Early detection of cutaneous melanoma improves prognosis

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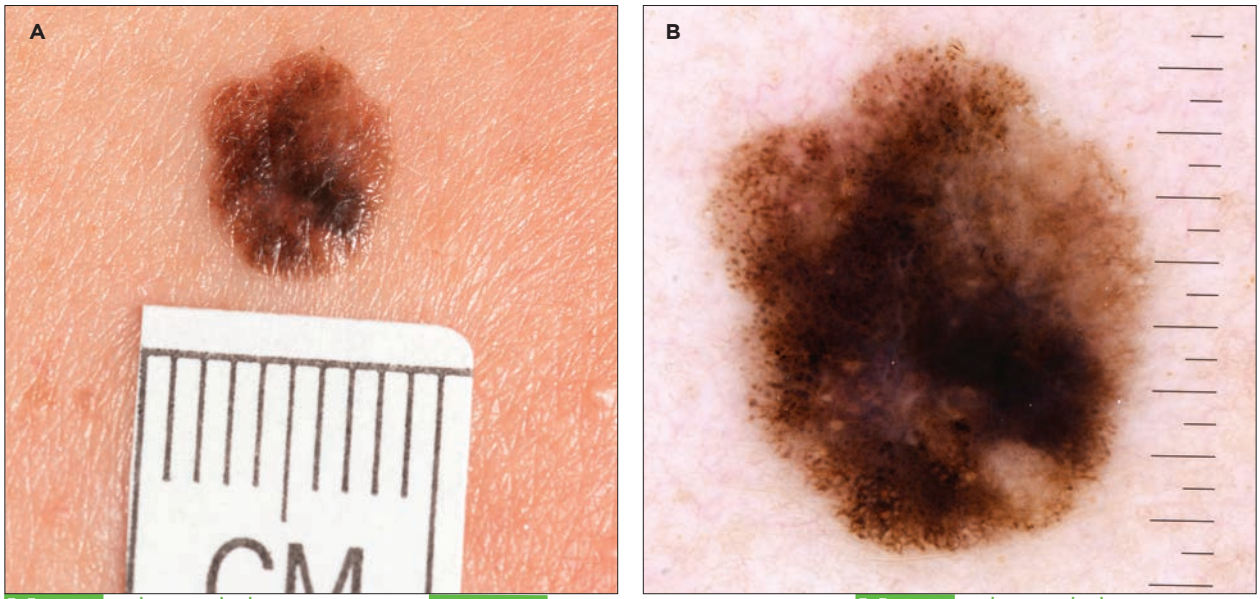


FIGURE 1
A Superficial spreading melanoma (SSM) on the right shoulder, Breslow depth 0.7 mm presenting with a variably pigmented patch and irregular borders
B Dermoscopic image of the SSM showing an atypical asymmetrical pigment network of blotches, dots and globules with evidence of a blue-white veil

How should patients be assessed?

MELANOMA IS THE FIFTH MOST COMMON CANCER IN THE UK.[1] THE INCIDENCE OF MELANOMA IN THE UK has increased by around 135% since the early 1990s, with more than 16,000 people diagnosed each year.[1] In the USA, the incidence has increased six-fold over the past 40 years.[2]

Early detection of melanoma, especially if limited to in situ disease, improves prognosis.[1] Invasive melanoma has metastatic potential.

Diagnosis may be challenging for GPs who on average would be expected to see a single case of melanoma every two years.

RISK FACTORS

The risk of developing melanoma increases with age. Each year more than a quarter (28%) of all new melanoma cases in the UK are diagnosed in people aged 75 and over and almost half (47%) of melanoma deaths occur in this age group.[1]

Exposure to intermittent intense sunlight and sunburn (especially in childhood) are the most common modifiable risk factors for melanoma.

Social trends have led to increased use of sun tanning beds which largely emit UVA radiation. Iatrogenic exposure may occur through the use of PUVA and necessitates caution with repeated use.[3]

Individuals with lighter skin tones are at greatest risk (Fitzpatrick skin types I-II) because of their increased susceptibility to sunburn. Blue eyes, numerous freckles and fair or red hair are also common in this phenotype (see box 1, below).

What are the treatment strategies?

A history of melanoma confers an eight-fold increased risk of a further melanoma.[4] Approximately 5-10% of melanoma cases are estimated to be familial (i.e. where two first-degree blood relatives or any three blood relatives on one side of the family have had a melanoma).[5] Risk factors for melanoma are listed in table 1, p22.

Approximately one third of melanomas are thought to arise from existing naevi with the remaining occurring de novo.[6] Patients with high counts of naevi (> 50) and clinically atypical moles (defined as benign melanocytic naevi with clinical features overlapping with melanoma such as size > 5 mm, asymmetrical, irregular and multicoloured) are also at increased risk. Large congenital naevi, measuring > 20 cm have the propensity to evolve into melanoma.

Genetic conditions such as familial »

How should patients be followed up?

Box 1

Fitzpatrick skin types and associated features

Skin type	Clinical features	Tanning ability
I	● Pale white skin, blue/green eyes, fair/red hair	● Always burns, does not tan
II	● Fair skin, blue eyes	● Burns easily, tans poorly
III	● Darker white skin	● Tans after initial burn
IV	● Light brown skin	● Burns minimally, tans easily
V	● Brown skin	● Rarely burns, tans darkly easily
VI	● Dark brown or black skin	● Never burns, always tans darkly

atypical multiple mole melanoma (FAMMM) syndrome, an autosomal dominant syndrome characterised by multiple melanocytic naevi, a positive family history of melanoma and the CDKN2A gene mutation also raise an individual's risk profile. Patients with xeroderma pigmentosa have a higher incidence of melanoma due to ineffective DNA repair mechanisms following photodamage.

Immunosuppressed patients such as those with an organ transplant or who have HIV or lymphoma, are also more likely to develop a melanoma which is often accompanied by a worse prognosis.[7,8]

ASSESSMENT

A comprehensive history should include the timeline of change, whether the lesion is new or occurred in an existing naevus, changes in size, shape and colour. Symptoms such as pain, itch and bleeding should be noted. The risk factors outlined in table 1, below, should be evaluated.

Table 1

Risk factors for cutaneous melanoma

- Intermittent intense UV radiation and sunburn (outdoor UV exposure, tanning beds, PUVA)
- Immunosuppression
- Personal or family history of melanoma
- Increasing age
- Fair skin, red or fair hair and blue eyes
- Previous sunburn – especially multiple blistering episodes in childhood
- Extensive solar lentigines/permanent freckling
- Multiple acquired melanocytic naevi (> 50)
- Presence of atypical naevi
- Large congenital melanocytic naevi (> 20 cm)
- Genetic syndromes: familial atypical multiple mole melanoma syndrome, xeroderma pigmentosa

Table 2

Melanoma can masquerade as other lesions listed below

Melanotic
- Seborrhoeic keratosis
- Verrucous melanocytic naevus
- Benign naevi, e.g. halo naevus, fried egg naevus, dysplastic naevus

Amelanotic
- Pyogenic granuloma
- Dermatofibroma
- Basal cell carcinoma
- Squamous cell carcinoma
- Bowen's disease
- Verruca

During examination, the lesion should be palpated and inspected closely in good light and its appearance and size documented.

A full body skin assessment is very useful and allows comparison of the index lesion with other skin lesions. A melanoma tends to be an outlier in its appearance that does not fit the individual's usual pattern of signature naevi; the ugly duckling sign.[9]

Various assessment tools may be employed during the skin assessment e.g. the ABCDE criteria (Asymmetry, irregular Borders, Colour variation, Diameter > 6 mm, Evolution) which are quick and easy to use.[10]

The 7-point checklist is recommended by NICE to help determine when a referral is indicated. Major features score 2 points and include change in size, irregular colour, irregular shape with minor features scoring 1 point such as; inflammation, oozing or crusting, diameter > 7 mm, sensory change or itch.[11] A score of 3 or more warrants an urgent referral. However, these checklists should not be used in isolation as some melanomas will be missed.

Amelanotic melanomas, estimated at 10% of all melanomas, remain a challenge as they are pink in colour and often have a global symmetric appearance which can result in delayed or missed diagnosis. The EFG tool, which assesses for elevation, firmness and continuous growth for more than a month, is recommended with these types of suspicious lesions.[12]

A high index of suspicion for melanoma is needed especially when: risk factors are present, there is a history of change and patient anxiety and the index lesion is clinically non-specific, and should prompt further evaluation.

For lesions on acral skin, nails and mucosa assessment by a dermatologist is indicated and is outside the scope of this article.

All lesions seen by a GP in which melanoma is suspected should be referred to secondary care via an urgent 2-week wait suspected cancer pathway referral.

The COVID-19 pandemic has resulted in reduced melanoma referrals during lockdown.[13] Many consultations carried out, both in general practice and secondary care, were virtual which carries an associated risk because of the variable quality of the clinical images submitted. In person assessment and examination is the gold standard especially in suspected melanoma.

DERMOSCOPY

Visual inspection alone will miss 1 in 10 melanomas. Dermoscopy is widely used to improve clinical diagnostic accuracy by detecting features not visible to the naked eye. For those GPs who are skilled in the use of dermoscopy attaching a dermoscopic image to the referral is very useful in triage.[14]

Dermoscopic features suggestive of melanoma include an asymmetrical atypical pigment network, irregular streaks and regression structures. The presence of a blue-white veil, milky pink areas and atypical vessels may be more commonly seen in nodular melanomas.

CLINICAL PRESENTATION

Melanomas are categorised into four histopathological subtypes. Although each subtype has distinct features, their heterogeneous clinical morphological presentations can lead to challenges in diagnosis.

Melanomas may mimic benign lesions (e.g. melanocytic naevi, seborrhoeic keratosis, dermatofibroma, pyogenic granuloma), inflammatory conditions or non-melanoma skin cancers (see table 2, below left and figure 2, p23).

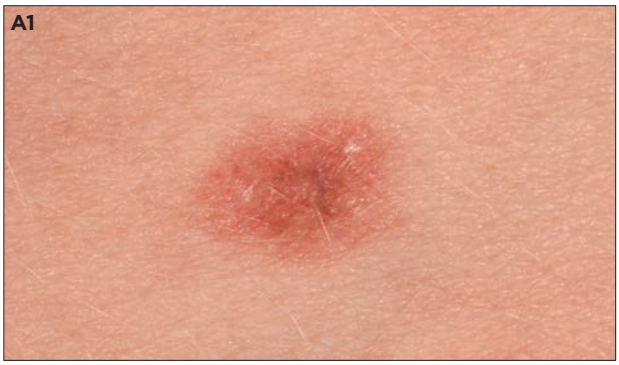
Subtypes

1 Superficial spreading melanoma (SSM) is the most common subtype accounting for approximately 70% of melanomas and is characterised by a slow radial growth phase.[15] It has a predilection for the trunk in men and lower limbs in women. It tends to appear as a variably pigmented macule or patch with irregular borders, (see figure 1, p21).

2 Nodular melanoma, the second most common subtype, commonly presents with a dome-shaped nodule, often with reduced or absent pigmentation and may masquerade as the more common non-melanoma skin cancers such as basal cell carcinoma and squamous cell carcinoma. It has a predilection for the head and neck.[12]

3 Lentigo maligna is typically an asymmetrical pigmented macule or patch on the head and neck area in elderly patients. These lesions are often slow growing, present for many years before sometimes developing nodular areas suggesting invasive transformation to lentigo maligna melanoma.

4 Acral lentiginous melanoma which affects acral sites especially the soles



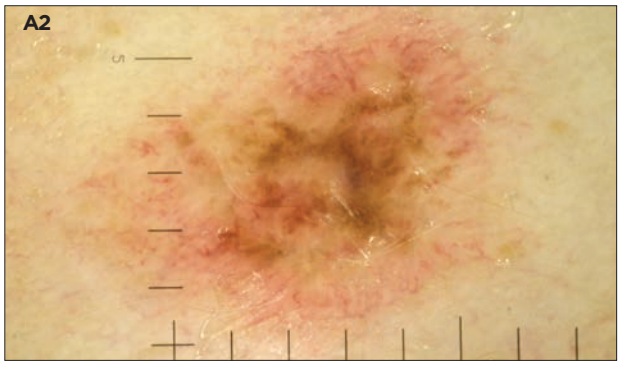
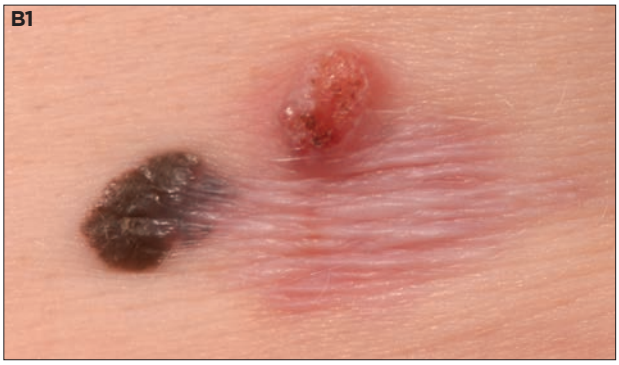
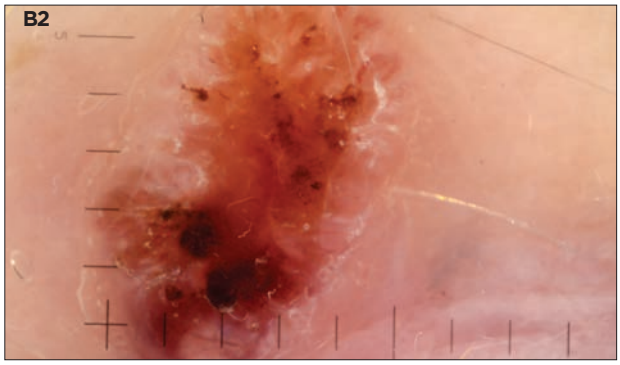
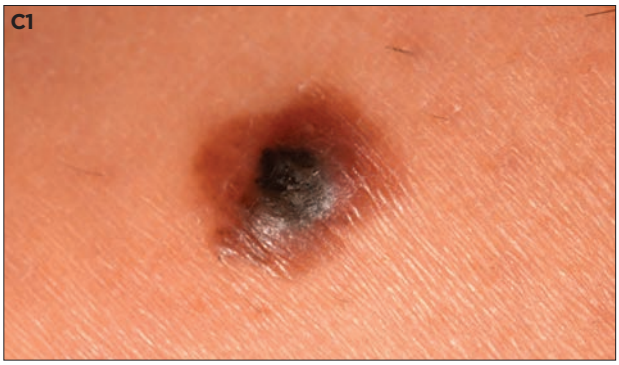


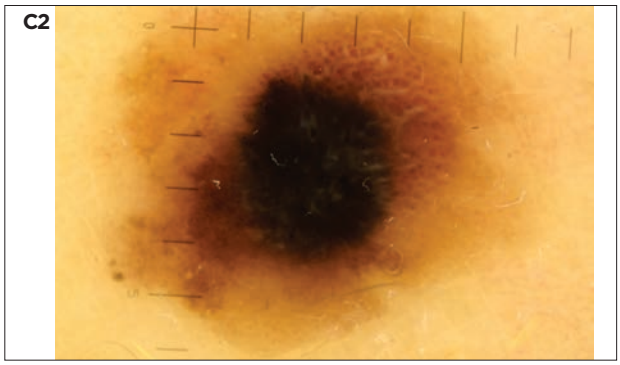
FIGURE 2
A1 Hypomelanotic melanoma in situ on the left flank mimicking a superficial basal cell carcinoma
A2 Corresponding dermoscopic image showing irregular pigment network and linear irregular vessels



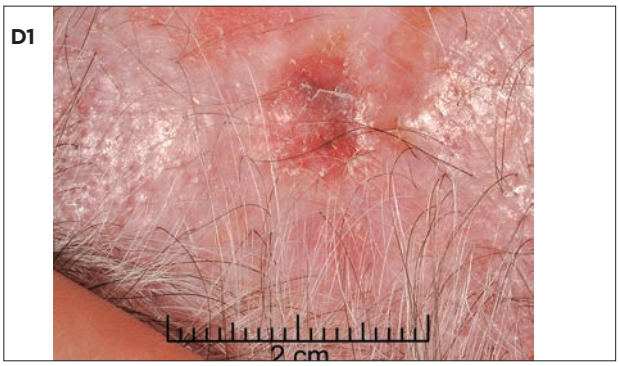


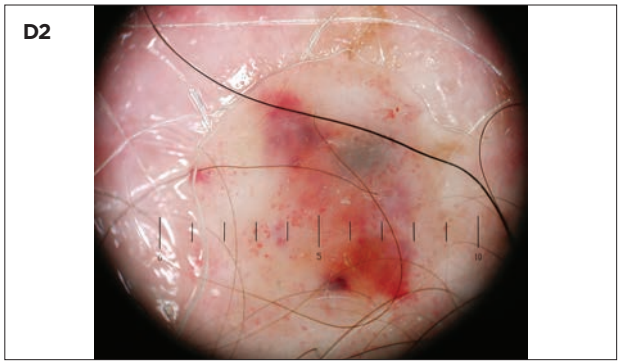
B1 Partly melanotic and hypomelanotic melanoma on the left lower back with regression features, Breslow depth 2.2 mm
B2 Corresponding dermoscopic image of the hypomelanotic portion



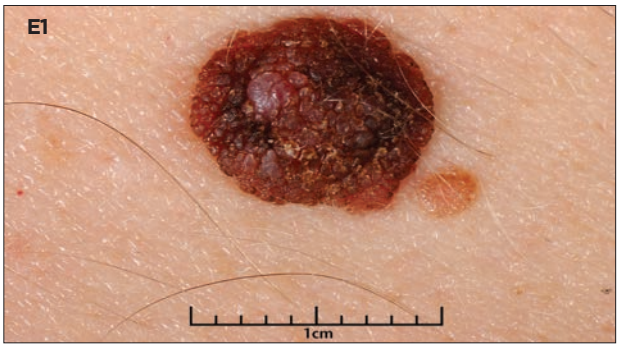


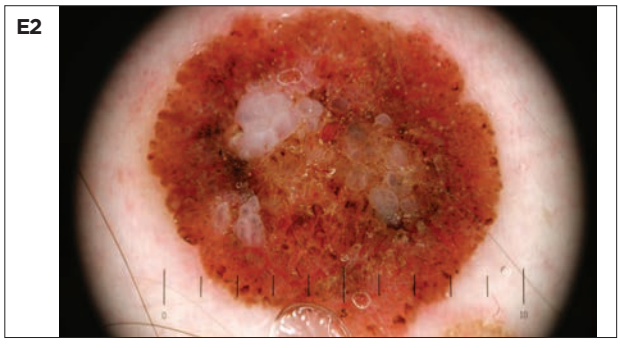
C1 Superficial spreading melanoma on the left medial ankle mimicking a benign 'fried egg' naevus, Breslow depth 0.7 mm
C2 Corresponding dermoscopic image showing an asymmetrical pigment network





D1 Desmoplastic melanoma on the scalp mimicking a non-melanoma skin cancer, Breslow depth 9 mm
D2 Corresponding dermoscopic image showing an amelanotic lesion with glomerular vessels





E1 Verrucous melanoma mimicking a seborrhoeic keratosis on the posterior neck, Breslow depth 2 mm
E2 Dermoscopic image showing a variably pigmented verrucous lesion

key points

SELECTED BY

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Melanoma is the fifth most common cancer in the UK. The incidence of melanoma in the UK has increased by around 135% over the past 30 years with more than 16,000 cases diagnosed each year. The risk of developing melanoma increases with age. Each year 28% of all new melanoma cases in the UK are diagnosed in people aged 75 and over and 47% of melanoma deaths occur in this age group. The estimated five-year survival rate for patients whose melanoma is detected early is around 99%, but in those with nodal involvement or distant metastasis, this falls to 66% and 27% respectively.

Exposure to intermittent intense sunlight and sunburn (especially in childhood) are the most common modifiable risk factors for melanoma. Individuals with lighter skin tones are at greatest risk (Fitzpatrick skin types I-II) because of their increased susceptibility to sunburn. Blue eyes, numerous freckles and fair or red hair are also common in this phenotype. A history of melanoma increases the risk of a further melanoma eight-fold. Approximately 5-10% of melanoma cases are estimated to be familial (i.e. where two first-degree blood relatives or any three blood relatives on one side of the family have had a melanoma).

The 7-point checklist is recommended by NICE to help determine when a referral is indicated. Major features score 2 points and include change in size, irregular colour, irregular shape with minor features scoring 1 point such as: inflammation, oozing or crusting, diameter > 7 mm, sensory change or itch. A score of ≥ 3 warrants urgent referral. These checklists should not be used in isolation as some melanomas will be missed. Amelanotic melanomas, estimated at 10% of all melanomas, remain a challenge as they are pink in colour and often have a global symmetric appearance which can result in delayed or missed diagnosis. The EFG tool, which assesses for elevation, firmness and continuous growth for more than a month, is recommended with these types of suspicious lesions.

For lesions on acral skin, nails and mucosa assessment by a dermatologist is indicated. All lesions seen by a GP in which melanoma is suspected should be referred to secondary care via an urgent 2-week wait suspected cancer pathway referral.

Melanomas are categorised into four histopathological subtypes. Although each subtype has distinct features, their heterogeneous clinical morphological presentations can lead to challenges in diagnosis. Melanomas may mimic benign lesions (e.g. melanocytic naevi, seborrhoeic keratosis, dermatofibroma, pyogenic granuloma), inflammatory conditions or non-melanoma skin cancers.

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of the feet and the nail unit is the rarest subtype and is outside the scope of this article. Assessment of lesions at these sites should always be undertaken in secondary care.

DIAGNOSIS

Diagnosis should always be confirmed by biopsy, ideally with an initial complete excision. Staging is performed in line with the 8th edition of the American Joint Committee on Cancer (AJCC) guidelines using the TNM classification system. The Breslow thickness is the measurement of the tumour depth and is the most important prognostic factor.

Other poor prognostic features include tumour ulceration, lymphovascular invasion, tumour subtype and mitotic activity which measures tumour growth. As a general rule, any patient with nodal metastasis has stage III disease and any patient with organ metastasis has stage IV disease.

All patients with melanoma should be discussed at a multidisciplinary team (MDT) meeting to determine the most appropriate treatment plan. This typically consists of dermatologists, plastic and maxillofacial surgeons, oncologists, radiologists and dermatopathologists.

COMPLICATIONS

Melanoma may metastasise to local lymph nodes or distant organs. If lymphadenopathy is detected clinically, fine needle aspirate or nodal excision is indicated for histological assessment. Imaging with CT, PET-CT or MRI is indicated in those with positive nodal disease to assess for further metastatic disease.

The estimated five-year survival rate for patients whose melanoma is detected early is around 99%, but in those with nodal involvement or distant metastasis, this falls to 66% and 27% respectively.[16]

TREATMENT

Surgery

National guidelines recommend that primary excision of the lesion should be undertaken in secondary care with a peripheral margin of 2 mm.[17,18] In certain anatomical areas such as the nose, ear and acral sites, in the case of large lesions or where diagnostic uncertainty exists, a diagnostic biopsy can be performed from representative parts of the lesion to help plan further management. Following diagnosis, a wide local excision is performed. The width and depth of the re-excision is dependent on the Breslow thickness and anatomical features.

Sentinel lymph node biopsy

Sentinel lymph node biopsy (SLNB) is the most sensitive method of detecting microscopic metastatic nodal disease and so providing further prognostic information. It is indicated in patients with melanoma > 1 mm Breslow thickness or 0.8-1 mm with ulceration.[19]

SLNB involves preoperative lymphoscintigraphy in which a blue dye and radioactive tracer is injected around the scar at the site of the initial melanoma excision. The sentinel node is identified as the first node to take up the dye and tracer and is removed and examined for micrometastasis. SLNB is best performed at the time of wide

Table 3

NICE recommendations on melanoma follow-up[18]

Clinical stage	Follow-up
Stage 0	Discharge after completion of treatment
Stage IA	2-4 times during the first year after completion of treatment, discharge at end of the year
Stage IB to IIB/IIC with negative SLNB	3 months for the first 3 years after completion of treatment, then every 6 months for the next 2 years, discharge at the end of 5 years
Stage IIC with no SLNB or III	3 months for the first 3 years after completion of treatment, then every 6 months for the next 2 years, discharge at the end of 5 years
Stage IV	Personalised follow-up recommended

local excision under a general anaesthetic.

Lymph node clearance

Total lymph node clearance is no longer routinely recommended after a positive SLNB, as there is no evidence of benefit.[20] However, it may be indicated in some individual cases after MDT discussion.

Systemic therapy

Systemic therapy may be indicated in those with nodal disease or metastatic organ disease. Eligible patients should be referred on to the oncology team for consideration.

In the past decade, the discovery of new systemic treatments has revolutionised the therapeutic landscape of metastatic melanoma including genetically targeted agents e.g. BRAF inhibitors and immunotherapy e.g. pembrolizumab.

Systemic treatments may be used as adjuvant therapy to reduce rate of recurrence or as primary therapy for unresectable metastatic disease. Conventional chemotherapy cytotoxic agents are now rarely used.

MONITORING AND FOLLOW-UP

Skin surveillance follow-up varies depending on the clinical staging of the melanoma (see table 3, p24). The optimal duration of follow-up remains controversial. Skin surveillance consists of a full skin assessment, examination of the scar and lymph node examination.

Patients should be educated on self-examination of their skin and lymph nodes, so that they can carry this out between appointments and following discharge.

CONCLUSION

Melanomas are a heterogeneous group of skin cancers and may be challenging to diagnose.

Classical variably pigmented lesions are obvious but there is a significant group of melanomas which mimic benign lesions and are harder to diagnose. GPs need to have a high index of suspicion to minimise the chance of missing such presentations.

Prompt referral is warranted when faced with a lesion suggestive of melanoma, atypical and clinically non-specific lesions that are evolving or whenever there is any diagnostic uncertainty. Early recognition of cutaneous melanoma leads to improved prognosis.

Competing interests: None

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Useful information

Melanoma UK
www.melanomauk.org.uk