

Recent developments in melanoma management

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The incidence of malignant melanoma is increasing and although men and women are equally affected, men appear to have poorer survival. In this article the authors describe identification of melanomas and the exciting new treatments that are significantly improving survival.



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VIDEO

Immunotherapy for advanced melanoma

Go to the *Trends* website to view an accompanying video by James Larkin

www.trendsinmenshealth.com/video

The incidence of malignant melanoma has been rising in the UK since the late 1970s. It now represents the fifth most common cancer diagnosed in the UK (after breast, prostate, lung and bowel) and is the seventh most common cancer in males. Generally speaking, men are affected by melanoma in equal proportions to women in the UK; however, over the last decade more males were diagnosed with melanoma relative to females (59% versus 36%).¹ A US study suggests that their survival is disproportionately worse, particularly among younger men.² This may be explained in part by the lower rates of healthcare utilisation by males compared with females.³

Risk factors for the development of melanoma include fair skin and exposure

to ultraviolet (UV) light from the sun and also from sunbeds. It is not just chronic sun exposure that elevates the risk, but also episodes of severe sunburn. There is a hypothesis that much of the predisposing damage is acquired early in life. Eighty-six per cent of melanoma cases are thought preventable and modification of sun exposure is the key to this.^{1,4} Although uncommon, some families may have a genetic predisposition to melanoma.

EARLY DETECTION

Along with prevention strategies, early detection of a changing mole is crucial to catch melanoma at an early stage. When detected early, the vast majority are curable. One recognised approach is to look for 'ABCDE' features in a changing mole

(Table 1).⁵ A 'nodular' melanoma may not present as a mole, but rather as a lump, and it may have the same colour as the surrounding skin. Thus, any growth on or under the skin warrants assessment as a potential melanoma.

BIOLOGY AND MOLECULAR PROFILE

Melanomas are derived from unregulated growth of melanocytes, the cells that generate the pigment melanin. The vast majority of melanomas are cutaneous (>90%); other types include mucosal (derived from the lining of the airway, digestive, genitourinary and reproductive tracts) and ocular.

Melanomas may have gene mutations that drive their growth. The most common is the BRAF V600 mutation, present in 40–50% of cutaneous melanomas.⁶ This is important to identify as it can guide treatment choice. Around 15% of cutaneous melanomas have an NRAS mutation⁷ and 15% of mucosal melanomas have a c-kit mutation.⁸ There is no apparent difference by gender in the rate of these mutations.

STAGING

Melanoma is staged by the 'Tumour Node and Metastasis' (TNM) system common to many tumour types.⁹ For primary moles the 'T' stage is characterised by their Breslow thickness, a cross-sectional measurement of their depth in millimetres (Figure 1). Thicker melanomas have a greater propensity to spread via lymphatic or blood vessels. The presence of ulceration at the surface and the mitotic rate (a measure of cell division) are also important features in primary melanomas that impact their staging. Stage I and Stage II melanomas are classified by these features (Table 2).

Melanoma may spread to local lymph nodes near the primary site and this characterises Stage III disease. This may be a microscopic lymph node deposit, for example picked up in a sentinel lymph node biopsy, or it may

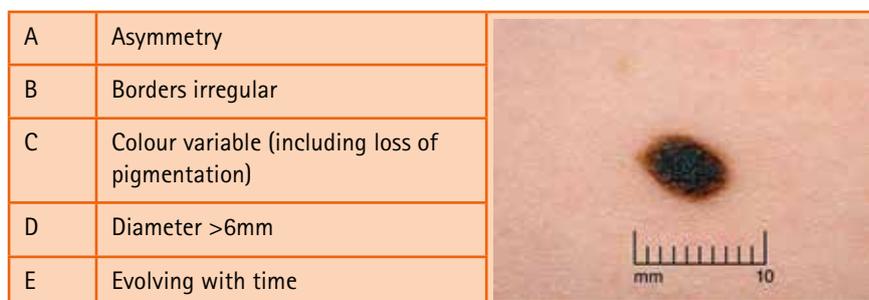


Table 1. The 'ABCDE' features of primary melanomas (photo courtesy of Dr Louise Fearfield)

be clinically detectable, for example a lump found on physical examination or imaging. Sometimes nodules of melanoma may develop en route from the primary mole along lymphatic channels. These are called 'in transit' deposits and the presence of these also denotes Stage III disease (Figure 2). Stage III disease may be cured by removal of affected areas at surgery; however, many patients will remain at a high risk of relapse.

Stage IV or 'metastatic' melanoma is divided into three categories:

- Affecting soft tissue areas (lymph node and subcutaneous disease) away from the original site
- Involving the lungs as well as soft tissues
- Spread to other organs, such as the liver or brain.

In the majority of cases, Stage IV disease is incurable and this is where drug treatments are often employed to control tumour spread and prolong survival.

SURGERY

Surgery is the key treatment for the majority of melanomas. All primary lesions should be removed surrounded by a border of normal tissue called a 'margin', the width of which is dictated by the Breslow thickness. Local lymph nodes that become involved are also usually removed surgically. Occasionally, patients with metastatic disease may undergo surgery if they have a solitary site of disease, or if this is required for pain and effective palliation of symptoms, such as in bowel obstruction. Surgery is often used to remove melanoma that spreads to the brain.

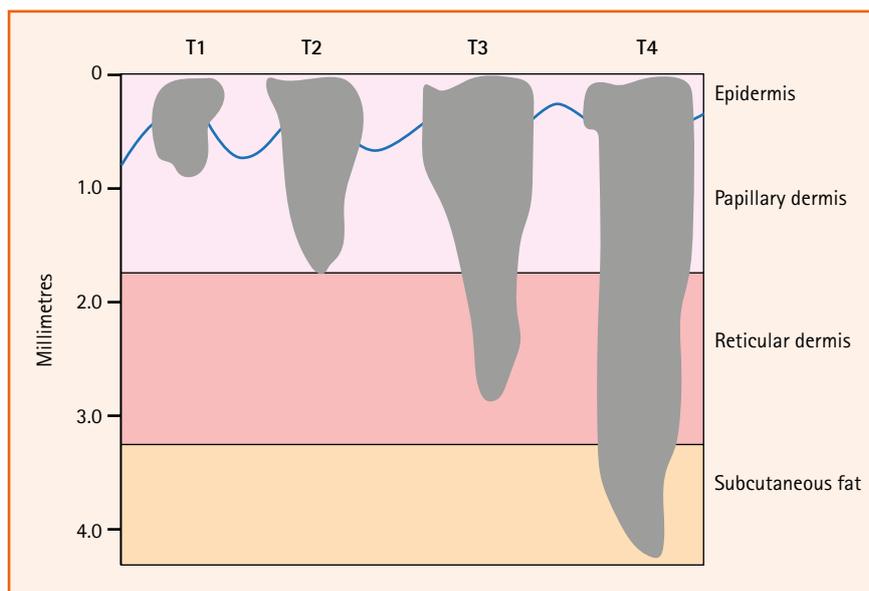


Figure 1. T-stage is characterised by the Breslow thickness of melanomas

	Primary tumour	Lymph nodes involved	Distant metastases
Stage I	≤2.0mm thick (if 1–2.0mm, no ulceration)	No	No
Stage II	1–2.0mm thick with ulceration >2.1mm thick (ulcerated or not)	No	No
Stage III	Any thickness	Yes (and/or in transit lesions)	No
Stage IV	Any thickness	Any lymph node status	Yes

Table 2. Tumour, node and metastasis (TNM) staging of malignant melanoma⁹

DRUG TREATMENTS

Drug therapy for melanoma has advanced considerably in recent years. Patients with unresectable Stage III and Stage IV disease used to have an overall survival around seven months,¹⁰ while patients may now live for many years. There are two main classes of drug treatments used: oral targeted therapy for patients whose tumours harbour a BRAF mutation and intravenous immune checkpoint agents that promote a person's own anti-tumour immune response (Table 3). The benefit of immune checkpoint agents is that durable responses may be seen, even beyond

cessation of therapy. For example, around 20% of patients treated with ipilimumab are alive at three, five and ten years and the standard treatment schedule involves only four doses.¹¹

Each class of drug therapy has its own particular side-effect profile. The BRAF inhibitors dabrafenib and vemurafenib may cause rash (Figure 3), nausea, diarrhoea, liver function derangement and thickened skin on the palms and soles, as well as development of non-melanoma skin cancers. The immune checkpoint agents pembrolizumab, nivolumab and ipilimumab



Figure 2. Melanoma can develop in lymphatic channels running away from the primary tumour. These are 'in transit' metastases (photo courtesy of Mr Dirk Strauss)

cause autoimmune side-effects where the body may attack itself. These include diarrhoea and bowel inflammation (colitis), liver inflammation (hepatitis) and skin inflammation (dermatitis). Some of these side-effects may be severe and treatments may be required to reduce the immune response.

Drug	Mechanism of action	Tumour shrinkage by >30%	Median duration of therapeutic benefit
Dabrafenib (Tafinlar) +/- trametinib (Mekinist)	BRAF inhibitor +/- addition of MEK inhibitor that enhances efficacy	70% in combination (50% dabrafenib alone)	12 months in combination (9 months dabrafenib alone)
Vemurafenib (Zelboraf) +/- cobimetinib (Cotellic)	BRAF inhibitor +/- addition of MEK inhibitor that enhances efficacy	70% in combination (50% vemurafenib alone)	12 months in combination (7 months vemurafenib alone)
Pembrolizumab* (Keytruda)	Anti-PD-1 antibody (targets a molecule that usually turns 'down' the immune response)	30%	5 months
Nivolumab* (Opdivo)	Anti-PD-1 antibody (targets a molecule that usually turns 'down' the immune response)	40%	7 months
Ipilimumab (Yervoy)	Anti-CTLA-4 antibody (targets a molecule that usually turns 'down' the immune response)	15%	3 months

*No direct comparative trials, considered equivalent in efficacy despite apparent differences in response and duration benefit; duration therapeutic benefit may exceed 5–7 months based on other criteria.

Table 3. Drug treatments for melanoma licensed in the UK^{12–15}



Figure 3. Each class of drug treatments has its own particular side-effects. This is a skin rash due to a BRAF inhibitor (photo courtesy of Peta Hughes)

Interestingly, there is a male predominance in the recent large clinical trials of BRAF targeted therapy and immune checkpoint agents, with 55–65% of the populations comprised of men.^{12–15} This may reflect higher rates of Stage IV disease in men, although other reasons may also account for this difference. A difference in treatment outcome by gender is not described.

OTHER TREATMENTS FOR ADVANCED DISEASE

Radiotherapy may be used in the treatment of metastatic melanoma, usually to sites of painful, secondary bone tumours, lymph nodes not amenable to surgery or to the brain. When melanoma involves the brain and there are four or less lesions, high dose radiotherapy known as 'stereotactic' radiotherapy or 'radiosurgery' may be employed; patients may otherwise receive 'whole brain' radiotherapy. With improvement in drug therapies, many of which cross into the brain, there is less enthusiasm for the 'whole brain' approach as it may result in medium- to long-term cognitive impairment.

ADJUVANT THERAPY

'Adjuvant' therapy in oncology aims to reduce any microscopic cancer cells that may remain after definitive treatment (usually surgery) removes the visible disease. In melanoma, historically interferon has been used in some high-risk Stage II and Stage III patients. This therapy has many side-effects that greatly impact quality of life and the overall survival benefit is very small.¹⁶

More recently, the targeted and immune checkpoint therapies that are useful in metastatic disease are being evaluated in the adjuvant setting. Ipilimumab reduces relapse rates compared with placebo at one, two and three years.¹⁷ Although the US FDA has licensed ipilimumab for this indication, it is not yet licensed in Europe. The rate of side-effects was very high in the trial and dissuades many clinicians from its use. A consensus of melanoma physicians in the UK supports close clinical follow-up and imaging, the rationale being to pick up relapsed disease earlier given the effective treatment options available.¹⁸

Adjuvant radiotherapy may be used in patients with Stage III disease after removal of affected lymph nodes. There is no survival benefit with this approach but local relapse rates are reduced.¹⁹ In many centres, the availability of good systemic treatment has seen this approach fall out of favour, particularly given the quality of life impairment seen with lymphoedema.

CONCLUSION

Melanoma is an increasingly common cancer amongst men and women. When detected early, the vast majority of cases are curable. An annual skin check by a GP may help identify moles that appear high risk. Some men are rarely seen by medical services, so when opportunities arise all healthcare professionals need to be vigilant and questioning about moles that may be changing or appearing. While therapeutic advances in the treatment of metastatic melanoma have greatly improved survival

outcomes, reducing the risk of developing primary melanoma through sun protection remains of paramount importance.

Declaration of interests

James Larkin is a non-remunerated consultant for Novartis, Pfizer, BMS, MSD and Roche/Genentech and receives institutional research support from Pfizer, BMS, Novartis, MSD. Lavinia Spain has no relevant disclosures.

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