Malignant Melanoma

Mazin Abdalla

MBBS, MRCGP-UK, National health Service, United Kingdom

Correspondence:
Dr Mazin Abdalla
National health Sevice
Unuted Kingdom
Email: mazin.abdalla1@nhs.net

Received: September 2021; Accepted: October 2021; Published: November 1, 2021.
Citation: Mazin Abdalla.. Malignant Melanoma. World Family Medicine. 2021; 19(11): 112-122
DOI: 10.5742/MEWFM.2021.94167

Abstract

A review of malignant melanima including epidemiology, risk factors, molecular and immune mechanisms, diagnosis, clinical manifestations, subtypes, dermatoscopy, histology, treatment, prognosis and prevention.

Key words: malignant melanoma

Introduction

Malignant melanoma (MM) is cancerous neoplasm of the melanocytes. It is the most aggressive type of skin cancer as it tends to metastasize early. Melanocytes reside in the basal layer of the epidermis in a ratio of 10-15 basal cells to 1 melanocyte. It can also present as non-cutaneous cancer as there are substantial numbers of melanocytes in the digestive, urogenital track and mucous glands.

Epidemiology

Melanoma is the 5th commonest cancer in the UK. It affects adults of any age but is extremely rare in children. The risk of developing malignant melanoma in the UK is 1 in 52 for men and 1 in 54 women (1).

Risk factors

Excessive sun exposure in childhood and early adult life is the most dominant risk factor in most cases of MM. Other risks include those with skin type 1 (always burn and never tan), people with red or blonde hair, freckles, high numbers of naevi >50, and strong family history of melanoma.

Table 1 Risk Factors for Cutaneous Melanoma

High risk (>50-fold increase in risk)	Intermediate risk (~10-fold increase in risk)	Low risk (2- to 4-fold increase in risk)
Persistently changing mole Clinically atypical moles in patient with two family members with melanoma Adulthood (vs. childhood) >50 nevi ≥2 mm in diameter	Family history of melanoma Sporadic clinically atypical moles Congenital nevi (?) White ethnicity (vs. black or East Asian ethnicity) Personal history of prior melanoma	Immunosuppression Sun sensitivity or excess exposure to sun

Source: Adapted from AR Rhodes et al: JAMA 258:3146, 1987.

Molecular and immune mechanisms

The mitogen-activated protein kinase (MAPK) pathway (Ras, Raf, MEK and ERK) plays a pivotal role in regulating gene expression, cellular growth and survival (2). This regulatory apparatus is tweaked in nearly 80% of all cases of malignant melanoma which was found to be due to mutation in either NRAS or BRAF. BRAF mutation accounts for nearly 90% of these cases. The activating mutation is formed by the replacement of glutamic acid for valine at the amino acid in position 600 (V600E).

The PI3K-AKT pathway is another major regulator of cell survival, growth and apoptosis. A key inhibitor of this pathway is PTEN, and inactivation of the gene that encodes PTEN via mutations, deletions, or promoter methylation also occurs in cutaneous melanomas. Thus, there is increased activity of the PI3K-AKT signalling pathway.

Figure 1: RAS-RAF-MEK-ERK (MAPK) and PI3K-AKT signalling pathways.

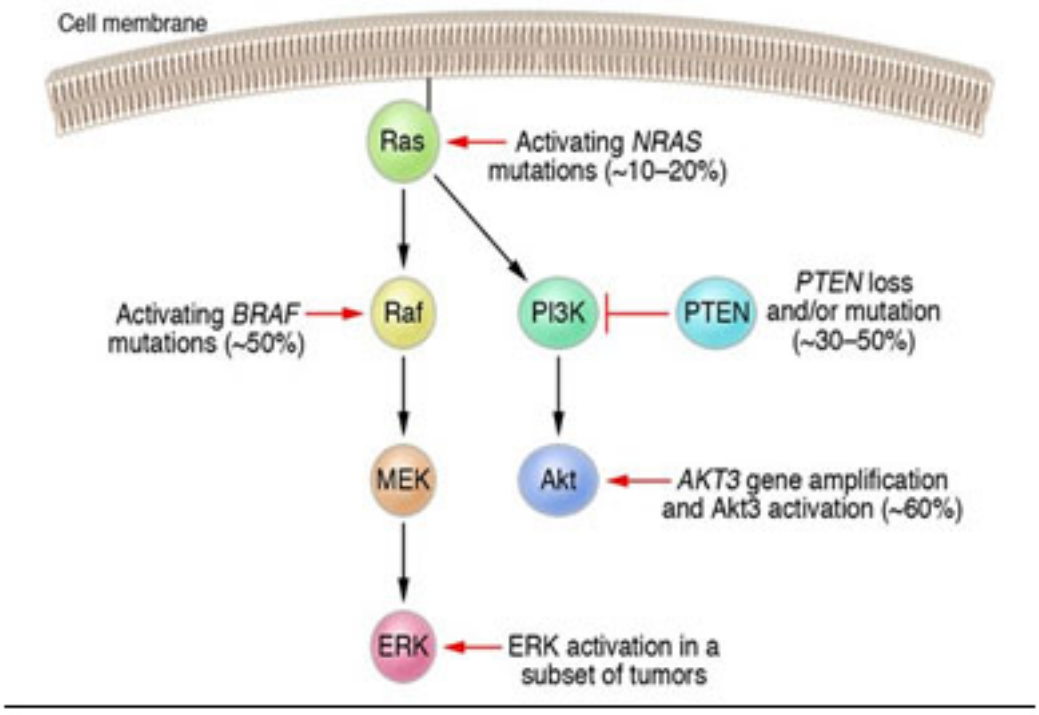
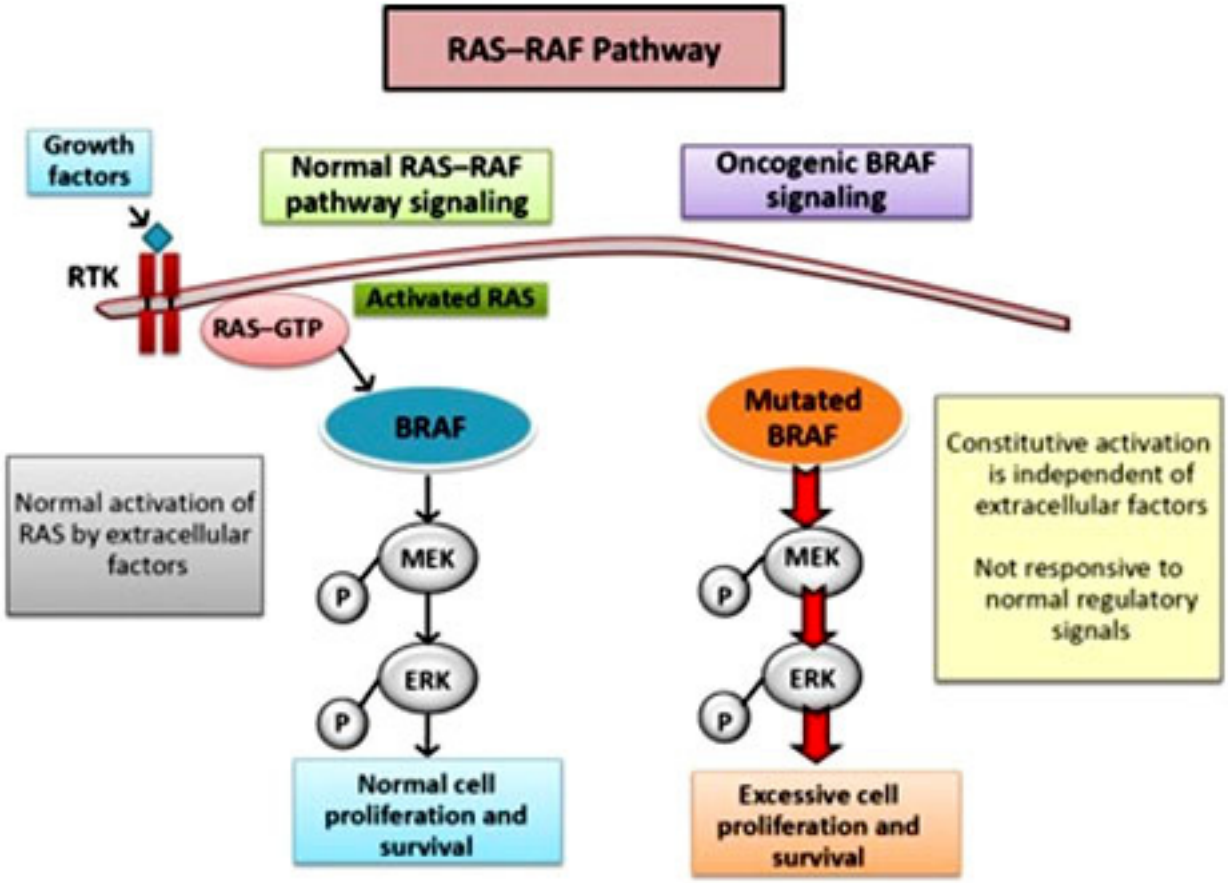


Figure 2: MAPK pathway is normally activated by growth factor binding to receptor tyrosine kinases which stimulate a cascade activation of the signalling molecules Ras, Raf, MEK and ERK. Activated ERK controls cellular proliferation.



Diagnosis

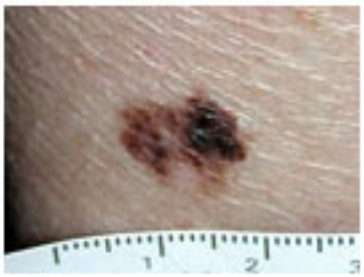
A. Clinical presentation:
ABCDE is an easy reminder of the worrying changes to a pigmented lesion which should prompt a 2-week rule referral to dermatologist for biopsy and histological diagnosis. ABCDE rule is:

Asymmetry, Border irregularity, Colour irregular, Diameter >6 mm and Elevation / Enlargement of any mole over short period.

There are other symptoms as well which should raise the alarm regarding possible MM i.e. bleeding/oozing, pain, and inflammation.

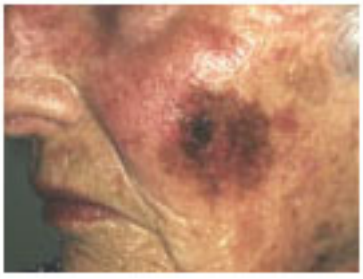
B. Subtypes of cutaneous malignant melanoma:

1. Superficial spreading malignant melanoma: This is by far the commonest type of MM. It is more prevalent at sites of excessive sun exposure, i.e. on the trunk in males (40%) and the legs in females (also 40%).



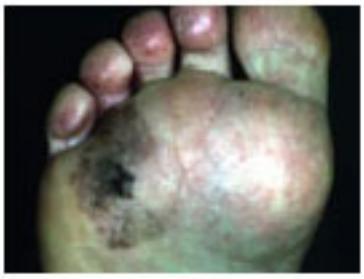
Picture 1: Typical SSMM

2. Lentigo maligna melanoma: This arises from lentigo maligna (areas of malignant transformation of melanocytes on sun damaged sites) which is still confined to the epidermis and defined as melanoma in situ. When it invades the dermis, it is call lentigo maligna melanoma.



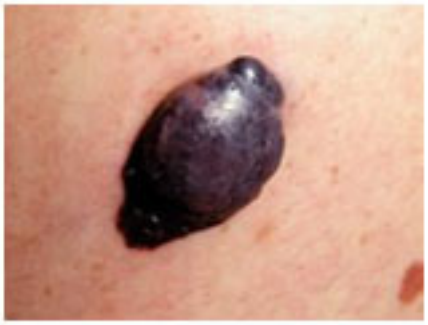
Picture 2: Lentigo maligna melanoma

3: Acral lentiginous melanoma: This affects the palm, sole and subungual areas.



Picture 3: Acral lentiginous melanoma

4. Nodular melanoma
This type presents clinically as a rapidly growing nodule over weeks to few months. It has the potential of early invasion and is capable of early metastasis.



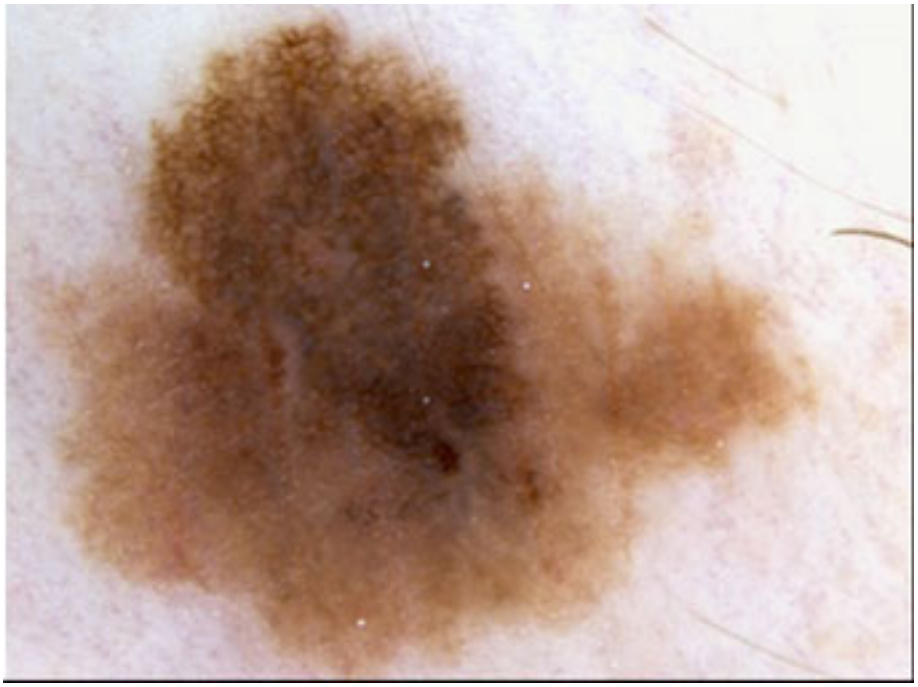
Picture 5: Nodular melanoma

5. Amelanotic melanoma
The lesions in this type of MM have no colour and lack the typical changes in pigmentation. It is often diagnosed histologically on excisional biopsy of rapidly changing nodule or suspected BCC.

Subtype	Frequency	Common site	Key distinguishing features
Superficial spreading melanoma	70%	Trunk of men Legs of women	RGP, 1–5 years
Nodular melanoma	10–25%	Trunk of men Legs of women	RGP, 6–18 months
Acral lentiginous melanoma	5%	Palms, soles, nails	Not related to sun damage All races affected Accounts for 30–70% of melanoma in dark-skinned individuals
Lentigo maligna melanoma	<1%	Head and neck of elderly	Associated with chronic sun exposure RGP, 3–15 years
Noncutaneous melanoma	5%	Ocular, mucosal	Not associated with sun exposure Prognostic features and treatment differ from that of cutaneous subtypes

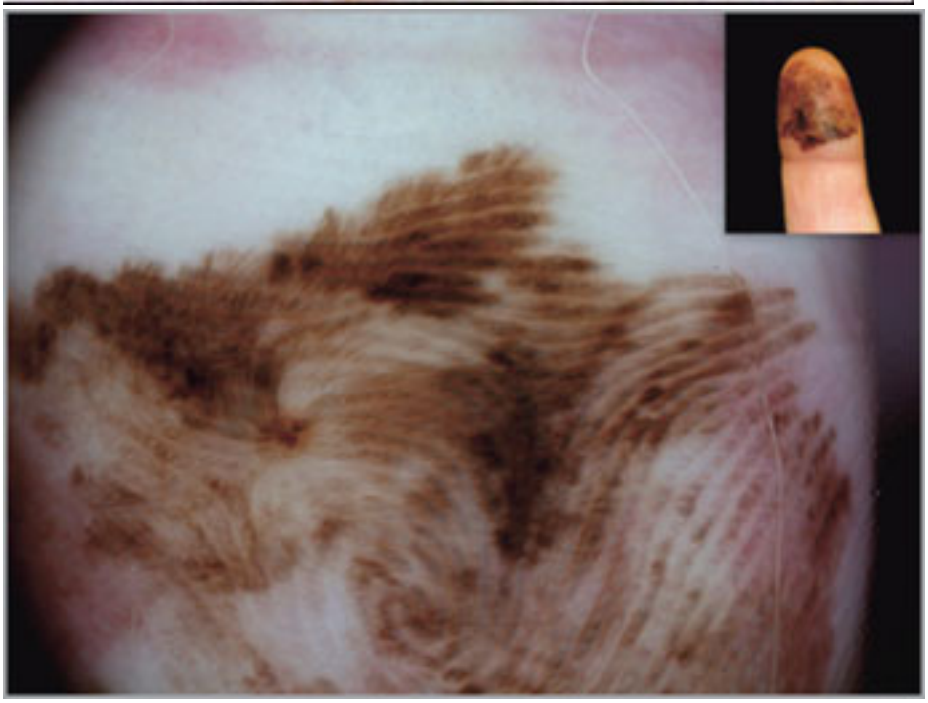
C. Dematoscopy:
This can provide quick information to differentiate common benign pigmented lesions from those which display features of MM. The following table shows some of these sinister features:

Table 2: shows dermatoscopic findings in each type of malignant melanoma. Source: www.dermnetnz.org/



Superficial melanomas and lentigo maligna melanoma

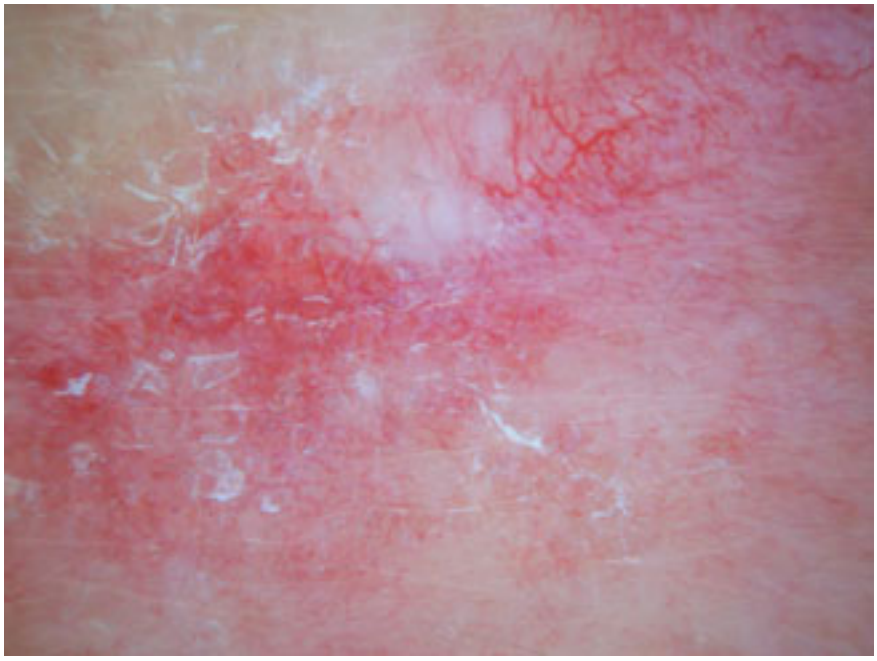
- Blue-white veil
- Radial streaming
- Scar-like depigmentation
- Peripheral black dots/globules
- Different colours
- Broad and irregular network
- Focal sharply cut-off border



Acral melanoma

- Different colours.
- Irregular borders
- Asymmetry
- Pigmentation involving the ridges rather than the benign parallel furrow pattern.
- Destruction of sweat ducts which normally appear as white dots on the ridges (acrosyringia)

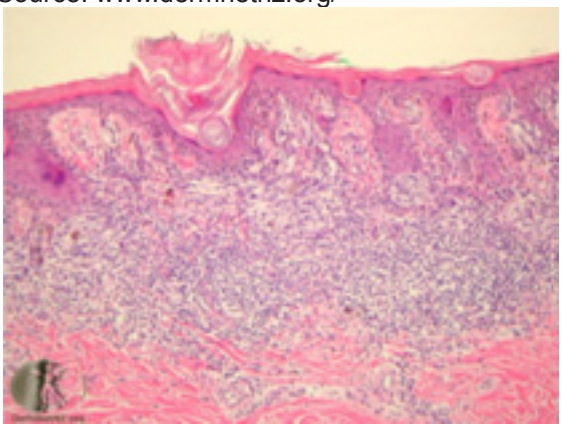
•



Amelanotic melanoma
This can be very tricky to diagnose by dermoscopy. Abnormal vascularity may raise the suspicion, with linear, dotted, corkscrew or polymorphous vessels. Pressing hard on the dermatoscopy may obscure the vascular pattern.

D. Histology:
The classical histological features of melanomas include destruction of the epidermis, upward spread of melanocytes, nests of atypical melanocytes with variable morphology (which may lack maturation), melanocytic invasion of lymphovascular spaces, increased apoptosis and atypical mitoses. These changes lead to architectural disturbance to the skin (3).

Figure 3: Shows the typical histological features of melanoma as described above.
Source: www.dermnetnz.org/



6. Metastasis:
Melanoma can spread via lymphatic channels or blood stream. Regional lymph nodes are a common site to find the earliest metastases hence lymphadenectomy is thought to control the disease. Haematogenous spreading usually affects the Liver, lung, bone, and brain.

7. Staging:
The following table (3) summarises the AJCC Cancer Staging Manual, 7th Edition 2010

ANATOMIC STAGE/PROGNOSTIC GROUPS							
Clinical Staging[3]				Pathologic Staging[4]			
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
Stage IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
Stage IIC	T4b	N0	M0	IIC	T4b	N0	M0
Stage III	Any T	≥ N1	M0	IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
Stage IV	Any T	Any N	M1	IV	Any T	Any N	M1

Table 3: AJCC TNM staging system 7th edition (2010): TNM categories.

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	a: Without ulceration and mitosis < 1/mm^2 b: With ulceration or mitoses ≥ 1/mm^2
T2	1.01-2.00	a: Without ulceration b: With ulceration
T3	2.01-4.00	a: Without ulceration b: With ulceration
T4	> 4.00	a: Without ulceration b: With ulceration
N	**No. of Metastatic Nodes**	**Nodal Metastatic Burden**
N0	0	NA
N1	1	a: Micrometastasis* b: Macrometastasis†
N2	2-3	a: Micrometastasis* b: Macrometastasis† c: In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	
M	**Site**	**Serum LDH**
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Abbreviations: NA, not applicable; LDH, lactate dehydrogenase.
*Micrometastases are diagnosed after sentinel lymph node biopsy.
†Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.

Source; Melanoma Molecular Map Project website.

8. Treatment

A. SURGICAL MANAGEMENT:

Excision: Once malignant melanoma has been confirmed by initial excision, a wide local excision should be performed to remove all cancerous cells to minimise the risk of local recurrence. Surgery can cure early disease which is still confined to the skin. The margin of this WLE will depend on Blow thickening. The current guideline from the British Association of Dermatologists recommend the following safe margin:

Melanoma in situ= 0.5 cm, <1 mm= 1cm, 1.1-2 mm= 1-2 cm, 2.1-4 mm= 2-3 cm, >4 mm= 3 cm.
This safe margin might be modified according the anatomical site of the lesion.

Sentinel lymph node biopsy:

This is considered to aid the staging of the disease.
It is indicated for patients with stage 1B–2C melanoma. It should be performed at the time of the WLE. It can helps predicting the prognosis, identify those who needs completion lymphadenectomy and those who might be eligible to participate in clinical trials of new treatments for melanoma. (4)

Completion lymphadenectomy:

This procedure should be considered when the histology result confirms the presence of cancerous cells in the sentinel lymph node (stage 3A melanoma). Although it reduces the risk of cancer recurrence in the same area, it has not shown any evidence of increasing the overall survival rate. (4)

Lymph node dissection

This is indicated for patients with stage IIIB–IIIC melanoma or nodal disease detected by imaging.

B. TREATMENT OF METASTATIC MALIGNANT MELANOMA

The aim of treatment in metastatic melanoma is to control the disease and prolong the survival rate.

• Chemotherapy and interleukin

• The main stream treatment for metastatic malignant melanoma was based on two agents (dacarbazine and interleukin-2) until recent years. No improvement was shown in the overall prognosis when using these agents (Tsao et al., 2004). Further studies have demonstrated a poor response rate from both agents (Dacarnazine - 15%-20%, interleukin 2 - 16%) (Middleton et al., 2000).

• Targeted therapies

BRAF inhibitors (Vemurafenib and Dabrefenib): these drugs selectively inhibit mutant BRAF protein in patients with V600E mutation. Using BRAF inhibitors alone can result in resistance (5).

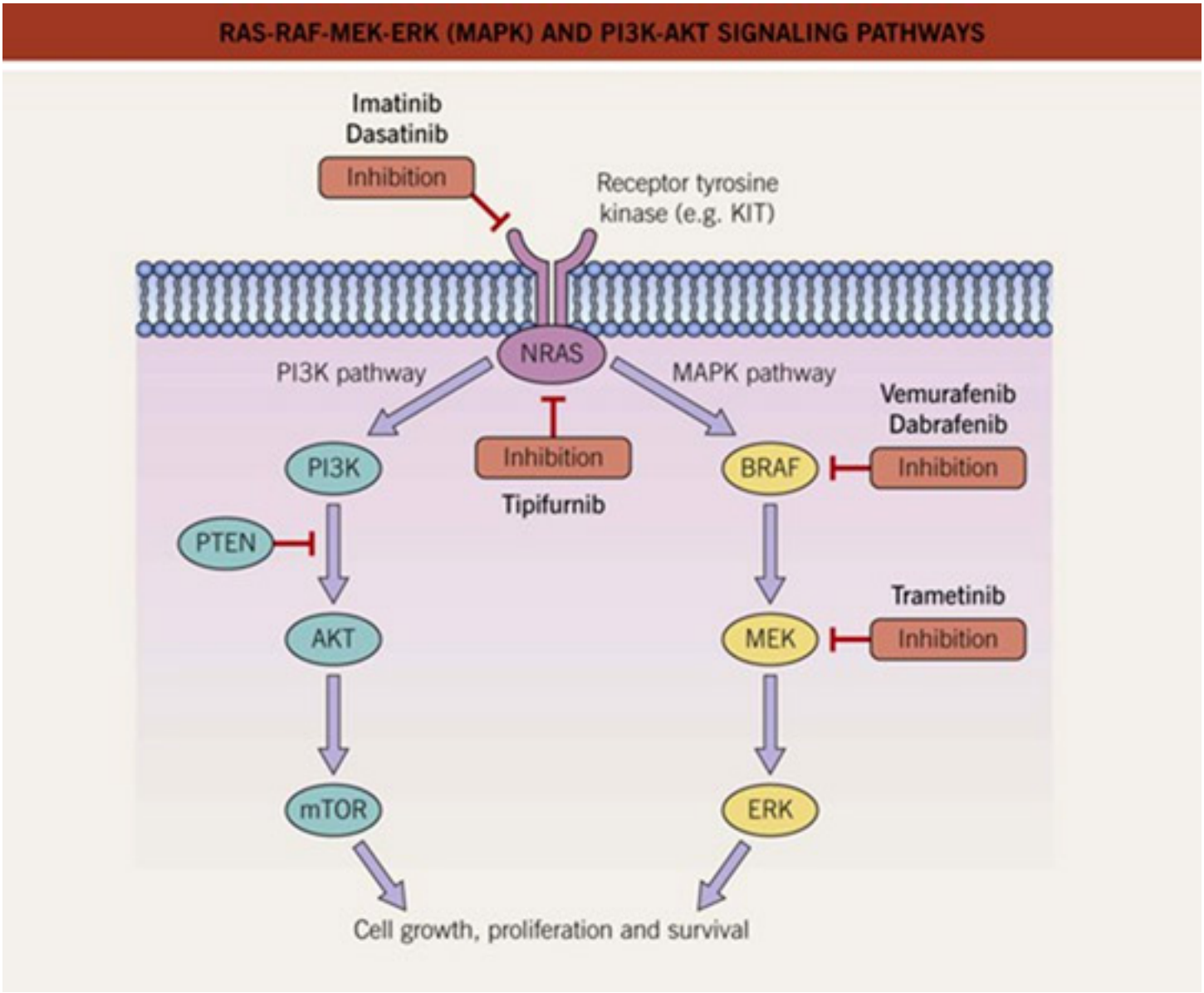
MEK inhibitors (Trametinib and cobimetinib): these drugs inhibit MEK, the MAPK node immediately downstream of RAF, which have shown to increase disease-free survival and reduce resistance rate when used in combination with BRAF inhibitors (5).

• Immunotherapy

• Tumour cells can escape the body's own immunity by expressing ligands to activate CTLA-4 and PD-1, inhibitory T-cell receptors, by that downregulating T-cell activity. To rectify this, therapeutic monoclonal antibodies (mAb) targeting these receptors have been researched and developed.

1. CTLA-4 inhibitors (ipilimumab and tremelimumab): these drugs help to overcome immune evasion by blocking tumour activation of CTLA-4, which acts as an inhibitory signal in CD4+ and CD8+ Tcells.

2. PD-1 inhibitors (nivolumab): Activation of PD1 on the surface of CD4+ and CD8+ T-cell plays a role in suppressing their proliferation and activity.



Adapted from Eggermont AM, Robert C. Melanoma in 2011: A new paradigm tumor for drug development. Nat. Rev. Clin. Oncol. 2012;9:74–76.

9. Prognosis

This is based on the survival rate in 5 year after diagnosis
Stage 0 (Tumour in situ) this can be cured with surgical excision.
Stage 1: 90% survival rate.
Stage 2: 80%
Stage 3: 50%
Stage 4: 10% of men and around 25% of women will survive their cancer for 5 years or more after diagnosis.
These statistics are based on patients treated around 10 years ago. Currently, there are new biological treatments available for patients with stage 4 melanoma. Hence, the survival rate is likely to be better than the figures above (6).

10. Follow-up

Stage 0 (melanoma in situ / lentigo maligna) - no follow-up is needed
Stage 1A: Review every 3-4 months for one year and then discharge. As part of the follow up all patients will be advised about self-examination, sun protection and red flags.
Stage 1B – IIIA: Review every 3-4 months for the first three years then twice yearly for another two years. They might be discharged after 5 years if they remain disease free.

Stage IIIB and upwards: Review every 3-4 months for the first three years then twice yearly to five years then annually to ten years (6).

11. Psychosocial impact:
A diagnosis of melanoma can have variable psychosocial impact in different patients and caregivers alike. Holistic needs assessment HNA is used as a universal measure to assess all patients for a variety of physical, psychological, social, spiritual and information needs. This should be carried out and repeated throughout the patient's journey from the diagnosis, assessment, and treatment phases (7).

12. Prevention:
Sun protection, self-examination and improving melanoma awareness are the key factors to achieve a reduction of the rising MM trend globally.

Conclusion

Malignant melanoma is the most serious skin malignancy. Historically metastatic melanoma had a very poor prognosis but thanks to the advances in understanding the pathogenesis and immunological mechanisms, new and novel treatments have been introduced leading to a better outcome. This area is developing fast and hopes are rising regarding reducing morbidity and mortality associated with metastatic disease.

References

1. Lifetime risk estimates calculated by the Statistical Information Team at Cancer Research UK. Based on data provided by the Office of National Statistics, ISD Scotland, the Welsh Cancer Intelligence and Surveillance Unit and the Northern Ireland Cancer Registry, on request, December 2013 to July 2014.
2. Knight T, Irving JA. Ras/Raf/MEK/ERK pathway activation in childhood acute lymphoblastic leukemia and its therapeutic targeting. Front Oncol. 2014;4:160. PMID: 25009801
3.https://www.dermnetnz.org/topics/melanoma-pathology
4. Melanoma: assessment and management of melanoma NICE guideline.
5. Melanoma Treatments: Advances and Mechanisms: MELANOMA TREATMENTS by Marzuka, Alexander; Huang, Laura; Theodosakis, Nicholas; More...Journal of Cellular Physiology, 11/2015, Volume 230, Issue 11.
6. Cancer research UK – Melanoma
7. A qualitative assessment of psychosocial impact, coping and adjustment in high-risk melanoma patients and caregivers. Melanoma Research. 24(3):252-260, June 2014.