Cutaneous melanoma

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Cutaneous melanoma is a malignancy arising from melanocytes of the skin. Incidence rates are rising, particularly in White populations. Cutaneous melanoma is typically driven by exposure to ultraviolet radiation from natural sunlight and indoor tanning, although there are several subtypes that are not related to ultraviolet radiation exposure. Primary melanomas are often darkly pigmented, but can be amelanotic, with diagnosis based on a combination of clinical and histopathological findings. Primary melanoma is treated with wide excision, with margins determined by tumour thickness. Further treatment depends on the disease stage (following histopathological examination and, where appropriate, sentinel lymph node biopsy) and can include surgery, checkpoint immunotherapy, targeted therapy, or radiotherapy. Systemic drug therapies are recommended as an adjunct to surgery in patients with resectable locoregional metastases and are the mainstay of treatment in advanced melanoma. Management of advanced melanoma is complex, particularly in those with cerebral metastasis. Multidisciplinary care is essential. Systemic drug therapies, particularly immune checkpoint inhibitors, have substantially increased melanoma survival following a series of landmark approvals from 2011 onward.

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Introduction

Melanoma is a malignant tumour arising from melanocytes. Melanocytes are cells that produce the melanin pigment and are found mostly in the skin, but also occur in the eyes, ears, leptomeninges, gastrointestinal tract, and oral, genital, and sinonasal mucous membranes. Cutaneous melanoma accounts for the bulk of melanoma diagnoses (>90%) in majority White populations, with melanomas of mucosal and uveal origin occurring more rarely (<1–5% of diagnoses, with country-specific variation). Cutaneous melanomas (typically acral) are also the most common among people with Black or Brown skin colour and in east Asian populations. Although most cutaneous melanomas are driven by exposure to ultraviolet radiation (UVR), there are several rarer subtypes that are not related to UVR exposure.[1,2]

The management of cutaneous melanoma has undergone several transformations over the past decade. Mortality rates in White populations decreased by 18% within 3 years following the introduction of effective systemic therapies,[3] which included effective treatment for asymptomatic brain metastasis. These therapies, particularly checkpoint immunotherapy, have been successfully used in the adjuvant setting and now have set a new standard in the neoadjuvant setting.[4] Simultaneously, important surgical trials have substantially altered practice around lymph node dissection in resectable melanoma.[5,6] The contemporary management of melanoma continues to develop as our ability to personalise care improves.

Epidemiological trends

The incidence of cutaneous melanoma has steadily risen in White populations worldwide since the 1950s, related to increased UVR exposure from natural sunlight and indoor tanning.[7,8] Incidence has far outpaced other cancers, which might reflect overdiagnosis from increased skin screening and skin biopsies, and histopathological overcalling of melanocytic neoplasms that might otherwise cause no harm.[9] The incidence of melanoma is approximately 25 new cases per 100 000 population in Europe, 30 cases per 100 000 population in the USA, and 60 cases per 100 000 population in Australia and New Zealand (figure 1).[10] In an analysis of six high-income countries with predominately European heritage, incidence rates of invasive melanoma doubled to quadrupled between 1982 and 2011.[13] Since the mid-1990s and early 2000s, the incidence of thin melanoma has been decreasing in young adults in the USA[14] and Australia,[15] suggesting the benefits of decades-long primary prevention programmes.[14,16] Mortality rates have dropped in White populations from high-income countries roughly since 2013 due to the rise of effective systemic therapies for advanced melanoma.[3] However, there has been no reduction in mortality observed in non-White populations or populations of lower socioeconomic status, who have instead shown an increase in prognostically poor thick melanomas.[17]

Search strategy and selection criteria

We searched PubMed (Jan 1, 2000, to Oct 31, 2022) using the terms "melanoma" in combination with the MeSH terms "incidence" or "mortality" or "overdiagnosis" or "risk factors" or "mass screening" or "dermoscopy" or "diagnosis" or "artificial intelligence" or "gene expression profiling" or "actinology" or "pathology" or "histopathology of biopsy" or "prognosis" or "treatment" or "classification" or "genomics" or "cancer staging". We also searched conference abstracts (2020–22) from the American Society of Clinical Oncology, European Society of Medical Oncology, and the Society for Melanoma Research annual congresses using the term "melanoma" in combination with the terms "immunotherapy" or "targeted therapy" or "neoadjuvant" or "adjuvant" or "circulating free DNA" or "radiotherapy" or "brain metastases" or "clinical trial". We focused on publications from the past 3 years, and select older publications that substantially affected the field of melanoma and cancer.

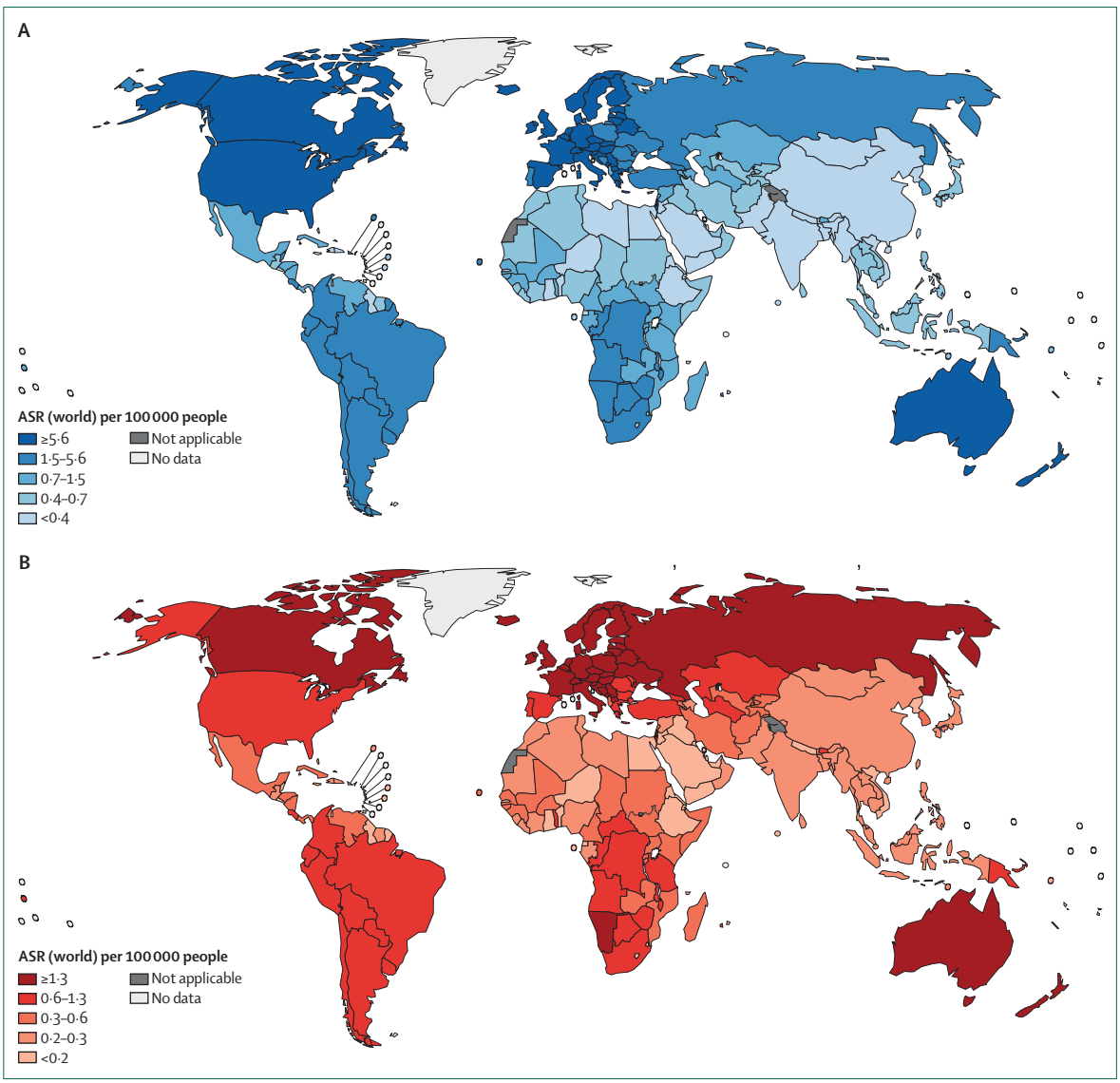

Figure 1: **Geographical burden of cutaneous melanoma**
Estimated global age-standardised incidence (A) and mortality (B) rates of cutaneous melanoma in 2020. Reproduced from Ferlay and colleagues [10,11] and Sung and colleagues,[12] with permission from the WHO International Agency for Research on Cancer. ASR=age-standardised rate.

For more on the **International Agency for Research on Cancer** see https://gco.iarc.fr/today/home

Causes

Cutaneous melanoma results from the stepwise accumulation of genetic mutations that alter cell proliferation, differentiation, and death (table 1).[29] Over 75% of cutaneous melanomas in White populations are estimated to be driven by the mutagenic effect of UVR.[7,30–32] UVR exposure has been shown to induce an addiction-like response in humans and pre-clinical models, mediated by the production of the opioid β-endorphin.[33]

Malignant transformation results from a complex interplay of UVR-initiated oncogenic aberrations (eg, mutations in *BRAF*, *NRAS*, or *KIT*), inherited germline genetic modifiers (eg, *CDKN2A*, *MC1R*, or *BAP1*), and phenotypic risk factors, including lighter skin tones, sun sensitivity, or naevus count or type (eg, dysplastic or large moles; table 1).[18–28,34] Melanomas on sun-protected skin, such as the trunk, tend to develop in patients with a higher naevus count and intermittent UVR exposure, and frequently carry somatic *BRAF* or *NRAS* mutations. Melanomas on the sun-exposed skin of the head, neck, and arms are associated with a low naevus count, chronic UVR exposure, severe sun damage, and *NRAS* mutations.[35,36] High naevus count and the presence of clinically atypical moles (also termed dysplastic naevi) are the most important phenotypic risk factors for melanoma development,[22] especially when combined with a family history of melanoma. Familial melanoma refers to melanomas that occur in at least two first-degree relatives and could result from heritable mutations or

shared environmental risk. Individuals with Fitzpatrick skin type I (ie, red hair with blue or green eyes) are also at elevated risk.[26] Increased risk of melanoma has been associated with immune perturbation following solid organ or haematopoietic cell transplantation, other immunodeficiencies,[27] and some genodermatoses (eg, xeroderma pigmentosum).[28]

Primary prevention aimed at reducing UVR exposure and increasing sun protective behaviours is recommended by cancer prevention authorities worldwide.[37,38] Regular sunscreen use has been shown to reduce the incidence of skin cancers, including melanoma, in a prospective randomised trial conducted in Australia.[39] Sunscreen UVR filters vary among countries and consumer safety concerns often impede their use. Sunscreen is an adjunct to the use of protective clothing, hats, and eyewear, as is sun avoidance during peak UVR hours.

Melanoma subtypes and molecular features

In the early 2010s, a better understanding of the inter-related molecular, clinical, and pathological features of melanoma tumours began to emerge,[40–43] resulting in the development of a novel classification system with nine melanoma subtypes or pathways (table 2).[2] This new system was developed by WHO and builds on the traditional Clark-McGovern clinicopathological system.[49,50] Each of the subtypes are characterised by distinct epidemiological, clinical, histopathological, and genomic features. Within the nine subtypes, precursor lesions and intermediate forms of neoplastic progression (collectively termed melanocytomas)[51] were formally recognised by WHO for the first time. In contrast to naevi, melanocytomas are characterised by having a second genetic mutation and an increased, although still low, risk of progression to melanoma.

The two main pathways of melanoma formation include superficial spreading melanoma (low cumulative sun damage melanoma) and lentigo maligna melanoma (high cumulative sun damage melanoma). Superficial spreading melanomas typically arise in sun-exposed skin with little solar elastosis on the trunk or back of younger adult patients, often in association with a precursor naevus, whereas lentigo maligna melanomas tend to occur on the head and neck of older patients and are associated with severe solar elastosis. Superficial spreading melanomas frequently possess *BRAF*^{V600E} (ie, Val600Glu) mutations, whereas lentigo maligna melanomas often do not, instead carrying mutations in *NF1* (loss-of-function) or *NRAS*.[40,52] Desmoplastic melanoma is an uncommon subtype that typically occurs in severely sun-damaged skin of the head and neck in older patients and can be difficult to diagnose, both clinically and pathologically. Compared with other subtypes, pure (≥90%) desmoplastic melanoma has less frequent involvement of the sentinel lymph node (SLN)[53] and a better response to immunotherapy,[54] probably due in part to its higher tumour mutation burden.[44,55]

	Relative risk measure
Ultraviolet radiation overexposure	
Natural sunlight	
Total sun exposure*[18]	1·3
History of sunburn[18]	2·0
First episode of sunburn in childhood (age <13 years)[19]	2·3
Severe sunburns (ten or more burns)[20]	2·4
Indoor tanning beds[21]	
Any use (one or more sessions)	1·3
Early exposure (age ≤20 years)	1·5
High frequency use (ten or more sessions per year)	1·5
Non-modifiable	
Male sex[20]	1·7
High naevus count (>100)†[22]	6·9
Atypical naevi[22]	10·1
First-degree relative with melanoma[23]	1·7
Previous melanoma[24]	10·4
Previous non-melanoma skin cancer[25]	2·7
Red hair colour[26]	2·4
Blue eye colour[26]	1·6
Immunosuppression[27]	2·1–3·4
Xeroderma pigmentosum[28]	193

Most studies were conducted in White populations. *History of any kind of sun exposure, including intermittent exposure, chronic exposure, or sunburns. †Compared with patients with fewer than 15 naevi.

Table 1: **Risk factors for cutaneous melanoma**

Role of screening

Screening for melanoma, whether led by patients or physicians, should facilitate the early detection of tumours that will have metastatic or lethal potential if left untreated. Melanomas detected by physicians tend to be thinner, and are therefore associated with a better prognosis, than those detected by patients or family members. However, screening programmes have not shown any subsequent reduction in melanoma-specific mortality (aside from a concerted screening effort in northern Germany,[56,57] where the survival benefit was lost when the programme was rolled out nationally).[58,59] In the absence of prospective randomised trials to confirm a survival benefit, the US Preventive Services Task Force considers there to be "insufficient evidence to balance the benefits and harms" of skin cancer screening.[60] Primary care-based screening following directed skin cancer training in the USA resulted in increased detection of in situ and thin melanomas over 5 years of follow-up, but no reduction in thicker melanomas (figure 2).[63,64] New technologies to facilitate screening efforts, including artificial intelligence (AI)-based image classification approaches, are in development. Overall, however, population-based screening for melanoma is not recommended in most countries. Current screening efforts are targeted at individuals at high risk (eg,

	Solar						Non-solar					
	1				2	3	4	5	6	7	8	9
Pathway endpoint	Low-CSD melanoma (especially superficial spreading melanoma)	Low-CSD melanoma (especially superficial spreading melanoma)	Low-CSD melanoma (especially superficial spreading melanoma)	Low-CSD melanoma (especially superficial spreading melanoma)	High-CSD melanoma (lentigo maligna melanoma)	Desmoplastic melanoma	Spitz melanoma	Acral melanoma	Mucosal melanoma	Melanoma arising in a congenital naevus	Melanoma arising in a blue naevus	Uveal melanoma
Typical age at melanoma diagnosis	Young and middle-aged adults	Young and middle-aged adults	Young and middle-aged adults	Young and middle-aged adults	Older adults	Older adults	Children and adolescents	Middle-aged and older adults	Middle-aged and older adults	Children	Middle-aged adults	Middle-aged and older adults
Type of melanoma	Cutaneous	Cutaneous	Cutaneous	Cutaneous	Cutaneous	Cutaneous	Cutaneous	Cutaneous	Mucosal	Cutaneous	Cutaneous	Uveal
Common sites	Trunk in men, legs in women	Trunk in men, legs in women	Trunk in men, legs in women	Trunk in men, legs in women	Head and neck	Head and neck	Any	Glabrous skin (volar aspect of fingers and toes, palms and soles, or nail beds)	Mucosae (genital sites, oral and nasal cavities, or conjunctiva)	Trunk, lower extremities, or scalp	Scalp and gluteal or sacral region	Choroid, ciliary body, or iris
Associated CSD	Low	Low	Low	Low	High	High	Low or incidental	Low or incidental	Low or incidental (higher in conjunctival)	Low or incidental	Low or incidental	Low or incidental
Potential precursor lesion	Naevus	Naevus	Naevus	Naevus	AMP	AMP	Spitz naevus	Acral naevus	Melanosis with or without AMP	Congenital naevus	Blue naevus	Uveal naevus
Intermediate lesions*	Melanoma in situ (superficial spreading melanoma in situ)	*BAP1*-inactivated naevus or melanocytoma	Deep penetrating naevus or melanocytoma	Pigmented epithelioid melanocytoma	Lentigo maligna melanoma in situ	Melanoma in situ	Atypical Spitz tumour (melanocytoma)	Acral melanoma in situ	Mucosal melanoma in situ	Atypical proliferative nodule or melanoma in situ in congenital naevus (melanocytoma)	(Atypical) cellular blue naevus (melanocytoma)	..
Malignant neoplasms	Low-CSD melanoma or superficial spreading melanoma	Melanoma in *BAP1*-inactivated naevus (rare)	Melanoma in deep penetrating naevus (rare)	Melanoma in pigmented epithelioid melanocytoma (rare)	High-CSD melanoma or lentigo maligna melanoma	Desmoplastic melanoma	Malignant Spitz tumour or Spitz melanoma	Acral melanoma	Mucosal lentiginous melanoma	Melanoma in congenital naevus	Melanoma in blue naevus	Uveal melanoma

(Table 2 continues on next page)

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	Solar				Non-solar								
	1				2	3	4	5	6	7	8	9	
(Continued from previous page)													
Relative TMB[44-46]	High	High	High	High	Very high	Very high	Low (scarce data)	Low	Low (except conjunctival melanoma, which is high)	Variable (usually low)	High	Very low (iris > other sites)	
Common mutations[12,47]	*BRAF*[V600E]† or *NRAS*†	*BRAF*† or *NRAS*† and *BAP1*†	*BRAF*†, *MAP2K1*† or *NRAS*†, and *CTNNb1*† or *APC*†	*BRAF*† and *PRKAR1A*† or *PRKCA*†	*NRAS*†, *BRAF*† (non-V600E), *KIT*†, or *NF1*†; *TERT*, *CDKN2A*, *TP53*, *PTEN*, or *RAC1*	*NF1*†, *ERBB2*, *MAP2K1*, *MAP3K1*, *BRAF*, *EGFR*, or *MET*; *TERT*, *NFKBIE*, *NRAS*, *PIK3CA*, or *PTPN11*	*HRAS*†, *ALK*†, *ROS1*†, *RET*†, *NTRK1*†, *NTRK3*†, *BRAF*† or *MET*†; *CDKN2A*	*KIT*†, *NRAS*†, *BRAF*†, *HRAS*†, *KRAS*†, *NTRK3*†, *ALK*†, or *NF1*†; *CDKN2A*, *TERT*, *CCND1*, or *GAB2*	*KIT*†, *NRAS*†, *KRAS*†, or *BRAF*†; *NF1*†, *CDKN2A*, *SF3B1*, *CCND1*, *CDK4*, or *MDM2*	*NRAS*†, *BRAF*[K601E]† (small lesions), or *BRAF*†	*GNAQ*†, *GNA11*†, or *CYSLTR2*†; *BAP1*, *EIF1AX*, or *SF3B1*	*BAP1*, *EIF1AX*, *GNA11*, *GNAQ*, or *SF3B1*[48]	
Chromosomal structural variants[44,46]	Low	Low	Low	Low	Low	Low	Low	High	High	Low	Low	Very low	

Modified from Elder and colleagues;[7] by permission of David Elder. AMP=atypical melanocytic proliferation. CSD=cumulative sun damage. TMB=tumour mutation burden. *Including melanocytomas. †Genes present in benign or borderline lesions.

Table 2: **Nine pathways of melanoma formation**

first-degree relatives of patients with melanoma). In Australia, observational studies have shown benefit from melanoma screening in groups at high risk.[65–67] Clinical trials investigating targeted screening on the basis of genotypic, phenotypic, and molecular risk are underway.[68]

Diagnosis

Clinical diagnosis

To the naked eye, melanomas are typically darkly pigmented lesions in varying shades of tan, brown, and black (figure 3A). However, they can also be the colour of a patient's skin or pink (amelanotic), which can hinder early detection. Any changing or growing pigmented or clinically amelanotic skin lesion warrants clinical evaluation, preferably by a dermatologist or primary care physician with appropriate expertise. The use of dermoscopy (figure 3B) has revolutionised our ability to examine suspicious skin lesions, although training is essential for diagnostic accuracy.[69] Total body photography and serial digital dermoscopy are standard approaches to monitoring patients with multiple atypical moles (or dysplastic naevus syndrome) to aid early detection. Additional imaging techniques, including reflectance confocal microscopy, optical coherence tomography, electrical impedance spectroscopy, and AI, can guide decision making around the need for skin biopsy. Advances in molecular diagnostic techniques might also reduce the need for skin biopsy. However, many of these techniques (particularly gene expression profiling) show high sensitivity and low specificity for melanoma, and could lead to more biopsies of banal melanocytic neoplasms. Although AI approaches for melanoma detection showed high performance during their development,[70] pitfalls in diagnostic accuracy and sources of bias[71] were observed in real-world use.[72] Prospective studies are needed before widespread clinical implementation of AI is warranted.[73] In addition, commonly used AI training sets (such as the International Skin Imaging Collaboration: Melanoma Project) are typically derived from fair-skinned populations, resulting in poorer performance in people with Black or Brown skin.[74,75] Ongoing development of AI tools and other imaging technologies should improve early detection of melanoma in future.

For more on the **International Skin Imaging Collaboration** see https://www.isic-archive.com/#!/topWithHeader/wideContentTop/main

Pathological diagnosis

Although melanoma might be suspected clinically, a biopsy and pathological assessment are necessary for definitive diagnosis in most cases. An appropriate biopsy (an excision biopsy with narrow margins is generally recommended) and clinical information is essential for an accurate diagnosis and optimal initial management.[76] Important information to contextualise the pathology includes patient age, site of the lesion, whether the lesion is new or there is evidence of recent

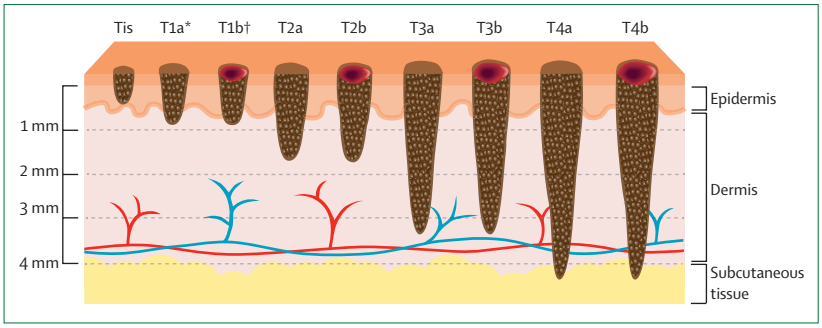

Figure 2: **Cutaneous melanoma T categories**
Representation of the cutaneous melanoma T categories as per the American Joint Committee on Cancer 8th edition staging manual.[61,62] T categories are defined by tumour thickness and the presence or absence of ulceration in the primary tumour. Tis=melanoma in situ. *Thinner than 0·8 mm without ulceration. †Thinner than 0·8 mm with ulceration or 0·8–1·0 mm thick with or without ulceration.

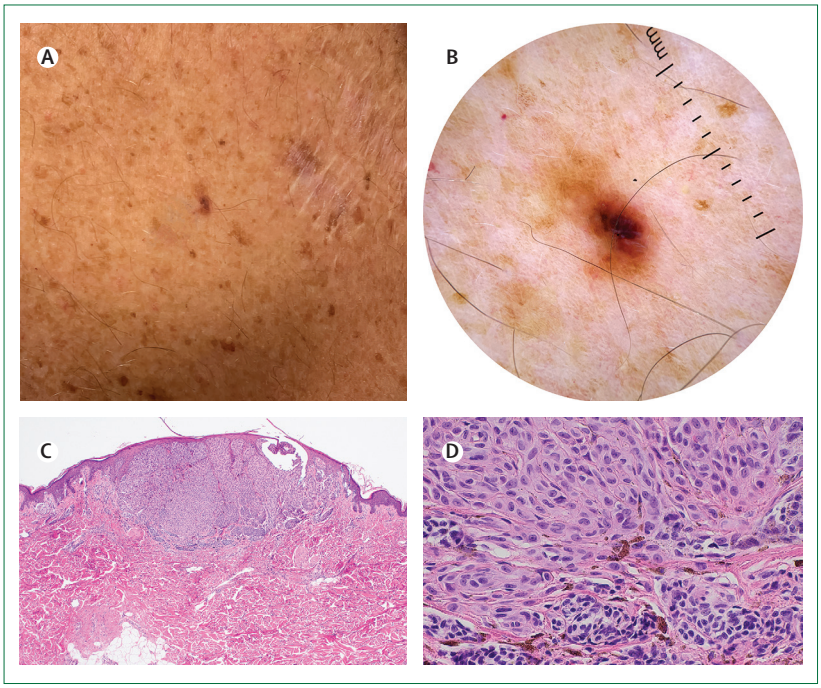

Figure 3: **Clinical, dermoscopic, and histopathological features of cutaneous primary melanoma**
Primary cutaneous melanoma arising from a pre-existing naevus on the right interscapular region of a man aged 66 years. The lesion had recently changed with development of an enlarging asymmetrical and variegated dark brown focus within the pre-existing pale brown macule (clinical photograph [A] and dermoscopic photograph [B]). Histopathology showed a non-ulcerated 1·0 mm thick (pT1b)[61,62] melanoma with an associated naevus (40x magnification [C] and 400x magnification [D]).

See Online for appendix

change within a pre-existing lesion, and any previous lesional trauma or biopsy. Clinical photographs (figure 3A) often assist with pathological interpretation.

Histopathology (figure 3C, D), interpreted in the clinical context, is the gold standard for a melanoma diagnosis, sometimes supplemented by immunohistochemistry or molecular testing, or both. Classification of nine melanoma subtypes (table 2)[47] in 2018 has resulted in the development of new tools to aid in tumour classification, including various immunohistochemical antibodies.[77–82] Fluorescence in situ hybridisation,[83] comparative genomic hybridisation, targeted gene sequencing,[84] and gene expression profiling[85] are useful in select cases. Occasionally, the classification of a melanocytic tumour is uncertain. Such lesions have been described under several terms including borderline tumours and melanocytic tumours of uncertain malignant potential.[86,87]

Pathological overcalling of benign melanocytic lesions as melanoma (eg, severely dysplastic naevi being misdiagnosed as in situ or thin invasive melanomas) has emerged as an important concern.[9,88] Overlapping histopathological features exist between atypical naevi and in situ and thin invasive melanomas, resulting in low interobserver reproducibility of pathological diagnosis.[89] Furthermore, there is evidence of drift (lowering) of the diagnostic threshold for melanoma over time.[90]

Pathological features are crucial to informing initial disease management and must be clearly reported. Prognostic pathological features, including tumour thickness and ulceration (figure 2), mitotic rate, lymphovascular invasion, tumour-infiltrating lymphocytes, and regression, are particularly important.[91–93] Factors associated with local recurrence, including involvement of the tumour margins, presence and extent of a desmoplastic melanoma component, and nerve involvement (known as neurotropism), should also be documented. The use of a synoptic or structured format (appendix p 2) ensures that all relevant features are documented, and assists in communications; this approach is now mandated in many countries.[94]

Determining whether a patient has progressed to metastatic disease also requires histopathological confirmation, typically achieved with a fine needle or core biopsy.

Contemporary management of early melanoma

Management of primary cutaneous melanoma

Surgery

Primary cutaneous melanoma is typically managed with wide excision (sometimes termed excision with a safety margin). Surgical margins are radial and should be measured from the edge of the biopsy site or residual intact component. The width of the margin is determined by the histologically assessed tumour thickness. Wide excision is performed down to, but not including, the underlying muscular fascia, the extent of which might be modified to accommodate anatomical or functional considerations. For patients with invasive melanoma with a tumour thickness (figure 2) of 1·0 mm or less (T1) or greater than 2 mm (T3–T4), a 1 cm and 2 cm radial surgical margin, respectively, is recommended.[95–97] In Australia, a 1–2 cm margin might be considered for T2 and T3 melanomas.[61,62,97] For patients whose melanoma is between 1 mm and 2 mm thick (T2), guideline-based approaches vary and include 1–2 cm margins.[95–97] The potential for narrower excision margins in patients with high-risk primary tumours (≥T2b) is of

great interest, because this approach might improve surgical morbidity, reduce the need for skin grafts or other more advanced reconstructions, improve patient-reported outcomes, and harmonise international guidelines. To this end, the international Melanoma Margins Trial (NCT02385214) is currently investigating whether a 1 cm surgical margin is non-inferior to a 2 cm margin for patients with T2b–T4 melanoma. For melanoma in situ, excision margins of 0·5 cm are generally recommended. Margins of more than 0·5 cm might be required to achieve histologically negative margins for lentigo maligna (a type of melanoma in situ) resulting from subclinical extension.[95]

Margin controlled excision (also known as Mohs micrographic surgery) and staged excision with permanent sections provide comprehensive histopathological margin assessment, and are widely used for excision of non-melanoma (keratinocyte) skin cancers. These techniques are not typically recommended for melanoma, except in select cases of melanoma in situ or T1a lentigo maligna melanoma, particularly on anatomically constrained sites (eg, the face).[95] Surgical techniques that reduce sampling error when evaluating margin status and allow for more rapid surgical clearance of positive margins remain an area of active investigation,[98] and their consideration should be in the context of multidisciplinary team management.[99]

Non-surgical approaches

Non-surgical approaches to lentigo maligna, including the use of topical imiquimod 5% cream and radiation, have been suggested, but appear inferior to surgical excision.[100] Second-line use of imiquimod versus radiation for lentigo maligna is currently under investigation in the randomised RADICAL trial (NCT02394132).

Staging procedures and other prognostic tools

Role of sentinel node biopsy

In addition to wide excision of the primary tumour, management of newly diagnosed melanoma includes assessment of the patient's regional lymph node basin or basins. In patients with clinically node-negative disease, lymphatic mapping (LM) and SLN biopsy (SLNB) are routinely used to identify occult regional nodal metastasis by identification and histological examination of the SLN or SLNs. The prognostic significance of this approach has been established.[101,102] If LM and SLNB are indicated, they should be performed concomitantly with wide excision, where possible.[103]

LM and SLNB are generally recommended for patients whose risk of possessing a histologically positive SLN is at least 5–10%.[95–97] This range includes most patients with an American Joint Committee on Cancer 8th edition[61,62] primary melanoma T category of T2 or higher and a subset of patients with high-risk T1 melanoma (ie, T1b, or T1a melanomas with high-risk features including a mitotic rate of ≥2/mm², lymphovascular invasion, or a positive deep biopsy margin, particularly in younger patients [SLN positivity is inversely associated with age][104]). Only a small number of patients with T1a melanoma are typically offered LM and SLNB; the threshold for their use is also impacted by comorbidity and patient preference. Primary tumour regression appears not to be a risk factor for SLN positivity,[105] and is no longer used to recommend a patient for SLNB. Data suggest that adjuvant immunotherapy is effective regardless of nodal involvement,[106–108] and there could be an argument to omit SLNB in the case that management is unchanged.[106–108] Currently, however, SLNB remains the best method to accurately stage the draining nodal basins of clinically node-negative patients who are deemed to be at sufficient risk of harbouring occult regional nodal metastasis, providing prognostic information, improved regional basin control, and assistance with treatment selection after initial surgery.

Systemic staging at diagnosis

Systemic staging should be performed in all patients with a new diagnosis of invasive melanoma. This involves clinical examination of all skin and nodal basins to assess for clinically suspicious regional lymphadenopathy, in-transit or satellite metastases, and additional primary melanomas. In patients with stage IIB[61,62] disease or higher, guidelines recommend cross-sectional imaging (CT, PET-CT, or MRI), conventional CT or PET-CT imaging, and cerebral imaging (CT or MRI). PET-CT is particularly helpful in patients with primary tumours on the extremities. Imaging is important even in patients at high risk with clinically node-negative disease (ie, stage IIB or IIC), to exclude occult locoregional or distant metastases that would indicate systemic therapy. Overall, however, the incidence of synchronous radiographic-only evidence of regional or distant disease at diagnosis is low. Imaging studies also serve as a baseline for surveillance or as a component of screening for clinical trials.

For patients whose clinical nodal examination is associated with suspicious or equivocal findings, image-guided follow-up (typically with ultrasound) is recommended. Due to low sensitivity, routine ultrasonography of regional nodal basins is not recommended for patients with clinically node-negative melanoma.[109,110] If considered, all regional nodal basins at risk (per lymphoscintigraphic imaging) should be imaged. This technique requires specific expertise and the appreciation of findings that are concerning for nodal metastasis.[95] Importantly, ultrasound is not a substitute for SLNB.[109,110]

Risk prediction tools

A variety of tools have been developed to improve the predictive and prognostic assessment of patients with melanoma. These tools include nomograms and other models that incorporate weighted clinicopathological factors to predict the risk of SLN positivity,[111] as well as risk of non-SLN tumour involvement,[112,113] overall

survival, melanoma-specific survival, metastasis, and site-specific recurrence.[111,114–116] Mitotic rate and SLN tumour burden are particularly important conventional prognostic factors (but are not currently used for staging).[62,116,117] Gene expression profiling approaches can also be used in risk prediction, either as a standalone test or incorporated with staging parameters.[118,119] Despite national guidelines in the USA recommending against the routine use of gene expression profiling (due to the absence of proven clinical use beyond multiple relevant clinical and pathological factors),[95,98] practitioner uptake varies and may cause confusion for patients, especially in stage I disease in which false positive results are common. Other approaches under investigation include tumour mutation burden and interferon-gamma (IFN-γ) gene signatures, the latter being a measure of IFN-γ-responsive gene expression within tumour cells, which are expressed in a tumour microenvironment where IFN-γ is produced by immune cells. These tools are designed to identify patients with a high risk of recurrence[120] and other patients who might benefit from adjuvant anti-PD-1-based immunotherapy.

The role of circulating tumour DNA (ctDNA) as a predictive tool in early stage melanoma is developing. Studies in resected stage II or III melanoma suggest ctDNA positivity is associated with increased recurrence and poorer survival outcomes (although the prevalence of ctDNA positivity after complete resection of melanoma is low, ranging from 12% to 16%).[121–123] Loss of ctDNA positivity during adjuvant therapy has been associated with reduced risk of recurrence.[122]

Management of resectable locoregional metastases

Surgery

The surgical management of patients with locoregional metastasis is evolving. Although completion lymph node dissection has historically been the standard of care for patients with clinically negative nodes but SLN positivity, this approach is no longer routinely recommended. The randomised MSLT-II[5] and DeCOG-SLT[6] trials found no melanoma-specific survival benefit with completion lymph node dissection compared with nodal observation (via nodal basin ultrasound, termed active surveillance) for patients who are SLN positive (these trials were performed before the emergence of effective systemic therapies). Observations following the MSLT-II trial[124] suggest that isolated regional node recurrence can be salvaged in patients who are SLN positive receiving adjuvant therapy and active surveillance.

For patients with biopsy-proven regional nodal disease without distant metastasis, therapeutic lymph node dissection is typically performed concomitantly with primary tumour wide excision. Several trials have explored the role of neoadjuvant therapy in this context,[125,126] ushering in a shift towards multidisciplinary, team-based neoadjuvant therapy[95,126,127] that could preclude the need for therapeutic lymph node dissection in some patients.

Adjunct perioperative therapy

Post-surgical recurrence is common, particularly in patients with high-risk resectable melanoma (stages IIB or IIC, IIIB–IIID, and IV), and can be targeted with perioperative drug therapy. There are two approaches to perioperative drug therapy: adjuvant therapy, which is administered after surgery, and neoadjuvant therapy, which is administered before surgery. Adjuvant anti-PD-1 checkpoint immunotherapy or BRAF-targeted therapy is the current standard for patients with high-risk resectable melanoma, and has been shown to reduce the risk of recurrence and improve distant metastasis-free survival (table 3). An overall survival benefit is yet to be established for most agents. Neoadjuvant checkpoint immunotherapy is emerging as the new standard in clinically detectable and resectable stage III melanoma,[141] but is yet to enter routine care (table 3).

Adjuvant ipilimumab (an anti-CTLA-4 antibody) was the first checkpoint immunotherapy to show statistically significant and clinically meaningful recurrence-free and overall survival benefits in resected stage III melanoma compared with placebo; however, it had a poor safety profile and was not adopted as a standard therapy.[128–130] Adjuvant anti-PD-1 therapy (nivolumab or pembrolizumab) showed a significant and long-lasting[132,136] recurrence-free survival benefit over ipilimumab (hazard ratio [HR] 0·65, 97·56% CI 0·51–0·83; p<0·001) or placebo (HR 0·57, 95% CI 0·43–0·74; p<0·001) in the respective Checkmate-238[131] and EORTC 1325/KEYNOTE-054[134] phase 3 trials in resected stage III (and IV for Checkmate-238) melanoma. There was a similar significant improvement in distant metastasis-free survival in both studies,[132,135,137] but no improvement in overall survival for nivolumab versus ipilimumab.[132] Nivolumab and pembrolizumab were substantially more tolerable than ipilimumab.[131,142] The Checkmate 915 trial[133] examined whether outcomes with adjuvant nivolumab could be further improved for resected stage IIIB–IV melanoma, without compromising safety, by adding a low dose, low frequency regimen of ipilimumab 1 mg/kg every 6 weeks. There was no difference in recurrence-free survival, and a 20% increase in the rate of treatment-related grade 3 or 4 adverse events in patients who received ipilimumab versus those who did not.[133] This result was in contrast to the randomised phase 2 IMMUNED trial, which found an overall survival benefit with adjuvant ipilimumab (at the standard dose of 3 mg/kg) plus nivolumab versus placebo, but not nivolumab monotherapy versus placebo, in resected stage IV melanoma.[143] In 2023, a randomised phase 2 study of pembrolizumab plus a personalised mRNA-based melanoma vaccine showed a 44% reduction in the risk of recurrence (HR 0·56, 95% CI 0·31–1·02; p=0·0266) compared with pembrolizumab alone in patients with resected stage IIIB–IV melanoma,[140] and was granted breakthrough therapy designation by the US Food and Drug Administration.[144] Currently, however, single-agent anti-PD-1 therapy is the standard adjuvant regimen for

	Phase	AJCC stage (8th edition unless otherwise specified)	Efficacy outcomes							
			RFS hazard ratio (p value)*	pRR	2-year RFS	5-year RFS	2-year DMFS	5-year DMFS	2-year OS	5-year OS
Adjuvant										
Meta-analysis (2017;[128] N=7744)										
IFN-α group	2–3	III	0·86 (p<0·00001)	..	49%†	38%	NA	NA	69%†	49%
No IFN-α group	2–3	III	0·86 (p<0·00001)	..	45%†	34%	NA	NA	67%†	46%
EORTC 18071 (2015[129] and 2016;[130] N=951)										
Ipilimumab 10 mg/kg group	3	IIIA (>1 mm metastasis), IIIB, and IIIC‡	0·75 (p=0·0013)	..	52%†	41%	62%†	48%	83%†	65%
Placebo group	3	IIIA (>1 mm metastasis), IIIB, and IIIC‡	0·75 (p=0·0013)	..	44%†	30%	53%†	39%	75%†	54%
CheckMate-238 (2017[131] and 2020;[132] N=906)										
Nivolumab 3 mg/kg group	3	IIIB–IV‡	0·65 (p<0·001)	..	62%†	NA	70%†	NA	88%†	NA
Ipilimumab 10 mg/kg group	3	IIIB–IV‡	0·65 (p<0·001)	..	50%†	NA	64%†	NA	89%†	NA
CheckMate 915 (2023;[133] N=1833)										
Ipilimumab 1 mg/kg plus nivolumab 240 mg§ group	3	IIIB–IV	0·92 (p=0·269)	..	65%	NA	75%	NA	90%	NA
Nivolumab 480 mg group	3	IIIB–IV	0·92 (p=0·269)	..	63%	NA	77%	NA	92%	NA
KEYNOTE-054 (2018,[134] 2020,[135] 2021,[136] and 2022;[137] N=1019)										
Pembrolizumab 200 mg group	3	IIIA (>1 mm metastasis), IIIB, and IIIC‡	0·57 (p<0·001)	..	68%	55%	74%	61%	NA	NA
Placebo group	3	IIIA (>1 mm metastasis), IIIB, and IIIC‡	0·57 (p<0·001)	..	47%	38%	56%	44%	NA	NA
COMBI-AD (2017[138] and 2020;[139] N=870)										
Dabrafenib 150 mg plus trametinib 2 mg group	3	IIIA (>1 mm metastasis), IIIB, and IIIC‡	0·47 (p<0·001)	..	67%	52%	78%†	65%	91%	NA
Placebo group	3	IIIA (>1 mm metastasis), IIIB, and IIIC‡	0·47 (p<0·001)	..	44	36%	60%†	54%	83%	NA
KEYNOTE-716 (2022;[107,108] N=976)										
Pembrolizumab 200 mg group	3	IIB and IIC	0·65 (p=0·0066)	..	69%†	NA	90%†	NA	NA	NA
Placebo group	3	IIB and IIC	0·65 (p=0·0066)	..	74%†	NA	83%†	NA	NA	NA
CheckMate 76K (2022;[106] N=790)										
Nivolumab 480 mg group	3	IIB and IIC	0·42 (p<0·0001)	..	75%†	NA	83%†	NA	NA	NA
Placebo group	3	IIB and IIC	0·42 (p<0·0001)	..	53%†	NA	70%†	NA	NA	NA
KEYNOTE-942 (2023;[140] N=157)										
mRNA-4157 plus pembrolizumab 200 mg group	2b	III and IV	0·56 (p=0·0266)	..	NA	NA	NA	NA	NA	NA
Pembrolizumab 200 mg group	2b	III and IV	0·56 (p=0·0266)	..	NA	NA	NA	NA	NA	NA

(Table 3 continues on next page)

	Phase	AJCC stage (8th edition unless otherwise specified)	Efficacy outcomes							
			RFS hazard ratio (p value)*	pRR	2-year RFS	5-year RFS	2-year DMFS	5-year DMFS	2-year OS	5-year OS
(Continued from previous page)										
Neoadjuvant										
Pooled analysis (2021;[126] N=189)										
Dabrafenib 150 mg plus trametinib 2 mg group	1–2	III	NA	67%	47%	NA	NA	NA	86%	NA
Single-agent anti-PD-1 group	1–2	III	NA	34%	59%	NA	NA	NA	76%	NA
Anti-PD-1 plus anti-CTLA-4 group	1–2	III	NA	75%	80%	NA	NA	NA	96%	NA
SWOG S1801 (2023;[4] N=345)										
Neoadjuvant pembrolizumab 200 mg group	2	III and IV	0·58 (p=0·004)	NA	72%¶	NA	NA	NA	NA	NA
Adjuvant pembrolizumab 200 mg group	2	III and IV	0·58 (p=0·004)	..	49%¶	NA	NA	NA	NA	NA

Percentages rounded to nearest integer. AJCC=American Joint Committee on Cancer. DMFS=distant metastasis-free survival. NA=not available. OS=overall survival. pRR=pathological response rate. RFS=recurrence-free survival. *Hazard ratio at primary analysis for primary endpoint RFS. †Estimated from the Kaplan-Meier curve. ‡AJCC 7th edition. §Every 6 weeks. ¶Event-free survival

Table 3: **Key trials in systemic drug treatment for resected or resectable melanoma**

patients with resected stage III or IV melanoma (table 3).[95–97] Single-agent anti-PD-1 therapy (nivolumab and pembrolizumab) has also shown a statistically significant reduction in the risk of recurrence and distant metastasis in patients with resected stage IIB or IIC melanoma versus placebo (table 3).[106–108]

BRAF-targeted and MEK-targeted therapies are also available for adjuvant use in the 40% of patients with *BRAF*^{V600}-mutant melanoma. When compared with placebo in the COMBI-AD trial, dabrafenib plus trametinib significantly improved recurrence-free survival (HR 0·47, 95% CI 0·39–0·58; p<0·001) and distant metastasis-free survival (HR 0·51, 95% CI 0·40–0·65; p<0·001) in patients with *BRAF*-mutant stage III melanoma[138]—an effect that was maintained over time.[139] An overall survival benefit was also observed at the primary analysis, without crossing the prespecified boundary for significance (HR 0·57, 95% CI 0·42–0·79; p=0·0006).[138] The optimal selection of adjuvant drug therapy for patients with stage III *BRAF*^{V600} mutation-positive melanoma is unclear. Efficacy results in the advanced setting favour immunotherapy, and this experience often underpins choice of therapy in the adjuvant setting. However, the reversibility of toxicities with BRAF-targeted therapy, unlike some toxicities associated with checkpoint immunotherapy, might deliver a more favourable risk–benefit profile for the use of BRAF-targeted therapy in patients with low-risk stage III *BRAF*^{V600} mutation-positive melanoma. A trial of BRAF-targeted therapy in stage II melanoma is underway (NCT05270044).

Investigation of neoadjuvant drug therapy is ongoing (table 3).[141] Checkpoint inhibitors are anticipated to be particularly effective in this setting due to the presence of a large and heterogeneous tumour target. A key endpoint in neoadjuvant trials is the pathological response rate, which refers to the percentage of viable tumour remaining in the resected sample after treatment (either a complete response [ie, no viable tumour], near-complete response [ie, ≤10% viable tumour], partial response [ie, >10% and ≤50% viable tumour], or non-response [ie, >50% viable tumour]).[145] A pooled analysis of six key early phase neoadjuvant trials, including OpACIN[146] and OpACIN-neo[147] among others,[125,148–150] found a major pathological response (complete or near-complete) in 47% of patients given BRAF-targeted therapy and 52% of patients given immunotherapy (the latter driven by responses to ipilimumab plus nivolumab combination therapy [61%], and less so by anti-PD-1 monotherapy [26%]), correlating with improved recurrence-free and overall survival.[150] Neoadjuvant nivolumab combined with an anti-LAG-3 checkpoint inhibitor, relatlimab, showed a similarly high pathological response rate and durability.[151] BRAF-targeted therapy is associated with high response rates, but poor response durability.[126] In an updated survival analysis, neoadjuvant ipilimumab plus nivolumab achieved a 4-year overall survival rate of 90% (OpACIN) and 2-year overall survival rate of 95% (OpACIN-neo) in patients with high-risk resectable stage III melanoma.[152] The phase 2 SWOG S1801 trial reported a significant event-free survival benefit with neoadjuvant versus adjuvant pembrolizumab (HR 0·58, 95% CI 0·39–0·87; p=0·004), with 2-year event-free survival rates of 72% and 49%, respectively.[4] The phase 3 NADINA

(NCT04949113) trial is comparing adjuvant nivolumab with neoadjuvant nivolumab plus ipilimumab, and includes personalised post-surgical management.

On the basis of results from SWOG S1801,[4] neoadjuvant therapy has replaced adjuvant therapy as the standard of care for clinically detectable and resectable stage III melanoma. Adjuvant treatment will probably need to be used for patients with a poor pathological response to neoadjuvant therapy; equally, de-escalation of future treatment including surgery might be possible for those with a good pathological response.[153] High IFN-γ gene expression and high tumour mutation burden are independently associated with a better prognosis[120] and response to neoadjuvant therapy,[152] (and improved outcomes with anti-PD-1 immunotherapy in the advanced setting[154,155]). High IFN-γ, but low tumour mutation burden, are associated with improved outcomes with adjuvant BRAF-targeted therapy, presumably due to fewer resistance-inducing mutations.[120] In clinical trials, low IFN-γ and low tumour mutation burden are used to select patients better suited to escalation of therapy via experimental therapeutics;[152] this approach is likely to be adopted in future clinical practice.

Before effective systemic therapies were available, adjuvant radiotherapy to the nodal basin was found to reduce the risk of local recurrence versus observation (HR 0·56, 95% CI 0·32–0·98; p=0·041) in patients with resected stage III melanoma and high-risk nodal features (ie, high number or size, or extra-nodal spread).[156] No effect was found on recurrence-free or overall survival.[156,157] Adjuvant radiotherapy is no longer in standard use, but should be discussed by the patient's multidisciplinary team for local control, in situations in which salvage surgery (in the event of local failure) is likely to be associated with high morbidity (eg, in the head and neck).

Surveillance and follow-up for resected melanoma

Evidence-based surveillance and follow-up guidelines are typically stratified by melanoma stage,[61,62] both with respect to the intensity and the interval of visits.[95–97] Recommendations range from broad intervals without imaging for patients with early stage disease (eg, stage I–IIA: 6–12-monthly for 2–5 years) to more frequent visits accompanied by cross-sectional imaging for patients at higher risk (eg, resected stage IIB–IV: 3–6-monthly for 2 years, then 6–12-monthly for 3 years).[95–97] Most guidelines (and their supporting studies) were detailed before the era of effective systemic therapy and preceded advances in molecular and immune profiling of tumours and the tumour microenvironment. Guidelines will probably evolve rapidly as validated multimodality risk models incorporating pretreatment (and, where applicable, post-treatment) clinical, pathological, patient-specific, molecular, and immune factors inform enhanced clinical decision making.[95–97]

Contemporary management of advanced melanoma

Before 2010, the prognosis for melanoma associated with unresectable locoregional (ie, regional lymph nodes and in-transit metastases, stage III) or distant sites (ie, stage IV) was poor. With chemotherapy ineffective and traditional adoptive cell (ie, tumour-infiltrating lymphocyte) therapy appropriate for only a minority of patients, less than 10% of patients with advanced melanoma survived beyond a few years.[158,159] The advent of targeted therapy and, more impressively, checkpoint immunotherapy has dramatically improved outcomes. Durable disease control, and potentially cure, now occurs in approximately 50% of patients (appendix p 3).[160–162] The prognosis of advanced melanoma, once a lethal diagnosis, has thus been transformed.[3]

Drug therapy

As in the adjuvant setting, patients with advanced *BRAF*-mutant melanoma can receive targeted therapy with combination BRAF and MEK inhibitors. Three combinations (ie, dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib) have high initial response rates, with some degree of tumour regression in almost all patients, accompanied by rapid symptom improvement.[163–166] Toxicity is mild and reversible, with pyrexia (dabrafenib plus trametinib), hepatitis (vemurafenib plus cobimetinib), and photosensitivity (vemurafenib plus cobimetinib) more common with some agents. Although no head-to-head trials have been performed, cross-trial comparisons suggest that encorafenib plus binimetinib is the most active and least toxic regimen of the three. This finding is probably due, in part, to the fact that encorafenib is dosed higher in the combination than as a single agent, whereas vemurafenib is dosed on the basis of its single-agent maximum tolerated dose and dabrafenib is dosed at the recommended phase 2 (pharmacodynamic) dose. Despite impressive early activity, the major limiting factor of targeted therapy is acquired resistance. This resistance occurs in around 50% of patients within 1 year, and in 80% of patients within 5 years;[160,167,168] for around 30% of patients, resistance develops in the brain.[169] As such, targeted therapy is used as a palliative therapy for patients in need of rapid symptom improvement or who have no other treatment options,[160] and for patients for whom checkpoint inhibitors are unsuitable.

Checkpoint immunotherapy (ie, targeting PD-1, CTLA-4, and LAG-3) is suitable for patients with both *BRAF*-mutant and wild-type melanoma. Although checkpoint inhibitors have less initial activity than targeted therapy, they have the potential to durably control disease, and probably cure disease, in many patients (albeit at the cost of immune-related adverse events).[161,162,170] Ipilimumab was the first drug to show an improvement in overall survival in advanced melanoma.[171–173] Although response rates are low (10–15%),

approximately 20% of patients survive beyond 10 years.[170] The anti-PD-1 antibodies pembrolizumab and nivolumab have superior efficacy to ipilimumab, with higher response (33–44%) and survival rates (5-year progression-free survival 38–44%), and reduced toxicity.[154,155,161,174–176] Combination ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg) has the highest response rate (58%) and most durable survival (5-year progression-free survival 52%) of any immunotherapy to date, but at the cost of more frequent and severe toxicity (grade 3 or 4 adverse events 55%).[162,175] Ipilimumab, at lower doses than 3 mg/kg, in combination with nivolumab or pembrolizumab has less toxicity, but studies of the efficacy are inconclusive, particularly given the known dose-response relationship of ipilimumab alone.[177–179] A novel combination of nivolumab plus relatlimab (an anti-LAG-3 antibody) has shown improved efficacy (48% *vs* 36% 1-year progression-free survival) compared with nivolumab alone, with little additional toxicity.[180] No data exist comparing nivolumab plus relatlimab with ipilimumab plus nivolumab.

With several systemic options available for the treatment of advanced melanoma, the selection of therapy is challenging. Ipilimumab plus nivolumab appears to have superior efficacy when used as a first-line treatment, compared with second-line to targeted therapy, in patients with *BRAF* mutations.[181,182] PD-L1 status is not a helpful biomarker to exclude PD-1-based immunotherapy, nor to establish whether single-agent or combination immunotherapy will be more appropriate (although some regulators require this measure). Patients who appear to benefit most from ipilimumab plus nivolumab include those with asymptomatic brain metastases,[183,184] *BRAF*^{V600E} melanoma, elevated lactate dehydrogenase, higher disease burden, liver metastases, and possibly mucosal and acral subtypes of melanoma.[162,185–187] Trials of triplet therapy (BRAF inhibitor plus MEK inhibitor with anti-PD-1 or anti-PD-L1 agents) have shown unimpressive results when compared with targeted therapy alone, and none have been compared with combination immunotherapy.[188,189] Triplet regimens might have a role in managing patients with brain metastases who are unsuitable for ipilimumab plus nivolumab or patients with symptomatic or steroid-dependent disease.[190] Patients who are resistant to anti-PD-1 monotherapy in the metastatic or, increasingly, adjuvant setting might respond to ipilimumab alone or in combination with nivolumab, with the combination appearing most efficacious (appendix p 4).[191–194] Early data suggest that melanoma resistant to relatlimab (in combination with nivolumab) will also be resistant to ipilimumab, with the reverse also likely to be true.[195] Several studies have explored biomarkers of response and resistance to therapy, including clinical, tissue, and blood markers. No markers are sufficiently robust to inform treatment decisions in a routine practice setting beyond *BRAF* mutation status.[196]

Multidisciplinary management

Advanced melanoma is a complex illness, requiring multidisciplinary management. Surgery, once used frequently in oligometastatic situations as a first-line therapy, is now mainly reserved for oligometastatic or symptomatic drug-resistant disease.[197] Radiotherapy is also typically reserved for this setting and in treatment-naive patients with symptomatic lesions requiring rapid tumour regression. Concomitant radiotherapy and systemic therapy do not appear to increase toxicity; however, there are no data demonstrating an abscopal effect occurring in a clinically meaningful proportion of patients to recommend routine addition of radiotherapy to systemic therapy.[198] Patients with asymptomatic brain metastases can safely avoid up-front surgery or stereotactic radiotherapy if they are suitable for combination ipilimumab plus nivolumab (achieving a 3-year overall survival of 72%[199] and a 5-year overall survival of 51%[200] in this setting). Patients with symptomatic brain metastases gain little benefit from current systemic therapies (including only brief benefit with targeted therapy),[201] such that surgery and radiotherapy are often considered to minimise steroid burden and alleviate symptoms.[183,202] When used, stereotactic cerebral radiotherapy can lead to radionecrosis, particularly in patients who ultimately respond to immunotherapy, which can create substantial morbidity.[203,204] Randomised data are required to establish the role of routine cerebral radiotherapy in asymptomatic patients receiving immunotherapy (NCT03340129). Patients with in-transit melanoma that is drug resistant or unsuitable for drug therapy present a unique challenge. Local therapies, including intralesional therapies such as talimogene laherparepvec, are useful in this population, particularly in patients with more indolent disease.[205] Many patients have relative contraindications to systemic therapy, particularly immunotherapy, such that multidisciplinary care is required to select therapy and manage toxicity.[206,207] The management of patients after toxicity, including resumption of therapy, also requires multidisciplinary support.[208] The frequency and modality of imaging surveillance for advanced melanoma is dynamic, reflecting initial sites of disease, as well as the type, response to, and duration of systemic therapy. Cross-sectional imaging that includes the brain is performed initially at 3-monthly intervals after which it can reduce in frequency.

Despite recent advances in the last decade, approximately half of patients with advanced melanoma die from their disease, and novel therapies are required. Adoptive cell (ie, tumour-infiltrating lymphocyte) therapy has made a resurgence, with data showing activity in the anti-PD-1 refractory setting.[209,210] However, treatment is expensive, laborious, and toxic, limiting its potential in many patients. Several novel agents, including personalised melanoma vaccines (mRNA-based or using other emerging technologies)[209] or drugs targeting immune checkpoints (eg, TIGIT, LAG-3),[211] immune cells (eg, bispecific T-cell engagers, chimeric antigen receptor

T cells), the tumour microenvironment, or vasculature,[212] among others (appendix p 4), have shown promise in early trials, but randomised data in first-line, second-line, or third-line settings are required.

The future of cutaneous melanoma management

Deaths from melanoma are anticipated to continue to reduce over the next decade,[3] driven by improvements in diagnostic accuracy (ie, separating out the truly malignant from the benign), prognostic accuracy (ie, determining which patients will have disease recurrence after surgical excision, and which will not), and precision selection of drug therapy in patients predicted to have disease recurrence. These improvements will be underpinned by diagnostic and predictive tools that integrate the classic clinicopathological features of melanoma with multiomic analysis of tumour, tumour microenvironment, and host factors, and will rely on advances in clinical and histopathological imaging refined by AI programmes with large databases. However, prevention of new melanomas by the reduction of UVR overexposure and earlier detection of thinner tumours with lethal or metastatic potential remain the two most notable public health interventions that will reduce the incidence and mortality of cutaneous melanoma.[30–32]

Contributors

GVL and RAS contributed to the conception, design, and planning of the manuscript. All authors contributed to the first draft. All authors were involved in reviewing and editing the manuscript, and approved the submitted draft.

Declaration of interests

GVL is a consultant adviser for Agenus, AMGEN, Array Biopharma, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Evaxion, Hexal (Sandoz Company), Highlight Therapeutics, Innovent Biologics USA, Merck Sharpe & Dohme, Novartis, OncoSec, PHMR, Pierre-Fabre, Provectus Biopharmaceuticals Australia, Qbiotics, and Regeneron. AMM is a consultant adviser for Bristol-Myers Squibb, Merck Sharpe & Dohme, Novartis, F Hoffmann-La Roche, Pierre-Fabre, and QBiotics. JEG is a consultant adviser for Merck. RAS has received fees for professional services from MetaOptima Technology, F Hoffmann-La Roche, Evaxion, Provectus Biopharmaceuticals Australia, Qbiotics, Novartis, Merck Sharp & Dohme, NeraCare, AMGEN, Bristol-Myers Squibb, Myriad Genetics, and GlaxoSmithKline. SMS declares no competing interests.

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