**Title**

Melanoma of the foot

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**Synopsis (100-150 words)**

Melanoma is a rare form of skin cancer which is responsible for most skin cancer deaths in the world today. Tumours arising on the foot continue to be a particular challenge. Not only do patients present later but lesions are frequently misdiagnosed leading to more advanced disease with an overall poorer prognosis then melanoma elsewhere. In order to improve early recognition this paper reviews the clinical features of the disease along with published algorithms which may increase the practitioner’s awareness and lead to an earlier diagnosis and subsequently, improve the prognosis for the patient. Emerging assessment techniques such as dermoscopy is also discussed as a tool to improving clinical decision making. An overview of the contemporary drug therapies in the treatment of advanced disease is also discussed.

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*The authors have nothing to disclose.*

**Keypoints (3-5, 125 words total)**

1. Melanoma of the foot exhibits many unique characteristics compared to cutaneous melanoma elsewhere in terms of its presentation and prognosis.
2. Melanoma of the foot is frequently delayed in its presentation and diagnosis due to it highly variable appearance on the plantar surface and within the nail unit.
3. To assist the practitioner in earlier recognition the “CUBED” acronym can help to raise awareness of a possible foot melanoma diagnosis. In addition, the dermatoscope is a useful clinical tool which can improve clinical assessment of suspicious lesions.
4. New drug therapies targeting known melanoma mutations are showing promise in the treatment of melanoma, extending survival times for patients with the disease.

**Introduction**

The rise in incidence of cutaneous malignant melanoma worldwide continues to be of concern with around 132 000 new cases occurring globally every year [1](#_ENREF_1). Despite these increases, some data suggests that mortality from the disease is levelling, probably due to increase public awareness and earlier diagnosis of the disease [2](#_ENREF_2). However, melanoma which arises on the foot represents a subset of the disease, when compared to cutaneous melanoma elsewhere, that runs counter to these observed improvements. Foot melanoma exhibits its own unique peculiarities and clinically may present a greater diagnostic challenge as lesions often are presented and diagnosed late adversely affecting outcomes. Recent research has shown dermoscopy to improve recognition of early lesions but despite promising advances in treatment of established disease, excision remains the mainstay of therapy.

**Types of melanoma**

A melanoma is a malignant tumour arising from the melanocyte. The tumour can arise on any area of the skin, and up to half occur in pre-existing melanocytic naevi [3](#_ENREF_3). Melanoma can be categorised into sub-types based on histology and pathological characteristics. Lesions arising on the foot and hands, particularly the palms, soles or within the nails are often termed “acral” or “volar” melanoma – a reference to anatomical location rather than their sub-type. Although not all melanoma are classifiable, the main subtypes of melanoma that may arise on the skin are:

* Superficial Spreading Melanoma (SSM) (figure 1)
* Lentigo Maligna Melanoma (LMM)
* Nodular Melanoma (NM) (figure 2)
* Acral Lentiginous melanoma (ALM) (figure 3)

Across the whole body surface, SSM accounts for around 65% of all melanomas, whilst LLM 27%, NM 7% and ALM at just 1% [4](#_ENREF_4). However, on the foot, the ALM sub-type predominates being responsible for around 60% of all foot melanoma, with SSM and NM accounting for 30% and 9% respectively [5](#_ENREF_5). Other authors have concluded similar proportions with the ALM sub-types being the most prevalent lesion type [6](#_ENREF_6),[7](#_ENREF_7) with lentigo maligna melanoma being rarely found in areas other than the head and neck.

**Amelanotic Melanoma**

Within each of the main sub-types, a proportion of lesions may be categorised as amelanotic (or hypopigmented) where instead of being the usual dark brown/black colour, lesions maybe devoid of pigment appearing lighter in colour being pink or red (figure 4). Across the whole body, less than 8% of melanoma are classified as amelanotic [8](#_ENREF_8) however, within the specific sub-types hypomelanotic or amelanotic lesions may represent much higher percentages. Around 40% of nodular and acral lentiginous melanoma have been shown to have reduced or no pigment within them [9](#_ENREF_9) with amelanotic lesions being seen more frequently in areas such as the palms and soles [10](#_ENREF_10).

**Nail Melanoma**

Nail melanoma is not specifically a histological sub-type of melanoma but merely refers to lesions arising from within the nail unit (figure 5) - most of these lesions are acral lentiginous or nodular melanoma. Melanoma arising in the nail unit is rare and subsequently accounts for less than 2% of all melanoma cases [11](#_ENREF_11). As many lesions are nail unit located acral lentiginous melanoma, this type of melanoma occurs equally in all races.

**Figures 1-5:** The main variants of melanoma arising on the foot [10](#_ENREF_10)

**Figure 1:** Superficial Spreading Melanoma (SSM). A type which spreads radially before gradually becoming vertically invasive. On the foot the majority of this sub-type are found on the dorsum.

**Figure 2:** Nodular Melanoma (LM). A more aggressive melanoma than the SSM as it may rapidly become vertically invasive. The lesion is more common in older patients.

**Figure 3:** Acral Lentiginous Melanoma (ALM). The rarer sub-type of the disease but is most common on the foot, particularly on the soles and in the nail unit. This sub-type occurs at the same rate in all races/skin types.

**Figure 4:** Amelanotic Melanoma. A number of melanoma may lack pigment and are labelled as amelanotic. Amelanotic lesions are more frequent in acral areas such as the foot and are diagnostically more challenging.

**Figure 5:** Nail Melanoma.Most melanoma arising at this location are ALM but occasionally NM. Lesions may arise initially as a longitudinal melanonychia or as alterations in nail plate.

**How common are melanoma on the foot?**

The proportion of melanoma that occur on the foot is difficult to accurately ascertain as epidemiological studies have rarely categorised lesions on the foot exclusively tending amalgamate with lesions of the hand or with the lower extremity making accurate estimates difficult. One recent study of 1542 melanoma identified 6.6% of lesions as arising on the foot with a slight female preponderance which has been observed in other studies [12](#_ENREF_12). However, wide variation of this figure can be seen amongst different ethnic groups.

Non-white races, despite having a have a much lower rate of the disease generally, are more likely to develop lesions in acral locations such as the palmar, plantar surfaces and nail bed [13](#_ENREF_13). For example, Jimbow and colleagues reported that 40% of melanoma occurring in their Japanese cohort of patients were in acral locations with 80% of these lesions being diagnosed as acral lentiginous melanoma [14](#_ENREF_14). The acral lentiginous melanoma is the most frequently observed type of the disease in non-white populations [15](#_ENREF_15). Although melanoma can arise at virtually any age, they are rare before adulthood, increasing in incidence with age, with the majority of melanomas on the foot arising between the sixth and eighth decades of life [7](#_ENREF_7).

**Aetiology**

Intermittent and chronic sun exposure along with a history of sunburns is the major factor which is associated the development of cutaneous malignant melanoma. However, lesions arising in areas which are seldom exposed to the sun, such as the nail unit and soles of the feet brings into question the true aetiology for lesions in these areas – additional factors may contribute. The nail unit for example has a relatively small skin surface area but research has shown that actual melanoma density is 9 times the expected average for an area of this size [16](#_ENREF_16). In addition, much of the nail unit is shielded by the nail plate which at a thickness of greater than 0.5mm is a shield to virtually all UVB radiation reaching the nail bed [17](#_ENREF_17). Moreover, a recent study has highlighted how, despite increases in melanoma generally have occurred over the last few years, rates of melanoma on the foot have remained relatively constant [18](#_ENREF_18).

The role of trauma and the development of melanoma has been much debated but still remains unresolved. The feet, by virtue of their location, are likely to be subjected to more physical trauma than other areas of the body which has bolstered the traumatic aetiology theory. Whilst patients frequently report injuries as a possible cause of their melanoma, few scientific studies have objectively substantiated these claims. It has been suggested that in many cases a traumatic event to the affected area only serves to focus the patients attention to a previously existing lesion [19](#_ENREF_19).

Despite the lack of sun exposure to many areas of the foot, resemblance in nature to melanoma elsewhere on the body has been demonstrated. In a case-control study of Caucasian patients with palmar and plantar melanoma versus patients without melanoma, it was shown that that foot melanoma patients had a higher sun exposure level, higher total body mole count along with and a higher history of sunburn [20](#_ENREF_20). The authors suggest that despite lack of sun exposure to the plantar surface, total sun exposure may positively affect the development of plantar lesions. The presence of pre-existing plantar lesions were also found to be a risk factor in this work. Higher levels of junctional and compound naevi in less sun exposed sites, like the soles, have been suggested as an explanation for the occurrence of melanoma in these areas [21](#_ENREF_21). Exposure to agricultural and industrial chemicals has also been explored as a possible explanation with an increased risk being observed in one systematic review [22](#_ENREF_22).

**Clinical Presentation of Melanoma on the foot**

Timely diagnosis of melanoma relies on prompt presentation by the patient to their healthcare professional, permit recognition and diagnosis by the treating clinician. Delays in patient presentation have been recognised as an issue. Consequently, patients may present with more advanced melanoma, adding to a poorer prognosis.

Thorough assessment of any potential skin cancer by a treating physician is a key stage in diagnosis, however foot melanoma in particular frequently present challenges, resulting in diagnostic delay. Initial misdiagnosis rates for melanoma generally have been estimated at around 18% [23](#_ENREF_23) however figures for lesions arising on the foot have been shown to be much higher (between 25-36% [24](#_ENREF_24),[25](#_ENREF_25)) with the acral lentiginous melanoma sub-type and nail melanoma offering the greatest diagnostic challenge [26](#_ENREF_26). Reasons for this are under-researched but with a highly variable clinical appearance it can resemble, many common podiatric pathologies, particularly when it is lacking in pigment. The literature contains many published case reports documenting melanoma mis-diagnosed as more common skin conditions (see box 1).

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| **Ingrowing toe nail**  **Foot ulcer**  **Wart/verrucae**  **Tinea Pedis/Onychomycosis**  **Bruising**  **Foreign body** | **Sub-ungual haematoma**  **Pyogenic granuloma**  **Poroma**  **Hyperkeratosis-corns/callus**  **Necrosis**  **Paronychia**  **Ganglion** |

**Box 1:** Reported misdiagnoses for melanoma on the foot

Traditionally, the “ABCD” acronym has been used by the public and physicians in raising the suspicion of melanoma since 1985 [27](#_ENREF_27) (table 1), however its utility in the diagnosis of smaller and amelanotic lesions, and those arising on the foot has been questioned [4](#_ENREF_4),[24](#_ENREF_24). Recognising the issues around delayed and mis-diagnosis, a new acronym “CUBED” has been proposed [10](#_ENREF_10) (table 2). Any lesion scoring two or more should be referred or considered for a biopsy.

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| **Letter** | **Meaning** | **Description** |
| **A** | **Asymmetry** | One half of the lesion is not like the other half |
| **B** | **Border** | An irregular, scalloped or poorly defined border |
| **C** | **Colour** | Variegation of the colours |
| **D** | **Diameter** | Melanomas are usually larger than 6mm but can be smaller |
| **E\*** | **Evolving** | A mole or lesion that is changing in size shape or colour |

**Table 1:** The ABCDE Mnemonic [27](#_ENREF_27),[28](#_ENREF_28)

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| --- | --- |
| **C** | Coloured lesions where any part is not skin colour. |
| **U** | Uncertain diagnosis. Any lesion that does not have a definite diagnosis |
| **B** | Bleeding lesions on the foot or under the nail, whether the bleeding is direct bleeding or oozing of fluid. This includes chronic “granulation tissue”. |
| **E** | Enlargement or deterioration of a lesion or ulcer despite therapy |
| **D** | Delay in healing of any lesion beyond 2 months. |
| **Consider undertaking a biopsy or specialist referral if any two or more criteria apply** | |

**Table 2:** The CUBED acronym [10](#_ENREF_10)

More recently, within dermatology, the use of dermoscopy as part of the lesion assessment process has become mainstream [29](#_ENREF_29). The dermatoscope is a handheld device which offers magnification of the lesions (10x) and applied via gel or oil based medium or using polarised light which allows for visualisation of structures not normally visible to the naked eye (figure 6). The utility of the device, with training, has been shown to be more predictive in recognising the potential signs of melanoma than the naked eye [30](#_ENREF_30). Consequently, it allows earlier recognition of melanoma before they become advanced and reduces the excision rates for benign lesions. Moreover, having such a device increases clinician’s awareness of the need for vigilant assessment of pigmented lesions [31](#_ENREF_31).

**Figure 6:** The dermatoscope is a hand held device which allows visualisation of skin structures not normally observed by the naked eye.

**Presentation of melanoma of the nail unit**

Nail melanoma typically presents late and subsequently hold a poorer prognosis. Their variable appearance and relative rarity can make them a significant diagnostic challenge. Typically lesions may present in two ways. Firstly, as a longitudinal melanonychia stripe which eventually alters normal nail anatomy or secondly, as an amelanotic tumour which gives rise to some nail plate disruption. Sub-ungual bleeding is a common clinical condition which can give rise to diagnostic uncertainty. A good history and careful short term observation can offer clues to discern possible aetiology – a sub-ungual brown discolouration that clears proximally with time is almost certainly a haematoma. Also, it is important to remember that functioning melanocytes are almost always exclusively found in the matrix and nail folds, so a longitudinal stripe that arises half way up in the nail bed is very unlikely to be a melanoma. Table 3 below highlights the characteristics that may help discern sub-ungual bleeding from melanonychia.

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| **Melanonychia** | **Subungual bleeding** |
| The duration of history is from 3-6 months upwards to 20 years or more | The duration of history is rarely more than 6 months and is typically shorter |
| A history of trauma is quite common | A history of trauma or precipitating activity is quite common |
| Lateral margins within the nail are mainly straight and longitudinally oriented | Lateral margins may be irregular |
| Where margins merges with the nail fold, pigment may spread onto nail fold (Hutchinson’s sign) | Pigment rarely extends from beneath the nail plate |
| There are rarely any detectable transverse features | There may be a proximal transverse groove and/or transverse white mark within the nail |
| In the absence of clinical tumour, nail plate pigmentation is in continuity with a single zone | Haemorrhage may be broken up into a number of zones |
| Dermoscopy reveals   * continuous pigment between proximal nail fold and distal free edge * in the transverse axis, pigment may vary – whereas in the longitudinal axis it remains largely constant * There may be longitudinal flecks of darker pigment within the background pigment of the nail * Pigment is mainly brown black | Dermoscopy reveals   * Pigment may not be continuous in the longitudinal axis, with clear nail at either the proximal or distal margin * Pigment may vary in any axis * Droplets of blood may be seen separated from the main zone of pigmentation * Blood may be seen as a discrete layer of material on the lower aspect of the nail plate at the free margin * Pigment may be purple black, with increasing red hues at margins. It is rarely brown |

**Table 3:** Features of longitudinal melanonychia compared with those of subungual bleeding – all features are generally true, but there can be individual exceptions [10](#_ENREF_10).

Levit [32](#_ENREF_32) produced an ABCDE acronym to help in early recognition of nail melanoma, summarised in table X below:

|  |
| --- |
| **A:** Age Range 20-90, peak 5th – 7th decades.  **B:** Band (nail band): Pigment (brown-black). Breadth >3mm. Border (irregular/blurred).  **C:** Change: rapid increase in size/growth rate of nail band. Lack of change: failure of nail dystrophy to improve despite adequate treatment.  **D:** Digit Involved: Thumb > hallux > index finger > single digit > multiple digits.  **E:** Extension: Extension of pigment to involve proximal or lateral nail fold (hutchinson’s sign) or free edge of nail plate.  **F:** Family or personal history: Of previous melanoma or dysplastic nevus. |

**Box 2 :** The ABCDE of nail melanoma [32](#_ENREF_32).

**Dermoscopy**

Dermoscopy in assessment of pigmented lesions on the feet has been found to be useful. The unique properties of thickened, weight bearing plantar skin give rise to specific dermatoscopic patterns in benign and malignant melanoma. On the skin, close examination with the dermatoscope has demonstrated that benign lesions exhibit concentrated pigment patterns in the narrow furrows of the natural dermatoglyphics. This has been termed the “parallel furrow” pattern (figure 7a and 7b). However, in malignant melanoma pigmentation is frequently accentuated on the wider ridges of the dermatoglyphics along with lesion asymmetry and colour variegation [33](#_ENREF_33) (figure 8a and 8b).

**Figure 7a and b:** Parallel Furrow pattern – melanin is concentrated within the narrow furrows of plantar skin giving rise to the parallel furrow pattern observed with the dermatoscope.

**Figure 8a and b:** The parallel ridge pattern as seen with the dermatoscope. Pigment is concentrated upon the wider ridges of the natural plantar dermatoglyphics (viewed at the base of the lesion).

Dermoscopy has also been used as a technique for differentiating the various causes of melanonychia within the nail, including melanoma. Although, currently untested formally, the technique has been shown to help inform clinician’s decisions on whether a nail biopsy is appropriate [34](#_ENREF_34).

**Diagnosis and staging of melanoma**

A diagnosis of melanoma is made following histological analysis and interpretation of the report on the excised lesion. In order to assess the extent of the disease, staging is an important step to determine the optimum treatment strategy and establish a prognosis. Melanoma staging (table 4) is based around the following tumour characteristics: thickness of the tumour (Breslow’s thickness); the appearance of microscopic ulceration on the surface of a tumour and the mitotic rate of cells within the tumour. Staging is also based on presence and type of any nodal and distant metastases [35](#_ENREF_35).

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| **Stage** | **Features** |
| **Stage 0** | the melanoma is on the surface of the skin. |
| **Stage 1A** | the melanoma is less than 1mm thick. |
| **Stage 1B** | the melanoma is 1-2mm thick, or the melanoma is less than 1mm thick and the surface of the skin is broken (ulcerated) or its cells are dividing faster than usual (mitotic activity). |
| **Stage 2A** | the melanoma is 2-4mm thick, or the melanoma is 1-2mm thick and is ulcerated. |
| **Stage 2B** | the melanoma is thicker than 4mm, or the melanoma is 2-4mm thick and ulcerated. |
| **Stage 2C** | the melanoma is thicker than 4mm and ulcerated. |
| **Stage 3A** | the melanoma has spread into one to three nearby lymph nodes, but they are not enlarged; the melanoma is not ulcerated and has not spread further. |
| **Stage 3B** | the melanoma is ulcerated and has spread into one to three nearby lymph nodes but they are not enlarged, or the melanoma is not ulcerated and has spread into one to three nearby lymph nodes and they are enlarged, or the melanoma has spread to small areas of skin or lymphatic channels, but not to nearby lymph nodes. |
| **Stage 3C** | the melanoma is ulcerated and has spread into one to three nearby lymph nodes and they are enlarged, or the melanoma has spread into four or more lymph nodes nearby. |
| **Stage 4** | the melanoma cells have spread to other areas of the body, such as the lungs, brain or other parts of the skin. |

**Table 4:** Melanoma staging [35](#_ENREF_35)

Patients with melanoma arising on the foot are clinically examined, palpating of relevant lymph nodes in the groin of the affected limb. Any suspicious swelling identified would then be investigated further, usually with ultrasound and needle biopsy. However, nodal metastases may be non-detectable with clinical examination.

For melanoma patients considered at higher risk of lymph node metastasis, sentinel lymph node biopsy (SLNB) can be considered. This is a technique carried out under general anaesthetic at the time of wide local excision. A mildly radioactive dye is injected into the skin at the site of the previously excised melanoma. Dye is then tracked to the first group of lymph nodes, possibly aided by the use of a radioactivity scanner. One or more of these nodes (the sentinel nodes) are then excised and examined histologically. The presence of melanoma in a sentinel node would usually indicate the need for excision of all the regional lymph nodes from that site (lymphadenectomy).

SLNB is a technique to accurately stage melanomas. However, it is not a treatment for melanoma. Lymphadenectomy can reduce the risk of regional melanoma recurrence, but there is no convincing evidence that it prolongs survival. Therefore SLNB is not universally offered in the United Kingdom. Guidelines from the UK suggest doctors should consider using this test as a staging rather than a therapeutic procedure for people with stage 2B–2C melanoma with a Breslow thickness of more than 1 mm [36](#_ENREF_36). As reported in one study of 84 patients with primary acral lentiginous melanoma who underwent SLNB, a positive result was more likely with thick or ulcerated ALM, and was related to a significantly shorter melanoma-specific survival (5-year survival rate, 37.5% vs 84.3%) [37](#_ENREF_37).

**Prognosis**

Tumour thickness is the most important prognostic indicator in all types of melanoma, with tumour thickness up to 1mm being associated with a favourable prognosis. However, studies have highlighted that melanoma arising on the foot have a worse prognosis than melanoma elsewhere on the body [38](#_ENREF_38). This maybe in part because remote regions of the body, such as the foot, are rarely visualised and inspected by the patient and so lesions may be noticed at a more advanced stage. Moreover, even when a lesion is identified on the foot, patients may delay seeking medical attention. In one review of 27 cases of foot melanoma, the average time to seek medical attention was 13.5 months [24](#_ENREF_24).

A study of 1413 cases of ALM in the United States aligned with this suggestion, showing that only 41% of ALM cases were diagnosed with a thickness of up to 1mm, compared to 70% of cutaneous melanomas (CM) at other sites. In addition, ALM had significantly poorer melanoma-specific survival rates when compared to CM overall, even after controlling for thickness. This suggests that lower survival rates seen in ALM may be secondary to reported different biological characteristics of the melanoma subtypes [15](#_ENREF_15).

**Current and recent advances in the treatment of melanoma**

Following confirmation of a melanoma, wide excision of the lesion, or amputation of the affected digit and observation remain the mainstay of therapy. The width of the excision being guided by the thickness of the lesion (Table 5).

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| --- | --- |
| **Tumour Thickness** | **Recommended Margins** |
| In Situ | 0.5 cm |
| <2mm | 1.0 cm |
| > 2mm | 2.0 cm |

**Table 5:** Excision margins for melanoma [39](#_ENREF_39)

In patients with distant metastases surgical management of these has been shown to be of benefit. However, recent developments in drug therapies exploiting genetic mutations have shown promise.

Genetic mutations are present in the majority of melanomas. Different mutations are associated with specific clinical melanoma subtypes. In cutaneous melanoma for example, BRAF and NRAS mutations are seen in 40-50% and 15-20% of cases respectively. However, in acral and mucosal melanomas, these mutations occur in less than 10% of cases. Mutations in C-KIT are seen in approximately 15 to 20% of patients with acral or mucosal melanomas and in a smaller percentage of melanomas arising in areas of chronic skin damage.

As well as being associated with specific melanoma subtypes, the genetic mutations seen in melanoma have created new specific targeted therapies for advanced stage (metastatic melanoma). Tumours with BRAF mutations can be targeted with vemurafenib and dabrafenib (BRAF inhibitors), which result in progression-free survival of approximately 5-7 months [40](#_ENREF_40). Progression-free survival has been increased to over 9 months when BRAF inhibitors are combined with trametinib [41](#_ENREF_41).

In order to guide treatment options for advanced melanoma, samples from metastases can be sent for genetic testing. If BRAF mutations are not detected, then treatment options include the immune checkpoint inhibitors ipilimumab, and pembrolizumab [42](#_ENREF_42). The response to ipilimumab appears the same for acral melanoma as for other melanoma subtypes [43](#_ENREF_43). As mentioned previously, acral melanomas are more likely to express C-KIT mutation. Several phase II trials of imatinib, a KIT inhibitor, have produced mixed results and further studies are ongoing [44](#_ENREF_44)

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