TX Patients in whom nodes cannot be assessed Primary tumour cannot be assessed (has (e.g. previous excision) been curettage or has severely regressed) T0 N0 No evidence of primary tumour No node involvement Tis Melanoma in situ N1 a: <0.8 /uni00A0 mm, no ulceration T1 1 node b: 0.8–1.0 /uni00A0 mm, no <1.0 /uni00A0 mm ulceration; or <1.0 /uni00A0 mm with ulceration a: No ulceration N2 T2 b: With ulceration 2 or 3 nodes 1.01–2.0 /uni00A0 mm a: No ulceration N3 T3 b: With ulceration 2.01–4.0 /uni00A0 mm a: No ulceration T4 b: With ulceration

> 4 /uni00A0 mm Clinical staging of melanoma Stage IIa: T2b or T3a, N0, M0 Stage 0: Tis, N0, M0 Stage IIb: T3b or T4a, N0, M0 Stage Ia: T1a, N0, M0 Stage IIc: T4b, N0, M0 Stage Ib: T1b or T2a, N0, M0 LDH, lactate dehydrogenase; MSI denotes the presence of satellite lesions, in-transit lesions or local recurrence. Distant metastases M0 No detected distant metastases M1a a: Micrometastasis (no MSI) Skin, subcutaneous or distant lymph node b: Macrometastasis (no MSI) metastases (normal serum LDH levels) c: MSI present M1b a: Micrometastasis (no MSI) Lung metastases (normal serum LDH b: Macrometastasis (no MSI) levels) c: MSI present M1c a: Micrometastasis, >3 nodes All other visceral metastases or any distant (no MSI) metastases with elevated serum LDH b: Micrometastasis, >3 nodes levels or matted or 1 clinical node (no MSI) c: 1 clinical or occult node with MSI present M1d Brain metastases Stage III: any T, >N1, M0 Stage IV: any T, any N1, M1

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