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Original Research

Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline – Update 2016

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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, the European Association of Dermato-Oncology and the European Organisation of Research and Treatment of Cancer was formed to make recommendations on CM diagnosis and treatment, based on systematic literature reviews and the experts' experience. Diagnosis is made clinically using dermoscopy and staging

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Interferon-α;
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is based upon the AJCC system. CMs are excised with 1–2 cm safety margins. Sentinel lymph node dissection is routinely offered as a staging procedure in patients with tumours >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 an adjuvant therapy, as this treatment increases at least the disease-free survival 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. For first-line treatment particularly in *BRAF* wild-type patients, immunotherapy with PD-1 antibodies alone or in combination with CTLA-4 antibodies should be considered. BRAF inhibitors like dabrafenib and vemurafenib in combination with the MEK inhibitors trametinib and cobimetinib for *BRAF* mutated patients should be offered as first or second line treatment. 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 Organisation 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. 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 specialities 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 to metastasise and thus lead to a relatively unfavourable prognosis. Melanomas account for 90% of the deaths associated with cutaneous tumours. In this guideline, we concentrate on the treatment of cutaneous melanoma (CM) [1–8].

1.3. Epidemiology and aetiology

The incidence of melanoma is increasing worldwide in white populations, especially where fair-skinned peoples receive excessive sun exposure [9–11]. In Europe the incidence rate is <10–25 new melanoma cases per 100,000 inhabitants; in the United States of America (USA) it is 20–30 per 100,000 inhabitants; and in Australia, where the highest incidence is observed, it is 50–60 per 100,000 inhabitants. In recent years there has been a dramatic increase in incidence in people over the age of 60 and especially in men in parts of Europe but the incidence in many parts of Europe continues to increase at all ages and is predicted to continue to increase for some time [12]. The commonest phenotypic risk factor is skin that tends to burn in the sun, and inherited melanocortin-1 receptor variant is the most important underlying genotype. Individuals with high numbers of common naevi and those with large congenital naevi, multiple and/or atypical naevi (dysplastic naevi) are at a greater risk and this phenotype is also genetically determined [13–16]. The inheritance of melanoma is in most cases seen in people with common lower risk susceptibility genes but; 5–10% of melanomas appear in melanoma-prone families who carry high penetrance susceptibility genes [17,18]. The most important exogenous factor is exposure to UV irradiation, particularly intermittent sun exposure [19–21].

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 somatic mutation.

Four classical subtypes of melanomas can be identified clinically and histologically [22–24]:

Superficial spreading melanoma 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 predominantly on the sun-damaged faces of older individuals. It is characterised histologically by a lentiginous proliferation of atypical melanocytes at the dermoepidermal junction and histological features of solar elastosis.

Acral lentiginous melanoma is typically palmoplantar or subungual. In its initial intraepidermal phase (which may be protracted), there is irregular, poorly circumscribed pigmentation; later a nodular region reflects the invasive growth pattern.

In addition there are several rarer variants of melanoma, such as desmoplastic, amelanotic and polypoid melanomas, which constitute less than 5% of cases. Nodal melanoma in the absence of clear evidence of a primary tumour is also seen.

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 [19,20,25,26].

These recent advances open the possibility for a new generation of ongoing classifications of melanoma which will take into account not only epidemiology and pathology but also mutation profiles and probably other biological biomarkers. The most recent one proposes four different groups of melanomas [27]. 'Intermittent sun exposure' melanoma is mainly located on the trunk and extremities and frequently carries a *BRAF* mutation, which is present in ~45% of CMs. Melanoma on continuously exposed sites is located mainly in the head and neck region and has a moderate frequency of *NRAS* and other RAS mutations, present in about 15% of CMs. [28] Another group of roughly 10% of CMs seems to be characterised by mutations in the *NF1* gene. 'Non sun-related melanomas' are mainly located on acral and mucosal sites and carry a low frequency of *CKIT* mutations. [20,29,30] These rare subtypes of melanomas belong to the so-called 'triple wild-type' melanoma. The *BRAF, NRAS* and *NF-1* mutations described are held to be 'driver' mutations but melanoma is a tumour with an exceptionally high mutational load [31] postulated to be non-driver sun-related mutations, which favours likelihood of responding to immunotherapy and matters for treatment decisions.

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 as follows [32,33]:

- Vertical tumour thickness (Breslow's depth) as measured on histological specimen with an optical micrometre scale, and defined as histologic depth of the tumour from the granular layer of the epidermis to the deepest point of invasion.
- 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 [34].
- Mitotic rate (number of mitosis/mm^2) appears as an independent prognostic factor in several population studies and is used for sub-classification of thin melanomas in the 2009 AJCC classification [35].
- Level of invasion (Clark's level) is no longer part of the 2009 AJCC staging system.

Prognosis is also poorer with increased age, the male sex and truncal/head and neck tumours compared to melanomas on the limbs [36,37].

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:

- 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),
- Micrometastasis in the regional lymph nodes identified via sentinel lymph node biopsy [38,39]. In contrast to macrometastasis, micrometastasis is not clinically recognisable neither by palpation, nor by imaging techniques.
- Clinically recognisable regional lymph node metastases.

The 10-year survival is 30–50% for patients with satellite and in-transit metastases, 30–70% for patients

with lymph node micrometastasis and 20–40% for those with clinically apparent regional lymph node metastases [32].

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 aggressiveness of the individual tumour, evaluated on presence of internal organ involvement and serum levels of lactate dehydrogenase (LDH, Table 3). The new treatment options of targeted therapies in patients with the *BRAF* mutation and of checkpoint blockade in all patients with CM are clearly associated with longer overall survival (OS) and the results of clinical trials of novel agents are emerging so rapidly that the estimates are under constant revision.

In 2009, the AJCC proposed a new tumour-node-metastasis classification and staging for melanoma [32]. 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 difficult to assess but estimated to be around 70% [40].

The clinical diagnosis of the dermatologist is based on a combination of three analyses of any pigmented lesion: [1] Visual analysis of each lesion separately which generally excludes non-melanocytic lesions, although melanomas may rarely mimic pigmented seborrhoeic keratoses. Examination with the naked eye assesses the so-called A (asymmetry), B (irregular borders), C (inhomogeneous colour) and D (diameter ≥5 mm) criteria, which point to suspicious melanocytic lesions (ABCD rule). [2] Intra-individual comparative analysis, which is searching for the nevus that is not alike the others in the same patient (ugly duckling sign) [41]. [3] Chronologic analysis of changes which is looking for a rapid and recent change of a given pigmented lesion (E like evolution) at least when it can be attested by the patient or documented by comparison to previous pictures.

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% [42].

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 with multiple colours asymmetrically distributed. Additional criteria e.g. blue-whitish veil and polymorphic vessels are common in invasive melanoma [43–46].

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 [47–50]. This argues for urgent excision of any growing skin lesion suspicious for a skin tumour even if it looks more like a squamous lesion than a melanoma.

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	≤1.0 mm	a: No ulceration, no mitosis b: Ulceration or mitotic rate ≥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	≥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	Normal
	Any distant metastasis	Elevated

LDH, lactate dehydrogenase.

Table 4
Staging of melanoma.

Stage	Primary tumour (pT)	Regional lymph node metastases (N)	Distant metastases (M)
0	*In situ* tumour	None	None
IA	≤1.0 mm, no ulceration	None	None
IB	≤1.0 mm with ulceration or mitotic rate ≥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 ± ulceration	None but satellite and/or in-transit metastases	None
IIIC	Any tumour thickness with ulceration	Up to three macrometastases	None
	Any tumour thickness ± 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

The prototypical dermoscopic progression model for LMM on the face include four sequential patterns, that are hyper-pigmented follicular openings, annular-granular pattern, rhomboidal structures and atypical pseudo-network [51,52], whilst the importance of additional features such as increased vascular network and red rhomboidal structures have been linked to the development of tumour-induced neovascularisation [53].

Finally, a parallel ridge pattern and irregular diffuse pigmentation are distinguished features of early and invasive acral melanoma, respectively [54–58].

In high risk patients, mainly in the case of patients with atypical mole syndrome, the detection of changes in the lesions or newly appearing lesions by follow-up examination with digital dermoscopy and total-body photography is also helpful [59–61].

The differential diagnosis of melanoma involves other pigmented melanocytic lesions (congenital, atypical, common melanocytic naevi and actinic lentigo), non-melanocytic pigmented lesions (seborrhoeic keratosis, haemangioma, dermatofibroma, and pigmented basal cell carcinoma) and other non-pigmented tumours (haemangioma, basal cell carcinoma, squamous cell carcinoma).

In addition to dermoscopy new non-invasive methods have recently been introduced in the clinical setting to increase accuracy in the diagnosis of equivocal lesions. Reflectance confocal microscopy increases specificity in equivocal dermoscopic melanocytic lesions in two prospective studies [62]. This technology allows the diagnosis of subclinical lesions as amelanotic melanoma or better distinguishes the limits of the tumour [62], but has recently not been approved by NICE for routine use.

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 [63]:

1. Diagnosis and clinic-pathologic type; when there is uncertainty about malignancy it should be clearly stated in the report conclusion.
2. Tumour thickness in mm (Breslow's depth).
3. Presence or absence of ulceration.
4. Number of mitoses per mm^2 (in hot spots).
5. Microsatellites (if present), defined as any discontinuous nest of intralymphatic metastatic cells of >0.05 mm in diameter clearly separated by normal dermis or subcutaneous fat from the invasive component of the tumour by a distance of at least 0.3 mm.
6. Lateral and deep excision margins.

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

- Growth phase (horizontal or vertical).
- Presence or absence of established regression.
- Presence or absence of tumour infiltrating lymphocytes infiltrate preferably using the terms brisk, non-brisk or absent.
- 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 sampling of the metastatic tissue is not feasible, of the primary tumour is required for patients with distant metastasis or non-resectable regional metastasis, who are candidates for systemic medical treatment [64]. 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 [65].

NF1 mutations have been identified in around 10% of patients with CMs. Presently it is unknown, whether this type of mutation can be addressed with targeted therapies.

CKIT mutations should additionally be analysed in patients with acral and mucosal melanomas, although the positivity rate is lower than initially suggested in Europe. If present, patients can be treated with CKIT inhibitors [66,67].

In the near future, other genomic tests are expected to be identified as predictive markers for patients with stage IV melanoma. In the future testing may even be performed in blood samples instead of tumour tissue ('liquid biopsy') based on extracellular circulating DNA or circulating tumour cells.

2.4. Further staging

The most sensitive staging test for primary melanoma is sentinel node biopsy.

3. Surgical therapy

3.1. General principles

The primary treatment of melanoma is surgical excision [1,8,68]. 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. In such cases, dermoscopy may help to guide biopsy. Large studies have shown no evidence that incisional biopsies worsen prognosis as compared with immediate complete excisional biopsy [69,70].

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, United Kingdom (UK) and Australian recommendations.

The current recommendations are based on both prospective, randomised studies and international consensus conferences [1,4,7,71–73]. There are few data to suggest that margin has an effect on loco-regional recurrence, but there are weak data to support an impact of margin on survival in a recent meta-analysis [74] although a recent update from the UK suggested a survival deficit for patients with tumours thicker than 2 mm treated with a 1 cm margin [75].

3.3. Lentigo maligna

Lentigo maligna is a slowly growing melanoma *in situ*, which occurs typically in UV-exposed areas like the face [76]. Typically, the margin of excision chosen for lentigo maligna must consider the cosmetic/functional impact of the surgery and micrographic control of excision margins may be utilised in order to conserve tissue particularly in the face. 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% [77–79]. 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. Some centres utilise adjuvant imiquimod after surgery but the data supporting its use remain few.

Table 5
Recommended minimal excision margins for melanoma.

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

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 and therefore local recurrences are more frequent in these types of melanoma. Therefore, removal is usually attempted with increased safety margins (at least 1 cm) or by narrow margins with micrographic control (e.g. Mohs' technique and variants) [80–82]. The micrographic technique is intended to conserve tissue especially on the hands and feet.

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

No therapeutic advantage for ELND has been established [15]. The SLND was introduced in order to allow the evaluation of the first draining lymph node in the regional lymphatic system [38]. 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 OS time correlate clearly with the status of the sentinel lymph node [83,84]. SLND and radical lymph node dissection in patients with positive SLN prolong disease-free survival (DFS) but do not affect OS [83].

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 [85]. 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, 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 confirmed that radical lymph node dissection does not improve 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 + SLND) [39]. Nonetheless when the SLND shows micrometastases, radical lymph node dissection was usually recommended as approximately 5–12% of patients will have involvement of non-sentinel nodes. A German prospective randomised trial on the value of CLND in patients with positive SLN did not show any survival benefit after a 3-year follow-up for patients undergoing CLND [86]. Similarly in a matched cohort study across multiple centres no impact of CLND on survival could be demonstrated [87]. However these two studies involved a majority of patients with only small tumour deposits in the sentinel node (mainly tumours <1 mm), and they both have methodological weaknesses. Nevertheless these data at least suggest that indication of CLND should be critically discussed in patients with only small tumour deposits in the sentinel node. Potential benefits of CLND should be discussed with those patients carrying larger tumour deposits (>1 mm diameter) in the SLN.

3.8. Clinically-identified lymph node metastases

If lymph node metastases are diagnosed clinically or by imaging techniques, radical lymph node dissection is considered standard therapy [83].

3.9. Skin metastases

The treatment of choice for skin metastases is surgery, 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 has palliative value [88,89]. In stage III patients with satellite/in-transit 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 talimogene laherperepvec [90], interleukin (IL)-2, electrochemotherapy, or imiquimod.

3.10. Distant metastases

If technically feasible and reasonable (oligometastatic disease), then complete operative removal of distant metastases should be seen as therapy of choice. This is particularly true for patients with tumour markers LDH and protein S100B in the normal range [91]. In case of brain

metastases, stereotactic radiation therapy and surgery are considered equally effective. Many studies show that excision of solitary or few metastases can be associated with a favourable outcome for stage IV patients [92–95]. The possibility of neoadjuvant therapy followed by surgical excision of metastatic lesions can be considered [96].

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 (RT) for local disease control.

4. Radiotherapy

4.1. Primary melanoma

RT of the primary tumour is rarely indicated. However, in patients where the surgical will lead to severe disfigurement, RT can be applied with curative intent.

4.2. Regional lymph nodes

There is no established role for adjuvant RT of draining lymph nodes after excision of the primary melanoma. Adjuvant RT after lymphadenectomy can be considered for patients at high risk to improve regional lymph node field control [97].

When lymph node dissection is not complete or metastatic lymph nodes are inoperable, RT 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 RT alone [98].

4.4. Bone metastases

RT is effective to palliate pts with bone metastases. The response rate (CR + PR) is 67–85% [99–102]. 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 [99,103,104]. Headache responds to RT in approximately 80% of cases. Both stereotactic single-dose radiation therapy, and surgical resection are appropriate for solitary or few (typically up to 3–5), and not too large lesions (up to 3 cm in diameter). Treating solitary lesions (surgery or stereotactic RT) can be applied several times and appear to prolong DFS, although this has never been established in randomised trials [103–105].

5. Adjuvant therapy

5.1. General principles

Adjuvant therapy is offered to patients without evidence of macroscopic metastases but at high risk of having microscopic metastases. Since current possibilities with adjuvant medical therapy considerably reduce the quality of life, its indications and administration must be carefully considered and discussed with the patients. 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 cytotoxic 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 [1,2,4].

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 [106].

5.3. Adjuvant immunotherapy with interferon-α

Interferon (IFN)-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, also and impact on OS, albeit with significant toxicity [107–119]. Several meta-analyses have 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, $p = 0.002$) [120]. The meta-analysis did not show clear difference in the efficacy of the different dose schedules or of different treatment durations. Adjuvant IFN is offered in some European countries for high risk resected stage II or III melanoma on the basis of reduction in relapse-free survival (RFS), but not universally because of the small OS benefit and the significant toxicity.

A large-sized adjuvant trial on stage III melanoma patients treated with pegylated IFN α2b compared to observation alone was conducted by the EORTC Melanoma Group. The results indicate a statistically significant prolongation of RFS for all patients and a significant benefit of distant-metastasis free survival for

microscopically lymph node positive melanoma patients [119]. However, there was no significant benefit in terms of OS for IFN-treated patients. These findings are supported by a large randomised trial of the EADO, which compared the 3 years pegylated IFN α2b with 18 months classic IFN 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 IFN α2b.

Interesting is also the role of ulceration of the primary. In the EORTC 18952 and 18991 trials' meta-analysis and in meta-analysis of 15 trials ulceration of the primary was the overriding factor determining IFN-sensitivity [120–123] suggesting that no or low benefit was observed in patients with a non-ulcerated primary (70% of the total population) [124]. However this has to be confirmed prospectively.

5.4. Adjuvant immunotherapy with CTLA-4 or and PD-1 antibodies

The anti-CTLA-4 antibody ipilimumab was examined as adjuvant treatment in the EORTC 18071 double-blind, randomised phase III trial, and improved DFS was reported, whereas OS remains to be evaluated [125]. However, the high-dose ipilimumab scheme (10 mg/kg body weight for 3 years) used in the pivotal trial induced substantial toxicity. It led to an approval for stage III melanoma patients in the USA. A European approval is still outstanding [125].

There are ongoing clinical trials with PD-1 antibodies in the adjuvant setting. The earliest results will not be available before 2020.

5.5. Adjuvant use of BRAF/MEK inhibitors

There are two large-sized, prospectively randomised trials on either vemurafenib alone (BRIM8) or the combination of dabrafenib and trametinib (COMBI-AD). Preliminary results are expected for 2017.

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). From the long list of available cytostatic drugs, only a few have been able to induce tumour responses, but not prolonging survival. New targeted compounds and immunotherapeutic drugs have, however, been shown to prolong survival [126,127]. The two main goals of systemic therapy are as follows:

- 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 mitogen-activated protein (MAP) kinase and AKT pathways [128]. Numerous targeted inhibitors have already been developed or are under clinical investigation (Table 6).

About 45% of patients with CM carry an activating *BRAF* V600 mutation, for which several highly selective inhibitors have been developed. Vemurafenib and dabrafenib were 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) [126–129]. Vemurafenib and dabrafenib are approved for melanoma therapy in the USA and the European Union (EU). Vemurafenib is administered as an oral drug with a current standard dose of 960 mg twice daily and dabrafenib as an oral drug with a standard dose of 150 mg twice daily. Minor systemic (arthralgia, fatigue) but major cutaneous side-effects have been reported, including photosensitivity (only vemurafenib), development of epithelial tumours and in rare cases new primary melanomas. Development of secondary resistance to BRAF inhibitors with varying time courses is a frequent event. MEK inhibitors meanwhile supplement the inhibition of the MAP kinase pathway, and combinations of BRAF and MEK inhibitors like vemurafenib + cobimetinib and dabrafenib + cobimetinib were shown in three independent of care phase III trials to significantly increase objective response rate, progression-free and OS. Therefore, the combination of *BRAF* and MEK inhibition is the current standard in the treatment of patients with *BRAF* mutations where this treatment strategy is indicated (Table 7).

A small proportion of melanomas arising in sun-protected sites have mutations in cKIT and they have been treated with the cKIT inhibitor imatinib-mesylate. 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 (Table 7) [67].

An NRAS mutation is detected in 15–20% of CMs. Presently, there are no direct NRAS-inhibiting molecules available. However, trials have been performed in these patients with MEK-inhibitors like binimetinib (NEMO trial, NCT01763164) and pimasertib (EMD Serono, NCT01693068). Responses were observed, the exact analysis of these trials will be published in 2016.

6.3. Immunotherapy

Cytokines such as IFN-alpha and IL-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 in randomised clinical trials. Vaccination strategies have raised a lot of interest, but so far no efficacious vaccines have been

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 to 5 years)	Stage III

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

Medication	Dose	Response rate
BRAF mutation		
Dabrafenib	2 × 150 mg p.o. daily until tumour progression	64–67%
+		
trametinib	1 × 2 mg p.o. daily until tumour progression	
Long 2014, Robert 2014 [130]		
Vemurafenib	2 × 960 mg p.o. daily until tumour progression	54–68%
+		
Cobimetinib	1 × 60 mg p.o, daily for 21 d, followed by 7 d off, until tumour progression	
Ribas 2014, Larkin 2014 [131]		
cKIT mutation		
Imatinib mesylate Guo 2011 [67]	1 × 400 mg p.o. daily until tumour progression	23%
NRAS mutation		
Binimetinib	2 × 45 mg (3 × 15 mg tablets) p.o. daily until tumour progression	Not yet available
NCT01763164 [132]		
Pimasertib	2 × 60 p.o. daily until tumour progression	Not yet available
NCT01693068 [133]		

developed. In some trials, results may suggest even deleterious effects [134].

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 [127–129,134–138]. Ipilimumab is approved for melanoma therapy in the USA and in the EU. It is presently administered as four intravenous infusions at a dose of 3 mg/kg/infusion separated by 3 weeks. Serious 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.

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. Meanwhile, the introduction of PD-1 antibodies changed the role of ipilimumab, which, in the future, will no longer be considered as the treatment of choice for first-line therapy, but ipilimumab will likely be used in combination with PD-1 antibodies (Table 8).

The PD-1 antibodies nivolumab and pembrolizumab are approved for therapy of unresectable metastatic melanoma in the USA and Europe. Nivolumab was shown to improve progression-free and OS as compared to dacarbazine (CheckMate-066 trial) and as compared to ipilimumab (CheckMate-067 trial). Pembrolizumab showed improved progression-free and OS in comparison to ipilimumab (KEYNOTE-006 trial). Objective response rates of ~50% were achieved with PD-1 blockade. However, long-term survival data are not yet widely available, but in some studies a 2 year-survival rate of 50% seems to be achieved by PD1-blokers. PD-1 blockade will be the first-line treatment of patients with *BRAF* wild-type tumours in future, and may be considered for first-line treatment also in patients with BRAF mutation.

The combination of nivolumab with ipilimumab was shown to be superior in progression-free survival to ipilimumab and to nivolumab as single drugs (CheckMate-067 trial) leading to a FDA approval before OS data are available. However, there is clearly an increased toxicity as compared to the treatment with the single substances.

Table 8
Checkpoint blockade therapies for advanced cutaneous melanoma described in prospective randomised trials.

Medication	Dose	Response rate
Ipilimumab [127,138]	3 mg/kg i.v. every 3 weeks for four cycles	12–19%
Nivolumab [139,140]	3 mg/kg i.v. every 2 weeks until tumour progression	40–44%
Pembrolizumab Robert 2015 [141]	2 mg/kg i.v. every 3 weeks until tumour progression	33%
Nivolumab + **ipilimumab** Larkin 2015 [142]	3 mg/kg i.v. every 3 weeks for four cycles 1 mg/kg i.v. every 3 weeks for four cycles, continuation with 3 mg/kg every 2 weeks until tumour progression	58%

6.4. Chemotherapy

Chemotherapy was the only available systemic treatment as long as targeted therapy and immune checkpoint blockade were not available. Presently, chemotherapy may be considered in second and third line in patients with resistance to immunotherapy and targeted therapy. Chemotherapy still can have a role to play as first-line treatment in countries were the new drugs are not available or not reimbursed.

A number of agents with comparable effectiveness are available for systemic chemotherapy of advanced melanoma. Chemotherapy can lead to the 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% (Table 9) [143–146].

6.5. 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; NRAS, CKIT* in subtypes) is a prerequisite for treatment decisions, and should be performed preferentially in metastatic tumour tissue from AJCC stage IIIB onwards.
- PD-1 checkpoint blockade either as monotherapy or in combination with CTLA-4 blockade should be considered as a good option for first-line treatment for all patients with unresectable metastatic melanoma, independently from *BRAF* status.
- When BRAF-inhibitors are considered for BRAF mutated patients, they must be given in combination with MEK inhibitors.
- In BRAF mutated patients there are presently no data whether BRAF/MEK inhibition should be given in the first or second line, and trials on the best sequencing of targeted therapy and immunotherapy are ongoing.
- Chemotherapy may be considered in patients in good performance status with resistance to kinase inhibitors and checkpoint blockade.
- C-KIT inhibitors may have a role in the small proportion of c-KIT mutant melanomas

6.6. 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 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 10)

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. Diagnosing additional primary melanomas (occurs in about 10% of patients with CM) at an early stage and non-melanoma skin cancers,
3. Offering psychosocial support,

Table 9
Monochemotherapy and polychemotherapy 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 [147], Middleton 2000 [146]	250 mg/m^2 i.v. daily for 5 d every 3–4 weeks	12.1–17.6%
Chiarion Sileni, 2001 [148], Young 2001 [149]	800–1200 mg/m^2 i.v. daily on 1 d every 3–4 weeks	5.3–23%
Temozolomide Bleehen 1995 [150], Middleton 2000 [146]	150–200 mg/m^2 p.o. daily for 5 d every 4 weeks	13.5–21%
Fotemustine Jacquillat 1990 [151], Mornex 2003 [152]	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%
CarboTax Rao 2006 [153]	Carboplatin AUC6 i.v. day 1, after four cycles reduce to AUC4Paclitaxel 225 mg/m^2 i.v. day 1 every 3 weeks, after four cycles reduce to 175 mg/m^2	(12.1% second line)
DVC Verschraegen 1988 [154]	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%

4. Providing education on prevention, for the patient and his first-degree relatives.
5. Providing education of the patient and his family on skin self-examination to promote the early detection of melanoma.
6. Administering and monitoring adjuvant therapy, where appropriate.

7.2. Recommendations for structured follow-up

The classical follow-up 'rules' are variable across Europe, ranging in frequency from 2 to 4 times per year for 5–10 years, with few data to support the different schedules. In stage I–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 5 years, whereas for the 6th–10th year period attendance every 6 months seems to be adequate. In patients with thin CM ($\leq$1 mm) six monthly intervals may be sufficient and some guidelines support a limited follow-up of 1 year for stage IA melanoma. However, the introduction of the new treatments (targeted and immunotherapies) may lead to a complete revision of these algorithms, in order to promote earlier detection of metastases, depending on whether or not the impact on survival was proven to be better when they are given early than later in more advanced ones.

Table 10
Chemotherapy for advanced uveal melanoma.

Medication	Dose
Fotemustine Leyvraz 1997, Egerer 2001, Siegel 2007 [155–157]	Induction cycle 100 mg/m^2 intraarterial (hepatic artery) over 4 hours weekly for 4 weeks; then 5 week pause; then repeat every 3 weeks
Treosulfan/gemcitabine Pföhler 2003 [158]	Treosulfan 5 g/m^2 i.v. day 1 Gemcitabine 1 g/m^2 i.v. day 1 Repeat every 3 weeks

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, RT, 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 from Germany. In the first round dermatologists were involved who participated in national guideline development processes. In the second round the EORTC selected experts from different specialities who contributed to these guidelines. This process was first organised in 2008/2009 and the update was developed by the same groups in 2012 and 2015 (in 2015 Lars Bastholt substituted Alan Spatz). 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 3 years.

Conflict of interest statement

CG, AH, PS, MM, JJG, JM, HP, LB 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, Clovis, Eisai, Novartis and Immunocore, LB additionally from Eisai, AstraZeneca, Novartis and SOBI. KP has had advisory roles for and has received

honoraria from Roche, Leo Pharma, MEDA, and Novartis; AS has had consultant or advisory roles for and has received honoraria from Roche, LEO Pharma, MEDA and Novartis; JNB has received honoraria from Roche. CG has received research funding from Bristol-Myers Squibb, Merck Sharp & Dohme, Roche and Swedish Orphan Biovitrum; AH has received research funding from Bayer and Merck Sharp & Dohme; PS had consultant or advisory role for Amgen and Novartis and has received research funding from Roche; MM has received research funding from GlaxoSmithKline. All other authors declared that they have no conflicts of interest.

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