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Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline – Update 2012

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Abstract Cutaneous melanoma (CM) is potentially the most dangerous form of skin tumour and causes 90% of skin cancer mortality. A unique collaboration of multi-disciplinary experts from the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization of Research and Treatment of Cancer (EORTC) was formed to make recommendations on CM diagnosis and treatment, based on systematic literature reviews and the experts' experience. Diagnosis is made clinically and staging is based upon the AJCC system. CMs are excised with one to two centimetre safety margins. Sentinel lymph node dissection (SLND) is routinely offered as a staging procedure in patients with tumours more than 1 mm in thickness, although there is as yet no clear survival benefit for this approach. Interferon-α treatment may be offered to patients with stage II and III melanoma as

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an adjuvant therapy, as this treatment increases at least the disease-free survival (DFS) and less clear the overall survival (OS) time. The treatment is however associated with significant toxicity. In distant metastasis, all options of surgical therapy have to be considered thoroughly. In the absence of surgical options, systemic treatment is indicated. BRAF inhibitors like vemurafenib for *BRAF* mutated patients as well as the CTLA-4 antibody ipilimumab offer new therapeutic opportunities apart from conventional chemotherapy. Therapeutic decisions in stage IV patients should be primarily made by an interdisciplinary oncology team ('tumour board').

1. Introduction

1.1. Purpose

These guidelines have been written under the auspices of the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC) in order to help clinicians treating melanoma patients in Europe, especially in countries where national guidelines are lacking. This update has been initiated due to the substantial advances in the therapy of metastatic melanoma since 2009.

It is hoped that this set of guidelines will assist health care providers of these countries in defining local policies and standards of care, and to make progress towards a European consensus on the management of melanoma. It is not intended to replace recent national guidelines accepted in their original country. The guidelines deal with aspects of the management of melanoma from diagnosis of the primary melanoma through palliation of advanced disease. Prevention issues are not addressed. The guidelines are also intended to promote the integration of care between medical and paramedical specialties for the benefit of the patient.

These guidelines reflect the best published data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to deviate from these guidelines in the interest of specific patients or under special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, deviation from them should not necessarily be deemed negligent.

1.2. Definition

Melanoma is a malignant tumour that arises from melanocytic cells and primarily involves the skin. Melanomas can also arise in the eye (uvea, conjunctiva and ciliary body), meninges and on various mucosal surfaces. While melanomas are usually heavily pigmented, they can be also amelanotic. Even small tumours may have a tendency towards metastasis and thus a relatively unfavourable prognosis. Melanomas account for 90% of the deaths associated with cutaneous tumours. In this guideline, we concentrate on cutaneous melanoma (CM).[1–7]

1.3. Epidemiology and aetiology

The incidence of melanoma is increasing worldwide in white populations, especially where fair-skinned peoples receive excessive sun exposure.[8,9] In Europe the incidence rate is <10–20 per 100,000 population; in the USA 20–30 per 100,000; and in Australia, where the highest incidence is observed, 50–60 per 100,000. Individuals with high numbers of common naevi and those with large congenital naevi, multiple and/or atypical naevi (dysplastic naevi) are at greater risk.[10–13] The inheritance of melanoma is in most cases polygenic; 5–10% of melanomas appear in melanoma-prone families.[14,15] In addition to these genetic and constitutional factors, the most important exogenous factor is exposure to UV irradiation, particularly intermittent sun exposure.[16–18]

1.4. Different subtypes of melanoma

The classical subtypes are distinguished by clinical and histopathological features. Furthermore, in recent years these subtypes have been associated with epidemiological parameters and particular patterns of mutation.

Four main classical subtypes of melanomas can be identified clinically and histologically[19–21]:

Superficial spreading melanoma (SSM) begins with an intraepidermal horizontal or radial growth phase, appearing first as a macule that slowly evolves into a plaque, often with multiple colours and pale areas of regression. Secondary nodular areas may also develop. A characteristic histologic feature is the presence of an epidermal lateral component with pagetoid spread of clear malignant melanocytes throughout the epidermis.

Nodular melanoma in contrast is a primarily nodular, exophytic brown-black, often eroded or bleeding tumour, which is characterised by an aggressive vertical phase, with a short or absent horizontal growth phase. Thus, an early identification in an intraepidermal stage is almost impossible. When present, an epidermal lateral component is observed histologically within three rete ridges at the maximum.

Lentigo maligna melanoma arises often after many years from a lentigo maligna (melanoma *in situ*) located

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predominantly on the sun-damaged faces of elderly individuals. It is characterised histologically by a lentiginous proliferation of atypical melanocytes at the dermo-epidermal junction and histological features of chronic sun exposure (solar elastosis).

Acral lentiginous melanoma is typically palmoplantar or subungual. In its early intraepidermal phase, there is irregular, poorly circumscribed pigmentation; later a nodular region reflects the invasive growth pattern.

In addition to these main types, there are several rarer variants of melanoma, such as desmoplastic, amelanotic and polypoid melanomas, which constitute less than 5% of cases.

Recent molecular studies have shown the genetic heterogeneity of melanoma, with distinct molecular signatures identified in tumours at different anatomical locations and with different associations with reported sun exposure.[16,17,22,23] Intermittent sun exposure melanoma is mainly located on trunk and extremities and frequently carries a *BRAF* mutation.[24] Chronic sun exposure melanoma is located mainly in the head and neck region and has a moderate frequency of *NRAS* mutations. Non-sun-related melanomas are located on acral and mucosal sites and carry a low frequency of *CKIT* mutations.[17,25,26]

1.5. Prognosis and staging

About 90% of melanomas are diagnosed as *primary tumours* without any evidence of metastasis. The tumour-specific 10-year-survival for such tumours is 75–85%. The most important histological *prognostic factors for primary melanoma without metastases* as reflected in recent studies are[27,28]:

- *Vertical tumour thickness (Breslow's depth)* as measured on histological specimen with an optical micrometre.
- *Presence of histologically recognised ulceration*. Melanoma ulceration is defined as the combination of the following features: full-thickness epidermal defect (including absence of *stratum corneum* and basement membrane), evidence of host response (i.e. fibrin deposition, neutrophils), and thinning, effacement or reactive hyperplasia of the surrounding epidermis.[29]
- Mitotic rate (number of mitosis/mm^2) appears as an independent prognostic factor in several population studies.[30]
- *Level of invasion (Clark's level)* is only of independent significance for thin tumours ($\leqslant$1 mm thickness). It seems however that the mitotic rate is more predictive in thin tumours, and is now integrated in the 2009 AJCC staging system.

Prognosis is also poorer with increased age, the male sex and truncal/head and neck tumours rather than those on the limbs.[31,32]

Melanomas can metastasise either by the lymphatic or the haematogenous route. About two-thirds of metastases are originally confined to the drainage area of regional lymph nodes. A *regional metastasis* can appear as:

- *Micrometastases* in the regional lymph nodes identified via sentinel lymph node biopsy.[33,34] In contrast to macrometastasis, micrometastasis is not clinically recognisable neither by palpation nor by imaging techniques.
- *Satellite metastases* (defined as up to 2 cm from the primary tumour).
- *In-transit metastases* (located in the skin between 2 cm from the site of the primary tumour and the first draining lymph node).
- *Clinically recognisable regional lymph node metastases*.

The 10-year-survival is 30–70% for patients with micrometastasis, 30–50% for patients with satellite and in-transit metastases and 20–40% for those with clinically apparent regional lymph node metastases.[27]

Distant metastases have a grim prognosis with a median survival in untreated patients being only 6–9 months, although there is considerable variation depending on

Table 1
T classification of primary tumour for melanoma.

T classification	Tumour thickness	Additional prognostic parameters
Tis		Melanoma *in situ*, no tumour invasion
Tx	No information	Stage cannot be determined[a]
T1	$\leqslant$1.0 mm	a: No ulceration, no mitosis b: Ulceration or mitotic rate $\geqslant$1/mm^2
T2	1.01–2.0 mm	a: No ulceration b: Ulceration
T3	2.01–4.0 mm	a: No ulceration b: Ulceration
T4	>4.0 mm	a: No ulceration b: Ulceration

[a] Tumour thickness or information on ulceration not available or unknown primary tumour.

Table 2
N classification of the regional lymph nodes for melanoma.

N classification	Number of involved lymph nodes (LN)	Extent of lymph node metastases
N1	1 LN	a: Micrometastases b: Macrometastases
N2	2–3 LN	a: Micrometastases b: Macrometastases c: Satellite or in-transit metastases
N3	$\geqslant$4 LN, satellite or in-transit metastases plus node involvement	

Table 3
M classification of distant metastases for melanoma.

M classification	Type of distant metastasis	LDH
M1a	Skin, subcutaneous tissue or lymph node	Normal
M1b	Lungs	Normal
M1c	All other distant metastases	
	Any distant metastasis	Normal elevated

internal organ involvement and serum levels of lactate dehydrogenase (LDH, Table 3).

In 2009, the AJCC proposed a new TNM classification and staging for melanoma; it has now also been accepted by the UICC.[27] This new system now forms the cornerstone for classifying melanomas and is summarised in Tables 1–4.

2. Diagnostic approach

2.1. Clinical and dermoscopic diagnosis

In most instances, the clinical appearance of melanoma varies according to the melanoma subtypes (see above). Typical features are asymmetry of the lesion, irregular borders, variability in colour, diameter of 5 mm and more, growth of nodules and regression of lesional components. The sensitivity of clinical diagnosis of experienced dermatologists is about 70%.[35]

Dermoscopy should be used to clarify the differential diagnosis of pigmented lesions. In order to apply this technique, training and expertise are required. A meta-analysis of 22 studies showed that when experts employed dermoscopy, they achieved an increase in diagnostic accuracy over the clinical diagnosis alone in questionable lesions and thus reached a sensitivity of 89% and a specificity of 79%.[35]

Characteristic features for the diagnosis of melanoma, also called melanoma-specific criteria, include an atypical pigment network, irregular brown–black dots/globules, streaks and pigmentation. Additional criteria e.g. blue-whitish veil, polymorphic vessels and red lacunes are common in invasive melanoma.[36–39]

Amelanotic and featureless melanoma may represent a diagnostic challenge although suspicion should arise when a polymorphic vascular pattern is seen or when lesions do not display any of the well-known melanocytic or non-melanocytic characteristic dermoscopic features.[40–43]

The prototypical dermoscopic progression model for LMM on the face include four sequential patterns, that are hyperpigmented follicular openings, annular–granular pattern, rhomboidal structures and atypical pseudonetwork,[44,45] while the importance of additional features such as increased vascular network and red rhomboidal structures have been recently linked to the development of tumour-induced neovascularisation.[46]

Finally, a parallel ridge pattern and irregular diffuse pigmentation are distinguished features of early and invasive acral melanoma, respectively.[47–51]

In high risk patients, mainly in the case of patients with atypical mole syndrome, the detection of changes

Table 4
Staging of melanoma.

Stage	Primary tumour (pT)	Regional lymph node metastases (N)	Distant metastases (M)
0	*In situ* tumour	None	None
IA	$\leqslant$1.0 mm, no ulceration	None	None
IB	$\leqslant$1.0 mm with ulceration or mitotic rate $\geqslant 1/mm^2$	None	None
	1.01–2.0 mm, no ulceration	None	None
IIA	1.01–2.0 mm with ulceration	None	None
	2.01–4.0 mm, no ulceration	None	None
IIB	2.01–4.0 mm with ulceration	None	None
	>4.0 mm, no ulceration	None	None
IIC	>4.0 mm with ulceration	None	None
IIIA	Any tumour thickness, no ulceration	Micrometastases	None
IIIB	Any tumour thickness with ulceration	Micrometastases	None
	Any tumour thickness, no ulceration	Up to three macrometastases	None
	Any tumour thickness $\pm$ ulceration	None but satellite and/or in-transit metastases	None
IIIC	Any tumour thickness with ulceration	Up to three macrometastases	None
	Any tumour thickness $\pm$ ulceration	Four or more macrometastases, or lymph node involvement extending beyond capsule, or satellite and/or in-transit metastases with lymph node involvement	None
IV			Distant metastases

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in the lesions or newly appearing lesions by follow-up examination with digital dermoscopy and total-body photography is also helpful.[52–54]

The differential diagnosis involves other pigmented melanocytic lesions (congenital, atypical, common melanocytic naevi and actinic lentigo) and non-melanocytic pigmented lesions (seborrhoeic keratosis, hemangioma and pigmented basal cell carcinoma) and other non-pigmented tumours (hemangioma, basal cell carcinoma, squamous cell carcinoma). In patients with an established diagnosis of melanoma, physical examination at regular intervals remains essential to identify second primary tumours, as well as skin metastases.[55]

2.2. Histopathologic diagnosis

Whenever a suspicious skin lesion is removed a histological examination is warranted. Difficulties in the clinical diagnosis of melanoma can also be encountered on a histologic level. The specimen should be entrusted to a dermatopathologist experienced in the interpretation of pigmented lesions. The histopathologic report should include the following information[56]:

1. Diagnosis and clinicopathologic type; when there is uncertainty about malignancy it should be clearly stated in the report conclusion.
2. Tumour thickness in mm (Breslow depth).
3. Presence or absence of ulceration.
4. Number of mitoses per mm^2 (in hot spots).
5. Microsatellites (if present).
6. Lateral and deep excision margins.

Besides these absolutely necessary histologic features, additional informations can be provided, including:

- Growth phase (horizontal or vertical).
- Level of invasion (Clark level), especially for thin melanomas $\leqslant$1 mm in thickness.
- Presence or absence of established regression.
- Presence or absence of a dense tumour infiltrating lymphocytes (TIL) infiltrate.
- Lymphatic emboli.
- Vascular or perineural involvement.

In some instances, when the histologic diagnosis is unclear, immunohistochemical stains may be helpful (i.e. S-100 protein, HMB45 and Melan-A for the confirmation of the melanocytic nature of the tumour, HMB45 as an additional feature of malignancy when there is an inverted positive gradient, MIB-1 as a proliferation marker).

2.3. Molecular diagnosis

Molecular analysis of distant or regional metastasis or, if impossible, of the primary tumour is required for patients with distant metastasis or non-resectable regional metastasis, who are candidates for systemic medical treatment.[57] Currently, the main test performed involves the *BRAF* V600 mutational status, in order to identify patients eligible for treatment with BRAF inhibitors and MEK inhibitors.

NRAS mutations are identified in around 15% of samples and as *BRAF* and *NRAS* mutations are mutually exclusive a positive *NRAS* mutation serves as to reassure that a *BRAF* mutation has not been missed. Presently, NRAS inhibitors are under clinical development.[58]

CKIT mutations should additionally be analysed in patients with acral and mucosal melanomas, although the positivity rate is lower than previously expected in Europe. If present, patients can be treated with CKIT inhibitors.[59,60]

In the near future, other genomic tests are expected to be identified as predictive markers for patients with stage IV melanoma.

2.4. Further staging examinations

The value of additional staging examinations at first diagnosis in patients with primary melanomas and in subsequent follow-up examinations is controversial. It is widely agreed upon that in low-risk patients staging can be omitted and in high-risk patients staging examinations should be performed. However, definitions of low- and high-risk patients vary and as the efficacy of targeted therapies is clarified then thresholds for screening may change. Useful staging examinations should include: sonography of regional lymph nodes, and total body CT or PET-CT scans. LDH and serum protein S100 are routinely used as markers of relapse in some countries.[61,62]

3. Surgical therapy

3.1. General principles

The primary treatment of melanoma is surgical excision.[7,63] An excisional biopsy is preferred, both to give the dermatopathologist/pathologist an optimal specimen and to allow evaluation of the excision margins for residual tumour. Incisional biopsies should not be performed when an excisional biopsy is technically possible. Such procedures may result in diagnostic error as a result of sampling, and may compromise estimation of Breslow thickness. On occasion they are necessary to confirm the diagnosis, such as when dealing with a large lentigo maligna on the face, or with acral or mucosal lesions. Incisional biopsies are more difficult to interpret histologically, and carry the risk of not sampling the worst area of the tumour. Large studies have shown that incisional biopsies do not however worsen prognosis as

Table 5
Recommended minimal excision margins for melanoma.

Tumour thickness (Breslow)	Excision margin (cm)
In situ	0.5
⩽2.0 mm	1
>2.0 mm	2

compared with immediate complete excisional biopsy.[64,65]

3.2. Primary melanoma

The definitive surgical excision should be performed with safety margins preferentially within 4–6 weeks of initial diagnosis. The recommendations below (Table 5) are consistent with evidence that narrow excision margins are appropriate; the values given below are in concordance with the American, UK and Australian recommendations.

The current recommendations are based on both prospective, randomised studies and international consensus conferences.[3,6,66–69] There are limited data to suggest that margin has an effect on loco-regional recurrence, but there are no data to support an impact of margin on survival.

3.3. Lentigo maligna

Lentigo maligna is a slowly growing melanoma *in situ*, which occurs typically in UV-exposed areas like the face. Typically, lentigo maligna requires narrower margins for safety when it is excised, and micrographic control of excision margins may be involved in order to conserve tissue particularly in the face.[70] Surgical procedures should respect the anatomy of the face as well as aesthetic and functional aspects. Several retrospective analyses and phase II trials support a role for topical imiquimod as a potential alternative to surgery in selected cases. The complete response rate to imiquimod treatment is in the range of 75–88%.[71–73] However, patients should be informed that imiquimod will not allow a histological evaluation of the tumour area (and clinically unsuspected invasive melanoma may therefore be missed) and the peripheral margins will require a thorough follow-up.

3.4. Acral and mucosal melanomas

Lentiginous acral and mucosal melanomas are often poorly defined and multifocal with discrepancies between the clinically visible and histopathologic margins. Local recurrences are more frequent in these types of melanoma. Therefore, removal can be achieved with increased safety margins (at least 1 cm) or by narrow margins with micrographic control (e.g. Mohs' technique and variants).[74–76] Micrographic surgery based on paraffin-fixed tissue often allows a reduced safety margin and conservation of tissue. Similarly on the hands and feet, the micrographic technique serves to conserve tissue by making smaller margins possible.

3.5. Elective lymph node dissection (ELND)/sentinel lymph node dissection (SLND)

No therapeutic advantage for ELND has been established.[3] The SLND was introduced in order to allow the evaluation of the first draining lymph node in the regional lymphatic system.[77] SLND is a staging procedure, appropriate for patients in whom neither palpation nor lymph node sonography has suggested the presence of lymph node metastases. Multicentre studies have shown that the recurrence-free and overall survival (OS) time correlates clearly with the status of the sentinel lymph node.[78,79] SLND and radical lymph node dissection in patients with positive SLN prolongs disease-free survival (DFS) but does not affect OS.[78]

The evaluation of the SLN is not well-standardised, and the risk of missing a micrometastasis depends heavily on surgical expertise and the histological techniques employed (number of sections; H&E stain; immunohistochemical stains). Various studies have shown that a detection accuracy of 90% is first obtained after roughly 50 procedures have been performed. Thus, it seems appropriate to concentrate SLNB in larger centres where such experience can be acquired. This leads to both standardised surgical and histopathological procedures. Several classifications of the micrometastasis have been proposed, including measurement of their largest diameter and their location within the lymph node, and they seem to be of prognostic significance.

SLND has been established as a valuable staging tool. The positivity rate for melanomas <1 mm is so low that it is normally not recommended for patients in this group. Although some centres take additional poor prognostic features into account (ulceration, Clark IV, mitotic rate).

3.6. Procedure in patients with negative SLN

No further lymph node surgery is required.

3.7. Procedure in patients with micrometastases in SLN

Studies have not confirmed that radical lymph node dissection improves survival. The analysis of the MSLT-1 trial comparing survival in patients undergoing delayed lymph node dissection versus those who underwent a complete lymph node dissection (CLND) because of a positive SN is exploratory in nature and therefore non-conclusive. Moreover the claimed benefit is not reflected in the OS analysis of the primary endpoint of the trial (survival after wide excision (WE)

alone versus WE + SNLD).[34] Nonetheless when the SLND shows micrometastases, radical lymph node dissection is usually recommended as approximately 5–12% of patients will have involvement of non-sentinel nodes. The prognostic classification of the presence of micrometastasis within the SLN may help to select patients for CLND in the near future.

3.8. Clinically-identified lymph node metastases

If lymph node metastasis is diagnosed clinically or by imaging techniques, radical lymph node dissection is considered standard therapy.[80]

3.9. Skin metastases

The treatment of choice for skin metastases is surgical, but systemic therapies should be considered if numerous or extensive lesions are not amenable to surgery. For multiple lesions on a limb, isolated limb perfusion with melphalan ± tumour necrosis factor (TNF) has palliative value.[81] In stage III patients with satellite/intransit metastases the procedure can be curative, as indicated by the reported 5 and 10 years survival rates of 40% and 30%, respectively. Isolated limb infusion is a modification of this technique and is used in some centres. Alternative options include cryotherapy, laser therapy and intralesional/topical approaches such as IL-2, electrochemotherapy, miltefosine, interferon-α or imiquimod.

3.10. Distant metastases

If technically feasible and reasonable, then complete operative removal of distant metastases should be seen as therapy of choice. With brain metastases, stereotactic radiation therapy is equally effective. Many studies show that excision of solitary or few metastases can be associated with a favourable outcome for stage IV patients.[82–85] The possibility of neoadjuvant therapy followed by surgical excision of metastatic lesions can be considered.[86]

The value of debulking procedures must be viewed critically, as there is no evidence that they improve survival. In some circumstances there is a value for palliation, particularly in combination with postoperative radiotherapy for local disease control.

4. Radiation therapy

4.1. Primary melanoma

Radiation therapy of the primary tumour is very rarely indicated, performed exclusively in patients in whom surgery is impossible or not reasonable.

4.2. Regional lymph nodes

There is no established role for adjuvant radiotherapy of draining lymph nodes after excision of the primary melanoma. Adjuvant radiotherapy after lymphadenectomy can be considered for patients at high risk to improve lymph-node field control.[87]

When lymph node dissection is not complete or metastatic lymph nodes are inoperable, radiation therapy of the regional lymph nodes may be recommended, however, the value of this is unproven except for the palliation of symptoms.

4.3. Skin metastases

In-transit metastases, which are too extensive for a surgical approach, may be controlled by radiation therapy alone.[88] Depending on the extent and location, hyperthermia may be added.[89]

4.4. Bone metastases

Bone metastases can be palliated with radiation therapy. The response rate (CR + PR) is 67–85%.[90–93] The major indications are pain, loss of structural stability (fracture risk), and compression of the spinal canal with or without neurological symptoms.

4.5. Brain metastases

Melanoma has a marked propensity to metastasise to the brain. Patients with brain metastases have a life expectancy of only 3–5 months. Symptom control may be established in the short term with dexamethasone by reducing secondary oedema. With radiation therapy, the neurologic deficits may be improved in 50–75% of cases, an effect which is usually associated with an overall improvement in health.[90,94,95] Headache responds to radiation therapy in about 80% of cases. Both stereotactic single-dose radiation therapy (gamma knife) and surgical resection are appropriate for solitary or few (typically up to 3), and not too large lesions (up to 3 cm in diameter). Treating individual lesions (surgery or stereotactic radiation) can be applied several times and appears to prolong survival, although this has never been proven.[94,96,97]

5. Adjuvant therapy

5.1. General principles

Adjuvant therapy is offered to patients without evidence of metastases but at high risk for further tumour spread.[98–100] Since current adjuvant therapy can considerably reduce the quality of life, its indications and administration must be carefully considered.[101] In published trials adjuvant therapy age was predominantly used in patients with tumours thicker than 1.5 mm, or, by AJCC staging criteria, in patients with stage II and III melanoma.

5.2. Adjuvant chemotherapy

A number of controlled trials with adjuvant chemotherapy in stage II and III patients did not demonstrate any therapeutic advantage. There is as yet no indication for adjuvant systemic chemotherapy for melanoma outside the context of controlled studies.[2]

A large prospective, randomised multicentre study showed that adjuvant limb perfusion following the excision of primary high-risk melanoma did not increase the OS. Thus, this toxic therapy should no longer be used in the adjuvant setting.[102]

5.3. Adjuvant immunotherapy with various non-specific immunostimulatory agents

Prospective randomised studies using various non-specific immunostimulatory agents (Bacille Calmette Guerin/BCG, corynebacterium parvum, levamisol, mistletoe extract), cytokines (interferon-γ, interleukin-2, GM-CSF) and melanoma specific vaccines failed to show any therapeutic efficacy. In summary, none of the above-mentioned agents can be recommended for adjuvant therapy except in the setting of controlled studies.[2] Presently, the anti-CTLA-4 antibody ipilimumab and the MAGE-3 vaccine are being examined as adjuvant treatments in phase III trials. New agents such as antibodies to PD-1 and PDL-1 are additional options to be examined in clinical trials.[103]

5.4. Adjuvant immunotherapy with interferon-α

Interferon-α is the first substance in the adjuvant therapy of melanoma to have shown a significant improvement of DFS and in some prospective randomised trials,—of OS, albeit with significant toxicity.[104–116] A recent metaanalysis showed a significant improvement of DFS (hazard ratio of 0.82, $p < 0.001$) and a significant but less important improved OS (hazard ratio of 0.89, $p = 0.002$).[117] The metaanalysis did not show clear difference in the efficacy of the different dose schedules or of different treatment durations. Adjuvant interferon is offered in some European countries for high risk resected stage II or III melanoma on the basis of reduction in relapse free survival, but not universally because of the small survival benefit and the significant toxicity.

A large-sized adjuvant trial on stage III melanoma patients treated with pegylated interferon α2b compared to observation alone was conducted by the EORTC Melanoma Group. The results indicate a statistically significant prolongation of relapse-free survival (RFS) for all patients and a significant benefit of distant-metastasis free survival (DMFS) for microscopically lymph node positive melanoma patients.[116] However, there was no significant benefit in terms of OS for interferon-treated patients. These findings are supported by a large randomised trial of the EADO, which compared the 3 years pegylated interferon α2b with 18 months classic interferon α2b, and found no differences in the outcome of the patients. In both trials few patients tolerated the therapy longer than 2 years with pegylated interferon α2b.

6. Systemic therapy of metastatic disease

6.1. General principles

The major indications for systemic therapy are inoperable regional metastases and distant metastases (stage IV). Beside the long available cytostatic drugs, which were capable of inducing tumour responses but not of prolonging survival, new targeted compounds and immunotherapeutic drugs have been shown to prolong survival.[118,119] The two main goals of systemic therapy are:

- Prolongation of survival.
- Reduction of tumour size or load with a resultant increase in symptom-free course or a decrease in symptoms.

6.2. Targeted therapy

In melanoma different activating mutations have been described, mainly resulting in an increased signalling of the MAP kinase and the AKT pathways.[120] Numerous targeted inhibitors have already been developed and are under clinical investigation.

About 50% of patients with CM carry an activating *BRAF* V600 mutation, for which several highly selective inhibitors have been developed. Vemurafenib was shown to achieve a high rapid tumour response rate (roughly 50%) in patients carrying the V600E mutation and a substantial prolongation of progression-free and OS in comparison to dacarbazine (DTIC).[118,121] Vemurafenib is approved for melanoma therapy in the US and the EU. Vemurafenib is administered as an oral drug with a current standard dose of 960 mg twice daily. Minor systemic (arthralgia, fatigue) but major cutaneous side-effects have been reported, including photosensitivity, development of epithelial tumours and seldomly melanomas. Development of secondary resistance to vemurafenib with varying time courses is a frequent event. Other selective BRAF and MEK inhibitors are currently in clinical development and may be approved in the near future.[122,123] The BRAF inhibitor dabrafenib showed similar effectivity as vemurafenib in a phase III trial. [124] The MEK inhibitor trametinib likewise showed higher activity and prolonged survival as compared to dacarbazine in a phase III trial.[125] These targeted therapies are radically changing the management of stage IV melanoma, although the rapid emergence of resistance to single agent therapy in the majority means that they

remain of limited clinical utility as yet. Combined schedules of BRAF and MEK inhibitors are under clinical investigation with some evidence for reduced toxicity and increased efficacy in combination, and it seems likely that improved combined therapies will emerge in the next few years.[122]

A small proportion of melanomas arising in sun-protected sites have mutations in cKIT and they have been treated with the cKIT inhibitor imatinib. Responses have been described in case reports and a phase II trial revealed an objective response rate of 23% in patients with cKIT mutated melanoma.[60]

6.3. Immunotherapy

Cytokines such as interferon-α and interleukin-2 were examined in several clinical trials in melanoma and achieved moderate response rates in non-controlled trials. Improvement of survival has never been shown. Vaccination strategies have raised a lot of interest, but so far no efficacious vaccines have been developed. In some trials, results may suggest even deleterious effects.[126]

Blockade of the CTLA-4 and of the PD-1 molecules expressed by lymphocytes abrogates down-regulation of immune responses and leads to continued activation of lymphocytes enabling killing of tumour cells. This immunostimulation is non-specific and can lead to immunologically mediated toxicity. The anti-CTLA-4 antibody ipilimumab was the first immunotherapy that showed a benefit for OS in two controlled trials in metastatic melanoma.[119,127] Ipilimumab is approved for melanoma therapy in the US and in the EU. It is presently administered as four intravenous infusions at a dose of 3–10 mg/kg/infusion separated by three weeks. Severe autoimmune reactions including skin rashes, colitis, thyroiditis, hepatitis, hypophysitis and others can develop in some patients and require interdisciplinary management. Early recognition of these reactions is mandatory and requires specific training of the caring physicians (Tables 6–8).

The response rate to ipilimumab is only about 15%, but remarkable durable remissions were observed in stage IV patients previously treated with other drugs. Patients with stable disease or initial disease progression may likewise benefit with prolonged survival. Unfortunately, no predictive biomarkers are so far available.

PD-1 antibodies showed in a large phase II trial high efficacy with an objective response rate of 28% and a progression free survival rate of 41% after 24 weeks.[128,129] Similarly, PD-1L antibodies were tested in a phase II trial and achieved an objective response rate of 17% and the rate of progression-free survival at 24 weeks was 42%.[130] Preliminary evidence suggests that the expression of PD-L1 on the tumour tissue may select for patients with an improved response to PD-1 axis inhibitors.[129]

6.4. Chemotherapy

A number of agents with comparable effectiveness are available for systemic chemotherapy of advanced melanoma. Chemotherapy can lead to regression of tumours and a reduction in tumour-related symptoms. The longest-established monotherapy is dacarbazine (DTIC). Objective remissions (more than 50% reduction in tumour mass) were reported in the older literature in up to 28.6% of patients. Recent multicentre trials, however, have demonstrated that remission rates are in the range of only 5–12%.[131–134]

The combination of cytostatic agents and cytokines produces an increase in the objective response rate. No study, however, has shown a significant improvement in the OS time.[143,144] The tolerability of monochemotherapy is worsened when interferon-α or IL-2 is added.

The combination of multiple chemotherapeutic agents (polychemotherapy) or of multiple chemotherapeutic agents and cytokines (polychemoimmunotherapy) also achieves higher remission rates than monotherapy (12.7–45%), but, once again, it does not improve the OS (Table 9).

6.5. Special case: metastatic uveal melanoma

Melanomas of the eye involve the uvea, ciliary body or the retina. They have a different pattern of metastasis than CMs. Since the eye does not have a lymphatic

Table 6
Dosage schedules for adjuvant therapy of melanoma with interferon-α.

Schedule	Dose	Frequency	Duration	Indication
Low dose	3 million IU s.c.	Days 1, 3 and 5 every week	18 months	Stage II–III
High dose				
Initiation	20 million IU/m^2 iv. rapid infusion	Day 1–5 every week	4 weeks	Stage III
Maintenance	10 million IU/m^2 s.c.	Days 1, 3 and 5 every week	11 months	Stage III
Pegylated				
Initiation	6 μg/kg body weight s.c.	Day 1 every week	8 weeks	Stage III
Maintenance	3 μg/kg body weight s.c.	Day 1 every week	(up to5 years)	Stage III

Table 7
Monotherapies for advanced cutaneous melanoma described in prospective randomised trials or phase II studies if phase III trials were not available.

Medication	Dose	Response rate (%)
Dacarbazine		
Ringborg 1989, Middleton 2000 (134, 135)	250 mg/m^2 i.v. daily for 5 days every 3–4 weeks	12.1–17.6
Chiarion Sileni, 2001, Young 2001 (136,137)	800–1200 mg/m^2 i.v. daily on one day every 3–4 weeks	5.3–23
Temozolomide		
Bleehen 1995, Middleton 2000 (134,138)	150–200 mg/m^2 p.o. daily for 5 days every 4 weeks	13.5–21
Fotemustine		
Jacquillat 1990, Mornex 2003 (139,140)	100 mg/m^2 i.v. on days 1, 8 and 15; then 5 week pause, then repeat single dose every 3 weeks	7.4–24.2
Vindesine		
Nelimark 1983, Carmichael 1982 (141,142)	3 mg/m^2 i.v. every 14 day	12–26

Table 8
Polychemotherapy and chemoimmunotherapy of advanced cutaneous melanoma from prospective randomised trials or phase two trials.

Regimen	Dose	Response rate (%)
DVC Gundersen, 1987, Pectasides 1989, Jungnelius 1998 (1145–147)	DTIC 250 mg/m^2 i.v. days 1–5 Vindesine 3 mg/m^2 i.v. day 1 Cisplatin 100 mg/m^2 i.v. day 1 every 3–4 weeks	31.4–45
DVC Verschraegen 1988 (148)	DTIC 450 mg/m^2 i.v. days 1 + 8 Vindesine 3 mg/m^2 i.v. days 1 + 8 Cisplatin 50 mg/m^2 i.v. days 1 + 8 every 3–4 weeks	24
DBC McClay 1987, Chapman 1999, Creagan 1999 (149–151)	DTIC 220 mg/m^2 i.v. days 1–3 BCNU 150 mg/m^2 i.v. day 1 of every other cycle. Cisplatin 25 mg/m^2 i.v. days 1–3	18.5–31.9
CarboTax Rao 2006(152)	Carboplatin AUC6 i.v. day 1, after four cycles reduce to AUC4 Paclitaxel 225 mg/m^2 i.v. day 1 every 3 weeks, after four cycles reduce to 175 mg/m^2	(12.1 second line)

Table 9
Chemotherapy for advanced uveal melanoma

Medication	Dose
Fotemustine Leyvraz 1997, Egerer 2001, Siegel 2007 (153–155)	Induction cycle 100 mg/m^2 intraarterial (hepatic artery) over 4 h weekly for 4 weeks; then 5 week pause; then repeat every 3 weeks
Treosulfan/Gemcitabine Pföhler 2003(156)	Treosulfan 5 g/m^2 i.v. day 1 Gemcitabin 1 g/m^2 i.v. day 1 Repeat every 3 weeks

system, almost all metastases are found in the liver following haematogenous spread. For this reason, the prognosis of metastatic ocular melanoma is in general much worse than that of its cutaneous counterpart. On the other hand, when patients with liver metastases from ocular and CM are compared, there are no prognostic differences.

Because of the preferential metastasis to the liver, patients with ocular melanoma and liver metastases may be candidates for local-regional therapeutic measures. Few systemic schedules have been reported with objective responses (Table 9).

6.6. Looking for an algorithm

Presently, no sufficient data are available to establish a treatment algorithm for stage IV melanoma but, some general principles can already be acknowledged:

- Mutation testing of tumour tissue (at least *BRAF*; *CKIT* in subtypes) is a prerequisite for treatment decisions.
- Mutation testing of metastatic tissue selected for absence of necrotic tissue and melanin is recommended in order to reduce the likelihood of a failed test.
- *BRAF* mutated patients should be offered treatment with BRAF inhibitors or experimental drugs blocking the MAP kinase and PI3K pathways, preferably still in the context of clinical trials designed to reduce the emergence of drug resistance.
- Patients whose disease progresses on first-line treatment and with health status of presumably six or more months should be offered ipilimumab or other immunotherapies in the context of clinical trials as they are made available.
- Non-BRAF-mutated patients and those progressive under BRAF inhibitors and immunotherapies should be considered for chemotherapy.
- Ckit inhibitors may have a role in the small proportion of ckit mutant melanomas

7. Follow-up

7.1. General principles

The frequency and extent of follow-up examinations depends on the primary tumour characteristics. The first 5 years following surgery are most important, as 90% of all metastases occur during this time period. Late metastasis does however occur in melanoma and indicate the relevance of a follow-up beyond 5 years. Patients who have had a history of melanoma have an increased risk of a secondary melanoma primary, adding increased importance to regular clinical re-examinations. Follow-up of melanoma patients has the following goals:

1. Identifying tumour recurrence or disease progression at the earliest stage.
2. Early diagnosis of additional primary melanomas (occurs in about 10% of patients with CM) and non-melanoma skin cancers.
3. Offering psychosocial support.
4. Providing education on prevention, for the patient and his first degree relatives.
5. Education of the patient and his family on self examination to promote the early detection of melanoma.
6. Administering and monitoring adjuvant therapy, where appropriate.

7.2. Recommendations for structured follow-up

Follow up 'rules' are variable across Europe, ranging in frequency from 2 to 4 times per year for 5–10 years,[55,157] with few data to support them. In stage I to II melanoma, the intent is to detect early loco-regional recurrence so that the frequency of follow up examination is usually every 3 months for the first five years, whereas for the 6th to 10th year period attendance every 6 months seems to be adequate. In patients with thin CM ($\leqslant$1 mm) six monthly intervals may be sufficient and some guidelines support a limited follow up of 1 year for stage 1A melanoma. Clinical follow up is the standard procedure but there are data to support the additional use of ultrasonography. Staging by CAT scan is usual for stage III disease but, presently, there is no established role for subsequent regular imaging in the absence of curative systemic therapies for melanoma.

8. Consensus-building process and participants

These guidelines originate from contributors who were involved in the development of their national guidelines. These national guidelines were elaborated by the different specialities involved in the management of melanoma patients (dermatology, medical oncology, surgical oncology, radiotherapy, pathology).

These guidelines were prepared under the auspices of the EDF, the EADO and the EORTC. The basis for the elaboration of these guidelines was an English translation of the interdisciplinary melanoma guideline of the Dermatologic Cooperative Oncology Group (DeCOG) from Germany. In a first round dermatologists were involved who participated in national guideline development processes. In a second round the EORTC selected experts from different specialities who contributed to this guideline. This process was first organised in 2008/2009 and the update was developed by the same groups in 2012. Professor Claus Garbe, Tübingen, coordinated the activities of the selected experts and the final authors. These guidelines are planned to be updated at least every three years.

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Conflict of interest statement

CG, AH, PS, MM, JJG, JM, HP and AME have had consultant or advisory roles for and have received honoraria from Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, and Roche; CG additionally from Amgen, Philogen and Swedish Orphan Biovitrum, AH additionally from Amgen, Celgene, AstraZeneca, Bayer, Boehringer Ingelheim, Eisai, and Novartis, JM additionally from Amgen and Swedish Orphan Biovitrum, MM additionally from Astrazeneca and Clovis. AS has had consultant or advisory roles for and has received honoraria from Roche, Merck Sharp & Dohme, and Novartis; JNB has received honoraria from

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