Malignant Melanoma: A pictorial review

McCourt, C., Dolan, O., & Gormley, G. (2014). Malignant Melanoma: A pictorial review. *Ulster Medical Journal*, *83*(2), 103-110. http://www.ums.ac.uk/083_2.html

Published in:
Ulster Medical Journal

Document Version:
Early version, also known as pre-print

Title of manuscript:
Malignant Melanoma: A Pictorial Review

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Acknowledgements:

We would like to acknowledge David McCallum (Head of Department of Medical Illustration) and the Department of Medical Illustration, Royal Victoria Hospital, Belfast Health and Social Care Trust for their contribution of clinical photographs towards the manuscript.

Malignant Melanoma: *A Pictorial Review*

Overview

Introduction

Malignant melanoma (MM) is a malignancy of pigment-producing cells (melanocytes), which are located primarily in the skin, but also found in the ears, gastrointestinal tract, eyes, oral and genital mucosa and leptomeninges. For the purpose of this review the focus will be on malignant melanoma (hereby referred to as melanoma) affecting the skin i.e. cutaneous melanoma. Despite the fact that melanoma is the least common form of skin cancer (accounting for approximately 4% of all new cancer cases in UK), it has the highest mortality rate with more than 2000 deaths UK wide in 2011. [(1)] In Northern Ireland (NI) numbers of melanoma have increased from 103 cases per year in 1984–1992, to 258 per year in 2004–2009. [(2)] In addition, the risk of a second cancer has shown to be increased in patients in NI following the diagnosis of melanoma. [(3)] The incidence continues to rise worldwide and whilst some of the increase may be due to increased surveillance and earlier detection, most are considered to be linked to changes in sun-related behaviour e.g. increase in frequency of holidays abroad over time and the use of sunbeds. [(4-7)]

The diagnosis of MM can have devastating consequences for a patient and their relatives. Early detection of MM has been shown to significantly improve survival. [(8)]

In this review we will discuss pathophysiology and risk factors with a focus on history, examination and differential diagnosis. Assessment tools to aid early detection are reviewed and referral pathways based on how and when to refer to secondary care will be discussed briefly.

Pathophysiology

The sequence of events whereby normal melanocytes transform into melanoma cells (melanogenesis) is not fully understood. It is most likely due to a multistep process of genetic mutations that alter the cell cycle and render the melanocytes more susceptible to the carcinogenic effects of UVR. [(9)] Different pathways are likely to be involved in different subtypes of MM, for example superficial spreading MM (SSMM) is known to be associated with acute intermittent sun exposure and a high propensity to higher naevus counts. [(10,11)] In contrast lentigo maligna melanoma (LMM) more often occurs on chronically sun-exposed skin. [(11)]

Classification

Melanoma can be classified into 4 different clinical subtypes: superficial spreading melanoma (SSMM), lentigo maligna melanoma, nodular melanoma and acral lentiginous melanoma (characterized by the site of origin; palm, sole or subungal). Malignant melanoma in-situ and lentigo maligna are considered premalignant lesions.

SSSM

Commonly displays the ABCDE warning signs [(12)]

Table 1.

ABCDEs of melanoma	
A	Asymmetry
B	Border irregularity
C	Colour variation
D	Diameter > 6mm
E	Evolving (changing)

It tends to present as a flat or slightly elevated brown lesion with variegated pigmentation (i.e. black, blue, pink or white discoloration) with an irregular shape often > 6mm.

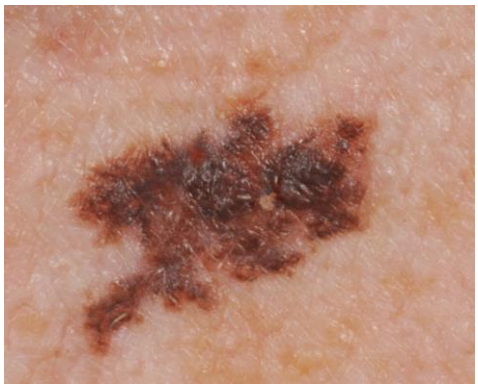
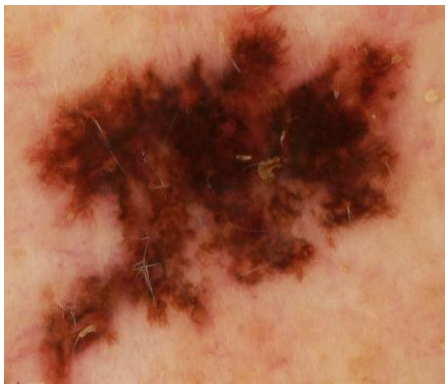
a)  **b)** 

Image 1 (a) Malignant melanoma –asymmetrical lesion with irregular borders and variegated pigment + (b) Dermoscopy image –irregular broad pigment network with radiating streaks at periphery of lesion

Lentigo maligna (lentigo maligna melanoma)

Lentigo maligna melanoma presents as a slowing growing or changing patch of discoloured skin with variegated shape and colour. They often show slow progressive changes from in situ lentigo maligna (LM) to invasive LMM and may be detected using the ABCDE rule.

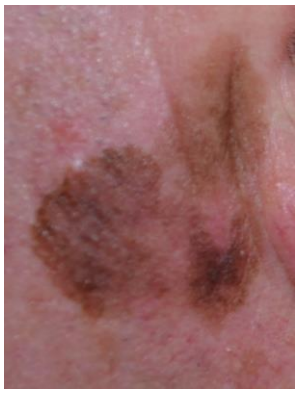


Image 2. Lentigo maligna – irregularly pigmented patch with irregular borders

Nodular melanoma

A nodular melanoma may arise on any site, but is most common on exposed areas of the head and neck and usually presents as a rapidly enlarging lump (weeks to months). One third of nodular melanomas are amelanotic i.e. non-pigmented and may be ulcerated. This can often lead to diagnostic difficulty. However any new ulcerated nodular skin lesion should alert the clinician to the high possibility of skin cancer.

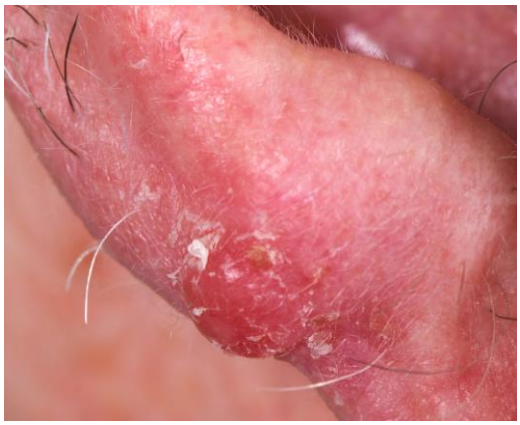
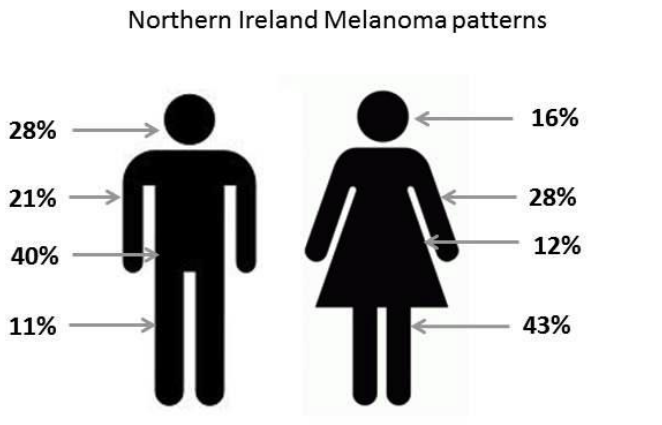


Image 3. Non-pigmented erythematous telangiectatic nodule at site of previous lentigo maligna melanoma

Acral lentiginous melanoma

This type of melanoma starts as a slowly enlarging flat patch of discoloured skin and tends to follow the ABCDE rule. Although initially smooth at first, it later becomes thicker with an irregular surface.

SSMM is by far the most common clinical subtype of melanoma in white skin and accounts for approximately 70% of cases diagnosed. In contrast, acral lentiginous melanoma is the least common subtype in white patients, more often seen in patients with African-American skin types. This is thought to be due to different genetic mutations, with kit mutations occurring in more of the later [(13)] and up to 50% SSMM demonstrating BRAF mutations. [(13)] Some of the newer treatments for metastatic MM target these mutations. There are also clear gender differences with regard to site of occurrence. Melanoma occurs most commonly on the trunk in white males (approximately 40% of cases) and the lower legs (approximately 43%) in white females. [(14)]



Percentage of lesions occurring on various body areas based on Northern Ireland Cancer Registry's report 'Care of Patients with Malignant Melanoma of Skin in Northern Ireland 2006'.

Figure 1.

Differential diagnosis

The differential of melanoma is wide and includes benign lesions such as seborrhoeic keratosis, benign melanocytic naevi, blue naevi and vascular lesions e.g. spider angiomas and pyogenic granulomas. Pre-malignant or malignant differentials include dysplastic naevi, squamous cell carcinoma, pigmented basal cell carcinoma and pigmented actinic keratosis.

Seborrhoeic keratosis

These lesions usually appear as slightly raised, skin coloured or brown spots, which gradually thicken and develop a rough warty surface. Over time they may darken to become dark brown to black. A clue to their diagnosis is the 'stuck on' appearance.

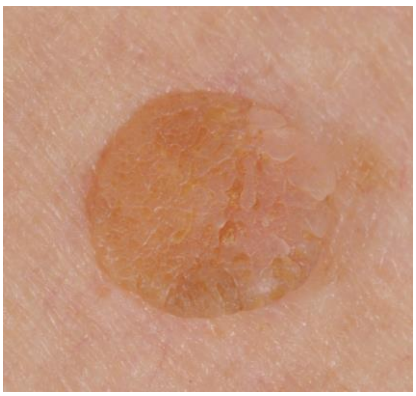
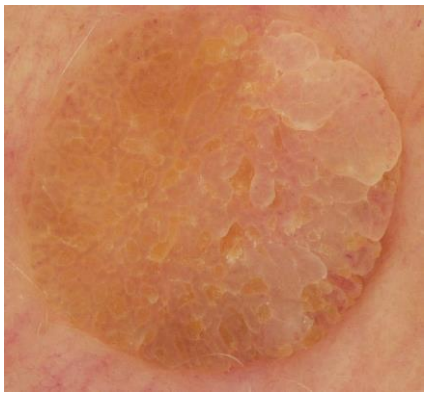
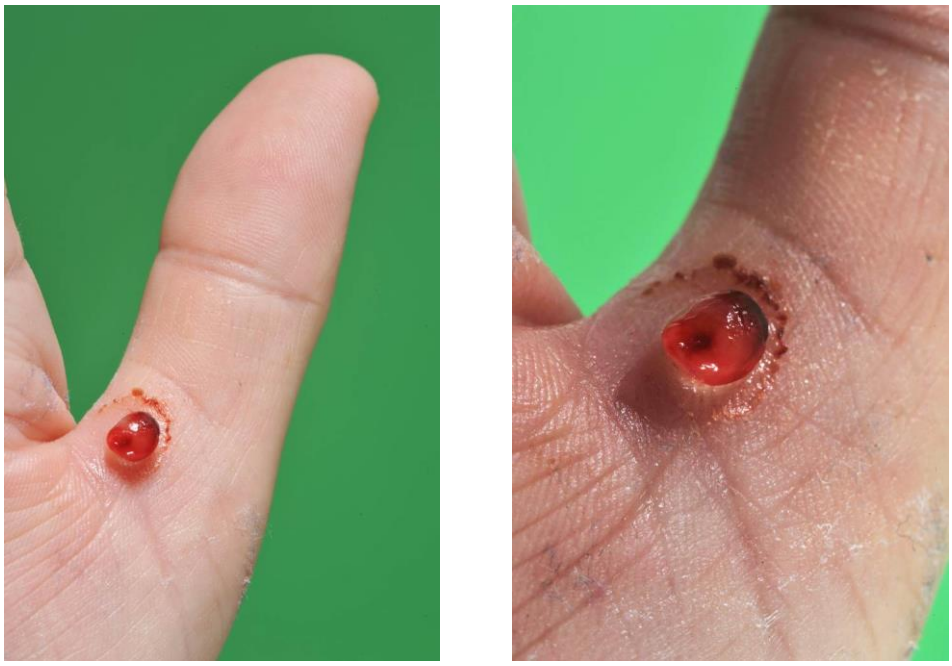
a)  **b)** 

Image 4 (a) Clinical appearance of seborrhoeic keratosis – stuck on appearance (b) Dermoscopy image – cerebriform appearance and lack of pigment network

Pyogenic granuloma
These lesions appear as small red papules that grow rapidly (weeks) and usually bleed easily and ulcerate. They are common in children and young adults, may follow trauma and most frequently appear on the head, neck, upper trunk and hands (fingers) and feet.



a) **b)**

Image 5. a) Friable vascular nodule on the base of the thumb b) close up

Benign melanocytic naevus
These can be divided into congenital or acquired (junctional, dermal, compound types) naevi. They are regular and symmetrical with uniform pigment.

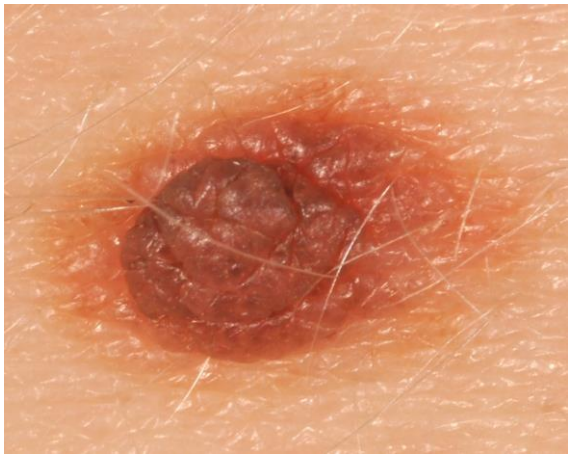


Image 6. Benign melanocytic naevus. Regular, symmetrical and uniformly pigmented lesion.

Dysplastic/atypical naevus
Unusual appearance with at least 3 of the following features: blurred or ill-defined borders, irregular shape, variegated colour, flat and raised components or size 6mm or more.

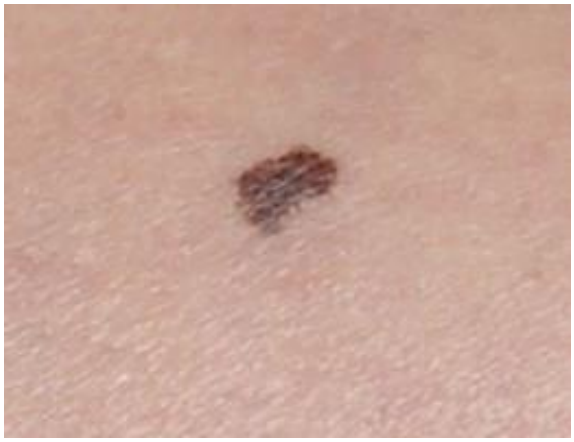


Image 7. Dysplastic naevus – irregularly shaped darkly pigmented naevus. 'Ugly duckling.'

Cherry angioma
These lesions usually develop on the trunk and can appear red or blue/black in colour. Cherry angiomas usually increase in number in middle-aged individuals and are otherwise known as Campbell de Morgan spots.

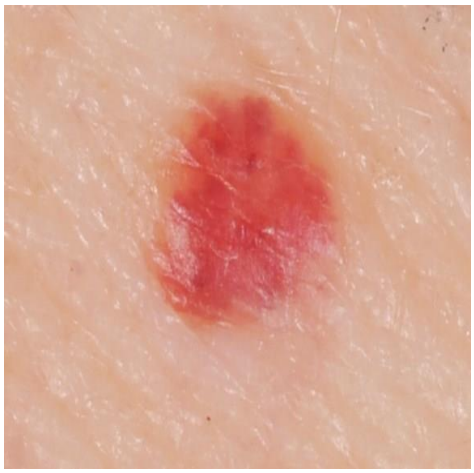
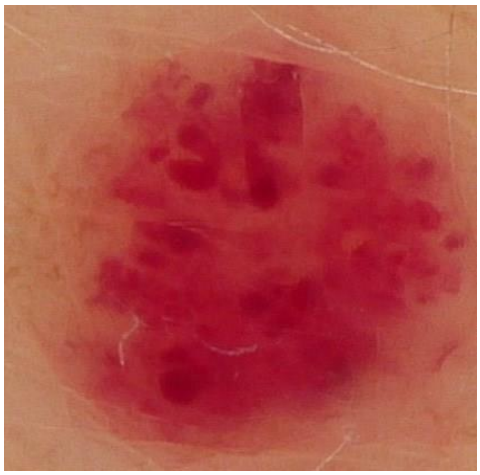
a)  b) 

Image 8 (a) Clinical image of cherry angioma with vascular appearance (b) Dermoscopic image – vascular lagunes visable.

Pigmented basal cell carcinoma
These tumours are typically slow growing over months to years. The pigmented type may mimic melanoma.

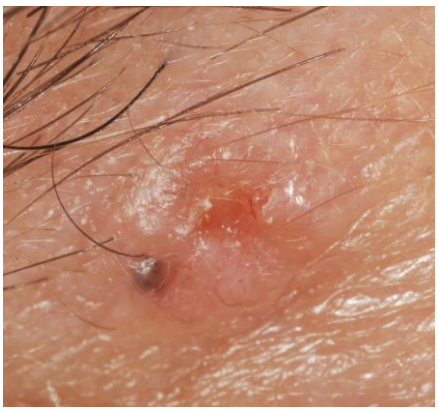
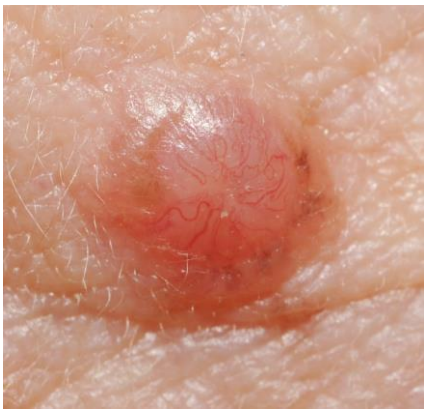
a)  b) 

Image 9 (a) + (b) Pigmented basal cell carcinoma. Pearly telangietatic nodules. Note peripheral pigmentation at bottom left in (a) and along right lateral edge in (b).

Dermatofibroma
These are benign slow growing dermal nodules, often occurring on the limbs. Although they may have a pigmented halo, they are symmetrical, helping distinguish them from melanoma.

Who is at risk of melanoma?
Clinical history and careful skin examination will assist the clinician in identifying those most at risk of developing melanoma.

History
Seven point checklist
When assessing a patient with a new or changing lesion the history is extremely important. There are several assessment tools available for assessing risk, one of which in widespread use is the Glasgow 7-point checklist [15] which awards 2 points to any of the major criteria; change in size, change in colour and change in shape with 1 point awarded to any of the following; ooze, change in sensation, inflammation or diameter >7mm. A score of 3 points or any one criterion with strong concerns about cancer should prompt a red flag referral to the dermatology service in secondary care. [16]

Table 2. Glasgow 7-point checklist

Major features	Minor features
• Change in size (2) • Irregular shape (2) • Irregular colour (2)	• Diameter > 7mm (1) • Inflammation (1) • Oozing (1) • Change in sensation (1)

ABCDE rule
Another commonly used tool for early detection of melanoma is the ABCDE acronym (Asymmetry, Border irregularity, Colour variegation, Diameter >6mm and Evolution or history of change) introduced to alert patients and health professionals to the diagnosis of melanoma. [12]

Table 3.

Northern Ireland Cancer Network (NICaN) Referral Guidelines for Suspected Skin Cancer
Urgent referral: • Melanoma: change in a lesion is a key element in diagnosing malignant melanoma. Do not excise in primary care. Lesions scoring 3 points or more (as below) are suspicious. • Major features of lesions • Change in size • Irregular shape • Irregular colour • Minor features • Diameter >7 mm • Inflammation/oozing • Change in sensation Squamous cell carcinomas: non-healing keratinizing or crusted tumours >1 cm in diameter with induration on palpation. Commmonly on face, scalp or back of hand; with documented expansion over 8 weeks New or growing cutaneous lesions after organ transplant – squamous cell carcinoma common with immunosuppression Histological diagnosis of squamous cell carcinoma Basal cell carcinomas can be referred non-urgently

It is important to be aware that although melanoma may develop in precursor melanocytic naevi (e.g. congenital naevi), up to 70% of cases are believed to arise de novo (ie, not from a preexisting pigmented lesion). In addition, for nodular and amelanotic subtypes, these algorithms are less accurate. In these cases the 'ugly duckling' sign may be more useful, whereby the melanoma can be recognised as an 'outlier' by differing clinical appearances. [17]

Skin type and Naevi Count

The most important phenotypic markers for melanoma are fair skin and above-average mole count.

Table 4.

Recommendation (adapted from the The prevention, diagnosis, referral and management of melanoma of the skin: concise guidelines. 2007)

1. Identifying people at risk

People should be considered to have higher risk (approximately 10-fold) if they have:

- >100 normal moles
- atypical moles
- two or more cases of melanoma in first-degree relatives.

Lower (approximately 2- to 3- fold) levels of risk are associated with:

- freckles
- red hair or skin that burns in the sun
- any family history of melanoma.

2. Primary prevention

- People at risk of skin cancer should protect their skin from the sun by avoidance and clothing primarily.
- They should also use a sun protection factor (SPF) of 20 to 30, and five star ultraviolet A (UVA)

3. Secondary prevention

- People who are in any of these higher risk (10-fold) categories above should be referred for risk estimation and education directed towards self-examination with a dermatologist specializing in moles and pigmented lesions (routine appointment)
- Base-line photography is a useful aid to monitoring moles

4. Urgent referral to a dermatologist

The following should be regarded as suspicious lesions requiring urgent referral to a dermatologist within 2 weeks:

- a new mole which is growing quickly over the age of puberty
- a long-standing mole which is changing progressively in shape or colour regardless of age
- any mole which has 3 more more colours or has lost its symmetry
- any new nodule which is growing and is pigmented or vascular in appearance
- a new pigmented line in a nail
- something growing under a nail
- a mole which has changed in appearance and which is also itching or bleeding

Summary of: (8) Bishop JN, Bataille V, Gavin A, Lens M, Marsden J, Mathews T *et al*. The prevention, diagnosis, referral and management of melanoma of the skin: concise guidelines. 2007.

Genetic factors include; Fitzpatrick skin type I (often burns and rarely tans)**,** red hair, blue eyes and freckles, >100 naevi, the presence of atypical naevi and a personal or family history of melanoma.

Table 5.

Skin Photo types

Skin Type	**Typical features**	**Tanning ability**
Type I	Tends to have freckles, red or fair hair, and blue or green eyes.	Often burns, rarely tans.
Type II	Tends to have light hair, and blue or brown eyes.	Usually burns, sometimes tans.
Type III	Tends to have brown hair and eyes.	Sometimes burns, usually tans.
Type IV	Naturally black-brown skin. Often has dark brown eyes and hair.	Rarely burns, often tans.
Type V	Naturally black-brown skin. Often has dark brown eyes and hair.	
Type VI	Naturally black-brown skin. Usually has black-brown eyes and hair.	

Adapted from: Fitzpatrick T B 1975 Soleil et peau *J. Med. Esthet.* **2** 33-4.

Atypical naevi are defined as moles with 3 or more of the following features; diameter >5mm, irregular shape, blurred outline, irregular margins, varying shades of colour and flat and bumpy components) Similarly, patients with Familial Atypical Multiple Mole-Melanoma syndrome (FAMMM), defined as one or more first-degree or second-degree relative with MM, the presence of numerous, often >50 naevi, some of which are atypical and naevi that are dysplastic on histopathology, are at higher risk of MM. [18] Although the majority of melanoma occurs in patients with fair skin type, a rare subset of melanoma known as acral lentiginous melanoma (i.e. affecting the acral skin of the hands and feet) is more common in African-American skin types. Because this type of melanoma presents at a later stage owing to the site, the prognosis is often poor

UVR exposure

The most important environmental cause of skin cancer is exposure to the sun. Patients should be asked about sun exposure including use of sunbeds, sunny holidays and blistering sunburns in childhood as well as the use of sun protection and sunscreen and sun protection measures. Ultraviolet radiation (UVR) is associated with the development of melanoma [19] and can be broadly categorised into UVA (315-400 nm), UVB (280-315 nm), and UVC (100-280 nm). All UVC and most UVB wavelengths are blocked by the ozone layer with only a fraction of UVB and all UVA reaching the Earth's surface. Indoor tanning or sunbeds have become the main non-solar source of exposure to UV light in light-skinned individuals. Indoor tanning equipment mainly emits UVA light with a small fraction (<5%) in the UVB range. Indoor tanning devices and the UV light spectrum were classified as a group 1 carcinogen to humans in 2009. [20]

A study published in 2011 [21] estimated that approximately 86% of malignant melanomas in the UK in 2010 were linked to exposure to UVR from the sun and sunbeds. Similarly, a large meta-analysis published in 2012 [22] based on 27 studies demonstrated that ever use of sunbeds was associated with a summary relative risk of 1.2 (95% CI 1.08-1.34). Furthermore, 13 of these studies demonstrated an overall summary relative risk of 1.87 (95% CI 1.41-2.48) with first use of sunbeds before 35 years. [22] It is hopeful that the Sunbeds Act (NI) 2011 [23] will lead to a reduction in the incidence of melanoma in future years.

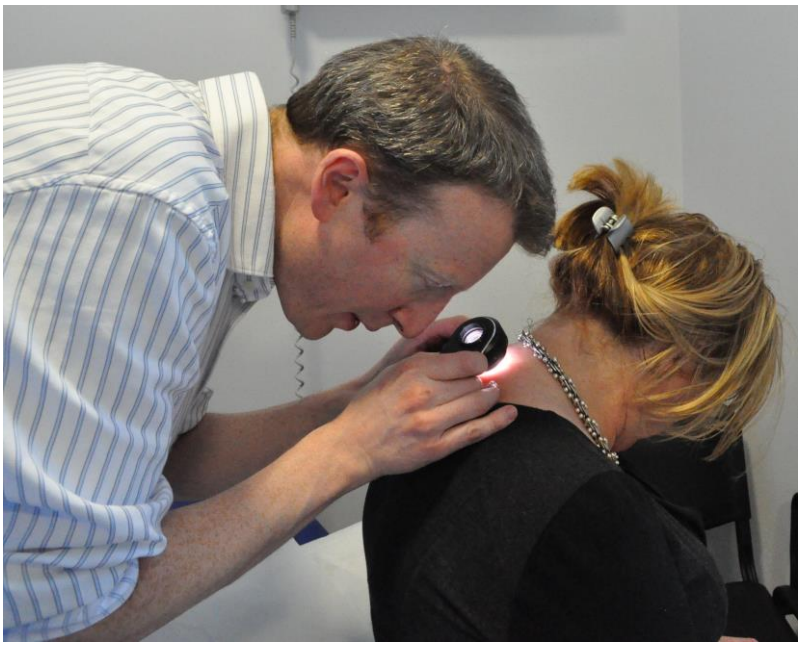
Examination

When assessing a patient with a new or changing naevus ideally a total-body skin examination should be performed. Not only does this increase the chances of diagnosing an incidental melanoma/melanoma in-situ, [24] but it also allows the clinician to compare the morphology of the index lesion to that of other naevi and recognise the so-called 'ugly duckling' sign. [17] Crucial to a good skin examination is a well-lit examination room. Ideally it would be good practice to perform a total body examination, taking account of the number of naevi present on the patient's skin and the using the ABCDE criteria used to differentiate early melanomas from benign naevi. If melanoma is suspected, the patient should also be examined for the presence of lymphadenopathy in all lymph node groups, particularly the draining basin corresponding to the lesion.

Dermoscopy and Photography

Dermoscopy or epiluminescence microscopy can be used by trained physicians to assess the patient's naevi rapidly.

Figure 2.



This involves using either a non-polarised light and surface oil or a polarised magnifying lens with no oil medium, to examine a lesion.

Useful adjuncts to management include serial photography techniques, such as 'mole-mapping' using dermoscopy. Computerized image analysis can then store images of the lesions and makes them available for comparison over time e.g. for monitoring patients in FAMM.

Dermatoscopy for triage (teledermatology)

With increasing constraints on the provision of healthcare and an increased volume of suspected skin cancer referrals to secondary care, teledermatology may be a useful triaging tool and is used with increasing frequency in Dermatology. The clinician in primary care is responsible for taking high quality photographs of the index lesion and corresponding digital dermoscopy images along with a clinical history (usually on an agreed proforma) to allow the dermatologist to triage the patient more appropriately. This 'store and forward' type of teledermatology is particularly useful as it lends itself to triage as it allows the clinician to review the stored images at a convenient time and place. It is important that if teledermatology is used it should complement the existing service and be part of an integrated local dermatology service. [25] In addition guidance on patient consent and information governance should be in place to monitor the effectiveness and safety of these pathways but also to protect patient confidentiality and ensure safe transfer of clinical information particularly photographic images.[25]

Referral pathways and management

If a patient with a suspected malignant melanoma is seen in primary care there are clear referral pathways for urgent/red flag referral to secondary care. The National Institute for Health and Care Excellence (NICE) [16] 'Referral Guidelines for Suspected Cancer' state that 'an urgent referral to a dermatologist or other suitable specialist with experience of melanoma diagnosis should be made and excision in primary care avoided.'[16]

The Northern Ireland Cancer Network (NICaN) [15] has issued clear guidance for referral of suspected skin cancer into secondary care (http://www.cancerni.net/files/file/ReferralGuidanceMay2007.pdf). As mentioned previously, a changing lesion or a score of 3 or more in the Glasgow 7-point checklist is suspicious of melanoma. The importance of clear accurate clinical information cannot be emphasized enough as this allows patients to be triaged appropriately and therefore seen in a timely manner. Patients should be referred into secondary care as a 'red flag' and are seen within 2-weeks. It is emphasised in the NICE Guidance that such lesions should not be excised in primary care and strongly recommended that incisional or incomplete excisions are avoided, particularly because of sampling error and the risk of inaccurate diagnosis. [8] All excised skin specimens even those regarded as benign should be sent for histopathological analysis.[16] The practitioner should also maintain a 'fail-safe' log of all procedures performed with details of the outcome and action following histological diagnosis.

Other considerations

Secondary prevention

Following a diagnosis of melanoma secondary prevention is paramount as a history of melanoma increases the risk of a metachronous melanoma. Patients should be counseled on the importance of effective sun protection measures, avoidance of sunbeds and the correct use of sunscreen. It is recommended that patients should use a sun protection factor (SPF) of 20-30 and five star ultraviolet A (UVA). [8] Regular self-examination of the skin should be encouraged. Useful resources are available to download from the British Association of Dermatologists website (http://www.bad.org.uk). [26]

Vitamin D

Once patients are diagnosed with melanoma, they are asked to use sun protection measures. The reason for this is two-fold; to reduce the risk of a second melanoma and to reduce the risk of immunosuppression from UV light. Often patients through fear of recurrence or worry over developing another skin cancer will completely sun avoid putting them at high risk of Vitamin D deficiency. This not only has implications for bone health but has also been associated with poorer survival following melanoma.[27] As the amount of time required for safe exposure to sunlight in order to promote skin stores of Vitamin D remains controversial, currently the advice for patients with a history of melanoma is still to sun protect and if concerned

about Vitamin D deficiency to take supplements.[28] Current guidance from NHS Choices recommends up to 1000 IU (25 micrograms) per day[29]. The Melanoma Genetics Consortium[30] currently recommend that patients with a history of melanoma consider taking between 600-1000 IU of vitamin D per day and that the dose should be discussed with their doctor, with consideration made for measuring baseline Vitamin D. It is also prudent to check baseline renal function and bone profile prior to initiating therapy. Rarely Vitamin D supplementation can unmask primary hyperparathyroidism so serum calcium levels should be checked one month after starting supplementation. It is advisable to wait at least 6 months after starting supplements before rechecking Vitamin D levels.

Summary and overview

In summary, the incidence of melanoma continues to rise. Health promotion measures, which highlight the risks of excessive sun exposure and use of sun beds are very important. It is also essential that there is ongoing education for clinicians in primary care on the early signs of melanoma and continued awareness of the appropriate referral pathway for suspicious lesions. Early detection is the key factor determining a good prognosis.

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