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## Guidelines

## European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics – Update 2019

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## KEYWORDS

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Mutation testing;  
Follow-up  
examinations

**Abstract** Cutaneous melanoma (CM) is potentially the most dangerous form of skin tumor and causes 90% of skin cancer mortality. A unique collaboration of multidisciplinary 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. The diagnosis of melanoma can be made clinically and shall always be confirmed through dermatoscopy. If a melanoma is suspected, a histopathological examination is required. Sequential digital dermatology and full-body photography can be used in risk persons to detect the development of melanomas at an earlier stage. Where available, confocal reflectance microscopy can improve clinical diagnosis in special cases. Melanoma shall be classified according to the 8th version of the AJCC classification. Thin melanomas up to 0.8 mm tumor thickness does not require further imaging diagnostics. From stage IB onwards, examinations with lymph node sonography are recommended, but no further imaging examinations. From stage IIC whole-body examinations with CT or PET-CT in combination with brain MRI are recommended. From stage III and higher, mutation testing is recommended, particularly for BRAF V600 mutation. It is important to provide a structured follow-up to detect relapses and secondary primary melanomas as early as possible. There is no evidence to support the frequency and extent of examinations. A stage-based follow-up scheme is proposed, which, according to the experience of the guideline group, covers the minimum requirements; further studies may be considered. This guideline is valid until the end of 2021.

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## 1. Introduction

### 1.1. Societies in charge

This guideline was developed on behalf of the European Dermatology Forum (EDF). The European Association of Dermato-Oncology (EADO) coordinated the authors' contributions as part of its Guideline Program in Oncology (GPO) under the leadership of Claus Garbe, Tübingen (first author). Alexander Eggermont (senior author) was responsible for the collaboration with the European Organization for Research and Treatment of Cancer (EORTC) to ensure the interdisciplinary quality of the guideline.

### 1.2. Disclaimer

Medicine is subject to a continuous development process. Therefore, all statements, in particular on

diagnostic and therapeutic procedures, can only correspond to the scientific knowledge current at the time of printing of this guideline. The attending physician invoking these guideline recommendations must take into account scientific progress since the publication of the guideline. In the selection and dosage of the drugs, attention was paid to compliance with the therapeutic recommendations given. Nevertheless, users are requested to use package inserts and technical information from the manufacturers as a backup, and in case of doubt, consult a specialist. The user remains responsible for all diagnostic and therapeutic applications, drugs, and doses.

### 1.3. Scope

This guideline has been written to assist the clinician in the diagnosis and follow-up of melanoma. Recent diagnostic strategies have been included in this

Table 1  
Oxford center for evidence-based medicine 2011 levels of evidence.

Question	Step 1 (Level 1 <sup>a</sup> )	Step 2 (Level 2 <sup>a</sup> )	Step 3 (Level 3 <sup>a</sup> )	Step 4 (Level 4 <sup>a</sup> )	Step 5 (Level 5)
<b>How common is the problem?</b>	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances <sup>b</sup>	Local non-random sample <sup>b</sup>	Case-series <sup>b</sup>	n/a
<b>Is this diagnostic or monitoring test accurate?</b> (Diagnosis)	Systematic review of cross-sectional studies with the consistently applied reference standard and blinding	Individual cross-sectional studies with the consistently applied reference standard and blinding	Non-consecutive studies, or studies without the consistently applied reference standards <sup>b</sup>	Case-control studies, or poor or non-independent reference standard <sup>b</sup>	Mechanism-based reasoning
<b>What will happen if we do not add a therapy?</b> (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomised trial <sup>a</sup>	Case-series or case-control studies, or poor-quality prognostic cohort study <sup>b</sup>	n/a
<b>Does this intervention help?</b> (Treatment Benefits)	Systematic review of randomised trials or <i>n</i> -of-1 trials	Randomised trial or observational study with dramatic effect	Non-randomised controlled cohort/follow-up study <sup>b</sup>	Case-series, case-control studies, or historically controlled studies <sup>b</sup>	Mechanism-based reasoning
<b>What are the COMMON harms?</b> (Treatment Harms)	Systematic review of randomised trials, systematic review of nested case-control studies, <i>n</i> -of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individually randomised trial or (exceptionally) observational study with dramatic effect	Non-randomised controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out common harm. (For long-term harms, the duration of follow up must be sufficient.) <sup>b</sup>	Case-series, case-control, or historically controlled studies <sup>b</sup>	Mechanism-based reasoning
<b>What are the RARE harms?</b> (Treatment Harms)	Systematic review of randomised trials or <i>n</i> -of-1 trial	Randomised trial or (exceptionally) observational study with dramatic effect			
<b>Is this (early detection) test worthwhile?</b> (Screening)	Systematic review of randomised trials	Randomised trial	Non-randomised controlled cohort/follow-up study <sup>b</sup>	Case-series, case-control, or historically controlled studies <sup>b</sup>	Mechanism-based reasoning

<sup>a</sup> Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is large or very large effect size.

<sup>b</sup> As always, a systematic review is generally better than an individual study.

guideline. Special emphasis has been placed on imaging diagnostics and follow-up examinations.

#### 1.4. Target population

These two parts of the melanoma guideline contain recommendations for the diagnosis, follow up, and treatment of patients with melanoma. The guideline is addressed to the attending physicians and the medical nursing staff. An attempt has been made to write the guideline in a way that is easy to understand so that patients can also understand the recommendations.

#### 1.5. Principles of methodology

The literature search was carried out by the authors using PubMed, and only articles published until September 2019 were included. Search strings were used, which cannot all be listed here. In principle, the search strings are constructed in such a way that the search is primarily carried out in the titles of the publication, e.g. *melanoma [ti] AND (radiotherapy [ti] OR irradiation [ti] OR stereotactic [ti])*.

All diagnostic and treatment recommendations summarised in specific tables are evaluated on the basis of evidence-based data or formulated as expert consensus when there is insufficient evidence. The methodology of these updated guidelines is based on the standards of the AGREE II instrument. The levels of evidence are graded according to the Oxford classification (Table 1) [1]. The degree of recommendation is also classified (Table 2).

The source guideline for guideline adaptation of recommendations is the German S3 guideline on malignant melanoma in the version from 2013 and the consultation version of 2019 [2,3].

#### 1.6. Financing

The authors did this work on a voluntary basis and did not receive any honorarium. Travel costs for participation in Consensus Conferences were reimbursed in part by EADO.

## 2. Definition

Melanoma is a malignant tumor that arises from melanocytes 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 also be amelanotic. Even small tumors may have a tendency to metastasise, thus leading to a relatively unfavorable prognosis. Melanomas account for 90% of the deaths associated with cutaneous tumors. In this guideline, we concentrate on the treatment of cutaneous melanoma [4–11].

## 3. Epidemiology and etiology

The incidence of melanoma is increasing worldwide in white populations, especially where fair-skinned people receive excessive sun exposure [12–14]. In Europe, the incidence rate is <10–25 new melanoma cases per 100,000 inhabitants; in the USA 20–30 per 100,000; and in Australia, where very high incidence is observed, 50–60 per 100,000. 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 are predicted to continue to increase for decades [15]. The commonest phenotypic risk factor is the skin that tends to burn in the sun, and inherited melanocortin-1 receptor (*MC1R*) variants are 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 greater risk, and this phenotype is also genetically determined [16–19]. 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 that carry high penetrance susceptibility genes [20,21]. The most important exogenous factor is exposure to UV irradiation, particularly intermittent high sun exposure [22–24].

## 4. Different subtypes of melanoma

Cutaneous melanoma is classified as melanoma in situ when confined within the epidermis, or invasive when atypical melanocytes progressively invade into the dermis. Subtypes of invasive melanoma are distinguished by clinical and histopathological features into four major histological subtypes: superficial spreading melanoma (SSM) (41%), followed by nodular melanoma (NM) (16%), lentigo maligna melanoma (LMM) (2.7%–14%) and acral lentiginous melanoma (ALM) (1%–5% in non-Hispanic White population and higher rates in Asian or African American population) [25–29]. Of note, clinical-pathologic subtypes are not included as prognostic factors in the current 8th edition of the American Joint Committee on Cancer (AJCC) staging system for melanoma [30].

Table 2  
Grades of recommendation.

Grade of recommendation	Description	Syntax
A	Strong recommendation	Shall
B	Recommendation	Should
c	Recommendation pending	May/can

SSM begins with an intraepidermal horizontal or radial growth phase, appearing first as a macule that slowly evolves into a plaque, often with multiple colors and pale areas of regression. A characteristic histologic feature is the presence of an epidermal lateral component with the pagetoid spread of clear malignant melanocytes throughout the epidermis. Secondary nodular areas representing the vertical growth phase of the tumor can develop in the further course.

NM, in contrast, is a primarily nodular, exophytic brown-black, often eroded or bleeding tumor, which is characterised by a predominant aggressive vertical growth phase. When present, an epidermal lateral component is observed histologically within and up to three rete ridges at the maximum. NM has been associated with greater Breslow thickness, and early clinical features not conforming to the well-established warning signs of ABCD, making early detection difficult [31–33].

LMM is defined as the invasive progression of the slow-growing lentigo maligna (melanoma in situ). LMM is a distinct subtype located predominantly on the sun-damaged faces of elderly individuals [34]. LMM is characterised histologically by a lentiginous proliferation of atypical melanocytes at the dermoepidermal junction, confluence, formation of nests in the dermis, and a perifollicular localization of melanocytes.

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

Desmoplastic melanoma (DM) is a rare subtype (1%–4%). It is defined as a variant of spindle cell melanoma in which the malignant cells are separated by collagen fibers or fibrous stroma [35]. According to the NCCN guidelines, the presence of pure desmoplastic melanoma (as opposed to the presence of desmoplasia with spindle cell and/or epithelioid cells) may impact the decision about diagnostic staging and treatment [36].

Amelanotic/hypomelanotic melanoma is defined as a form of melanoma with little or no pigment on macroscopic or dermoscopic evaluation, or as melanoma that lacks melanin in the cytoplasm of tumor cells on histological examination [37]. Amelanotic melanoma has been more frequently associated with the nodular and desmoplastic histological subtypes and more frequently localised on the ear, nose, and face [38].

In the updated WHO classification of skin tumors (4th edition, 2018), melanoma is classified based on the pathway concept of melanoma pathogenesis and its association with sun-exposed skin (Table 3) [29]. For melanomas arising in sun-exposed skin, further classification is based on the degree of cumulative sun damage (CSD) as assessed by the degree of solar elastosis on

Table 3

Classification of melanomas, including epidemiological, clinical, pathological, and common genomic features. Adapted from [29].

Type of UVR exposure/CSD	Subtype of melanoma	Affected genes
Low-CSD melanoma	SSM	BRAF V600 E/K or NRAS CDKN2A TP53 SWI/SNF TERT
High-CSD melanoma	LMM Desmoplastic melanoma	NF1, NRAS, BRAF, KIT CDKN2A TP53 SWI/SNF TERT
Low to no UVR exposure (or variable/incidental)	Spitz melanoma	HRAS, ROS1, NTRK1, NTRK3, ALK, RET, MET, BRAF, CDKN2A, TERT
	Acral melanoma	NRAS, KIT, NF1, SPRED1, BRAF, CCND1,
	Mucosal melanoma (genital, oral, sinonasal)	ALK, ROS1, RET, NTRK1, CDKN2A, CDK4, TP53, SWI/SNF, TERT
	Uveal melanoma	GNAQ, GNA11, CYSLTR2, PLCB4, BAP1, SF3B1, EIF1AX
	Melanoma arising in congenital naevus	NRAS
	Melanoma arising in blue naevus	GNAQ, GNA11, CYSLTR2, BAP1, SF3B1, EIF1AX

CSD = Cumulative sun damage.

biopsy. Melanomas arising in sun-exposed skin include low-CSD melanoma (SSM and a subset of NM) and melanoma in chronically sun-exposed skin (LMM, desmoplastic melanoma, and a subset of NM). Melanomas arising at sun-shielded sites or without known etiological associations with UV radiation exposure include Spitz melanoma, acral melanoma, mucosal melanoma (genital, oral, sinonasal), melanoma arising in congenital naevus, melanoma arising in blue naevus, uveal melanoma, nodular, and nevoid [29]. Distinct molecular signatures have been identified in tumors at different anatomical locations and with different associations with sun exposure. Melanoma of 'low UVR exposure/CSD' is mainly located on the trunk and extremities and frequently carries a *BRAF* mutation, which is present in ~45% of cutaneous melanomas. Melanoma of 'high UVR exposure/CSD' 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 cutaneous melanomas. 'Non-sun-related melanomas' are mainly located on acral and mucosal sites and carry a low frequency of *CKIT* mutations (Table 3) [34,39–41].

Pediatric melanoma is addressed separately. It is classified as prepubertal (congenital and childhood) pediatric melanoma occurring before the age of 10–12 years, or post-pubertal (adolescent) pediatric melanomas in patients of 10–19 years old. WHO classification of skin tumors describes four major histopathological subtypes of pediatric melanoma: [29]

- *De novo* melanoma;
- Melanoma arising in a congenital naevus;
- Spitzoid tumors and melanoma;
- Conventional adult-type melanoma;

Metastatic melanoma is defined as a secondary tumor derived from a primary melanoma. It may present as microsatellite, satellite, or in-transit metastases, as nodal or distant metastases. Metastatic melanomas of unknown primary occur in about 3% of the melanoma patients.

### 5. 8th AJCC melanoma classification and potential new biomarkers

About 90% of melanomas are diagnosed as primary tumors without any evidence of metastasis. The tumor-specific 10-year-survival for such tumors is 95–75%. The most important histological prognostic factors for primary melanoma without metastases, as reflected in recent studies, are:

- Vertical tumor thickness (Breslow's depth) as measured on the histological specimen with an optical micrometer scale, and defined as the histologic depth of the tumor 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 the 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 [42].
- Mitotic rate (number of mitosis/mm<sup>2</sup>) appears as an independent prognostic factor in several population studies [43] but is no longer used for sub-classification of thin melanomas in the 8th revision of the AJCC staging system (see below) [30].
- level of invasion (Clark's level) is no longer part of the AJCC staging system.

Prognosis is also poorer with increased age, the male sex, and truncal/head and neck tumors compared to melanomas on the limbs [44,45].

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

- Satellite metastases (defined as up to 2 cm from the primary tumor).
- In-transit metastases (located in the skin between 2 cm from the site of the primary tumor and the first draining lymph node).
- Micro-metastases in the regional lymph nodes identified via sentinel lymph node biopsy [46,47]. In contrast to macro-metastasis, micrometastasis is clinically not recognizable neither by palpation nor by imaging techniques.
- Clinically or radiologically recognizable regional lymph node metastases.

The 10-year-survival is 30–50% for patients with satellite and in-transit metastases, 69–75% for patients with lymph node micrometastasis, and 40–60% for those with clinically apparent regional lymph node metastases [48].

Distant metastases have a grim prognosis in untreated patients with a median survival of only 6–9 months, although there is considerable variation depending on aggressiveness of the individual tumor, which can be clinically defined by the number of organs involved, presence of brain metastases, and serum levels of lactate dehydrogenase (LDH, Tables 6 and 7).

In 2017, the AJCC issued the 8th TNM classification for the staging of melanoma [30]. This new system now forms the cornerstone for classifying melanomas and is summarised in Tables 4–7. This classification has been criticised, as the survival of the equivalent stage differs significantly from 7th to 8th TNM classification, and

Table 4  
T classification of primary tumor for melanoma.

T category	Tumor thickness	Additional prognostic parameters
Tis		Melanoma <i>in situ</i> , no tumor invasion
Tx	No information	Tumor thickness cannot be determined <sup>a</sup>
T1	≤1.0 mm	a: < 0.8 mm, no ulceration b: < 0.8 mm, with ulceration or 0.8–1.0 mm with or without
T2	>1.0–2.0 mm	a: No ulceration b: Ulceration
T3	>2.0–4.0 mm	a: No ulceration b: Ulceration
T4	>4.0 mm	a: No ulceration b: Ulceration

<sup>a</sup> Tumor thickness or information on ulceration not available or unknown primary tumor.

Table 5

N classification of the regional lymph nodes for melanoma.

N category	Number of involved lymph nodes (LN)	Presence of in-transit, satellite, and/or microsatellite metastases
NX	Not assessed (not required for T1 melanoma)	No
N0	0	No
N1	1 LN+ or any in-transit, satellite, and/or microsatellite metastasis	No
N1a	1 LN+, clinically occult	No
N1b	1 LN+, clinically detected	No
N1c	0 LN+	Yes
N2	2, 3 LN+ or any in-transit, satellite, and/or microsatellite metastasis with 1 LN+	No
N2a	2, 3 LN+, clinically occult	No
N2b	2, 3 LN+, clinically detected	No
N2c	1 LN+, clinically detected or not	Yes
N3	≥4 LN+, or any in-transit, satellite, and/or microsatellite metastasis with 2, 3 LN+	No
N3a	≥4 LN+, clinically occult	No
N3b	≥4 LN+, of which ≥ 1 clinically detected	No
N3c	≥2 LN+, clinically detected or not	Yes

LN+ denotes lymph node with melanoma deposit.

Table 6

M classification of distant metastases for melanoma.

M category	Anatomic site of metastasis	LDH level
M0	No evidence of distant metastasis	Not applicable
M1a	Skin, subcutaneous tissue and/or non-regional lymph node	Not recorded or unspecified
M1a(0)	idem	Not elevated
M1a(1)	idem	Elevated
M1b	Lung, with or without M1a sites of metastasis	Not recorded or unspecified
M1b(0)	idem	Not elevated
M1b(1)	idem	Elevated
M1c	Distant metastasis to non-CNS sites, with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)	idem	Not elevated
M1c(1)	idem	Elevated
M1d	Distant metastasis to CNS, with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)	idem	Not elevated
M1d(1)	idem	Elevated

may puzzle translation of the results obtained in one version to the other.

Prognostic biomarkers are the subject of intensive research, but except LDH serum level, none of them has reached enough clinical validation to be used routinely, including PDL-1 expression or tumor mutational burden assessed in tumor tissue(s). Better prognostic biomarkers are expected to emerge from molecular and immunological variables under investigation.

Recommendation 1

Stage classification	Consensus based recommendation
GCP	The classification into prognostic stages shall be performed according to the 8th edition of the AJCC classification. Consensus rate: 100%

## 6. Diagnostic approach

### 6.1. Clinical and dermatoscopic diagnosis

In most instances, the clinical appearance of melanoma varies according to the melanoma subtype (see above). Typical features are asymmetry of the lesion, irregular borders, variability in colors, diameter of 5 mm and more, growth of nodules, and regression within the lesion. The sensitivity of clinical diagnosis by experienced dermatologists is difficult to assess but estimated to be around 70% [49].

The clinical diagnosis by the dermatologist is based on a combination of 3 analyses of any pigmented lesion: (1) visual analysis of each lesion separately, which generally excludes non-melanocytic lesions, although melanomas may rarely mimic pigmented seborrheic keratoses. Examination with the naked eye assesses the presence of the so-called A (asymmetry), B (irregular borders), C (inhomogeneous color), and D (diameter ≥ 5 mm) criteria, which point to suspicious melanocytic lesions (ABCD rule). (2) Intra-individual comparative analysis, which is searching for the lesion that is not like the others in the same patient (ugly duckling sign) [50]. (3) Chronologic analysis of changes,

Table 7

AJCC Pathological (pTNM) prognostic stage groups.

When T is ...	And N is ...	And M is ...	Then the pathological stage group is ...
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b, or N3c	M0	IIIC
T1a/b-T2a	N1a or N2a	M0	IIIA
T1a/b-T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a-T3a	N2c or N3a/b/c	M0	IIC
T3b/T4a	Any N ≥ N1	M0	IIC
T4b	N1a-N2c	M0	IIC

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. Papular or nodular lesions may lack clinical diagnostic features. In these cases, the EFG rule, standing for Elevated Firm and Growing, is relevant for prompting excision of a potentially aggressive melanoma [51].

#### Recommendation 2

Clinical diagnosis	Consensus based statement
GCP	If melanoma is clinically suspected, it shall be confirmed by histopathology. Consensus rate: 100%

Dermatoscopy should be used to clarify the differential diagnosis of pigmented lesions. In general, a dermatoscopic examination should be performed. However, if it is not available without significant delay due to the lack of access to a dermatologist, the definitive diagnosis and excision should not be postponed. In order to apply this technique, training and expertise are required. A meta-analysis of 22 studies showed that when experts employed dermatoscopy, they achieved an increase in diagnostic accuracy over the clinical diagnosis alone in questionable lesions, reaching a sensitivity of 89% and a specificity of 79% [52].

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 colors asymmetrically distributed. Additional criteria e.g. blue-whitish veil and polymorphic vessels, are common in invasive melanoma [53–56].

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 dermatoscopic features [57–60]. This argues for urgent excision of any growing skin lesion suspicious for a skin tumor even if it looks more like a squamous lesion than a melanoma.

The prototypical dermatoscopic progression model for LMM on the face includes four sequential patterns that are annular-granular pattern, hyperpigmented follicular openings, rhomboidal structures, and atypical pseudo-network [61,62], while the importance of additional features, such as increased vascular network and red rhomboidal structures have been linked to the development of tumor-induced neovascularization [63].

Finally, a parallel ridge pattern and irregular diffuse pigmentation are the main dermatoscopic features of early and invasive acral melanoma, respectively [64–68].

Dermatoscopy should be applied to all lesions and not only on clinically suspicious ones. This is because dermatoscopy has the potential to uncover the natural asymmetry of melanoma before it becomes clinically recognizable.

#### Recommendation 3

Dermatoscopic diagnosis	Evidence based recommendation
Level of recommendation A	Dermatoscopy shall be used for the assessment of pigmented and non-pigmented skin lesions. Training in dermatoscopy is mandatory. Guideline adaptation [2,3] <i>De novo</i> literature research for nail and acral melanomas [67,69–73] Consensus rate: 100%
Level of evidence: 1b	

Sequential total body photography and digital dermatoscopy significantly contribute to early melanoma detection, especially in the context of high-risk individuals. All known high-risk groups (genetic predisposition, personal melanoma history, high total nevus count, etc.), might benefit from total body photography. Sequential dermatoscopic documentation is mainly meaningful in the context of high-risk individuals with multiple atypical moles, facilitating both the detection of melanoma and the reduction of the number of unnecessary excisions [74–78].

#### Recommendation 4

Whole-body photography	Evidence-based recommendation
Level of recommendation B	Whole-body photography with sequential examinations should be used for the early detection of melanoma in high-risk patients. <i>De novo</i> literature research [79–81] Consensus rate: 100%
Level of evidence: 2b	

#### Recommendation 5

Digital dermatoscopy	Evidence-based recommendation
Level of recommendation B	Sequential digital dermatoscopy can improve the early detection of melanoma and should be used in high-risk patients, with a high total nevus count. <i>De novo</i> literature research [82–85] Consensus rate: 100%
Level of evidence: 2b	

The differential diagnosis of melanoma involves other pigmented melanocytic lesions (congenital, atypical and common melanocytic naevi), non-melanocytic pigmented lesions (seborrheic keratosis, actinic lentigo,

hemangioma, dermatofibroma, and pigmented basal cell carcinoma) and other non-pigmented tumors (hemangioma, basal cell carcinoma, squamous cell carcinoma).

In addition to dermatoscopy, new non-invasive methods have been introduced in the clinical setting to increase accuracy in the diagnosis of equivocal lesions. Reflectance confocal microscopy increases diagnostic specificity in equivocal dermatoscopic melanocytic lesions both in prospective studies [86–88], and in a recent meta-analysis conducted by the Cochrane Collaboration [89]. Meta-analysis found reflectance confocal microscopy to be more accurate than dermatoscopy in studies of participants with any lesion suspicious for melanoma and in participants with lesions that were more difficult to diagnose, determining an increment of specificity of 82% for RCM, compared to 42% for dermatoscopy for any lesion suspicious for melanoma, and of 86% for RCM, compared to 49% for dermatoscopy for lesions that were more difficult to diagnose, concluding that 'RCM may have a potential role in clinical practice, particularly for the assessment of lesions that are difficult to diagnose using visual inspection and dermatoscopy alone, where the evidence suggests that RCM may be both more sensitive and specific in comparison to dermatoscopy.'

This technology also allows the diagnosis of subcutaneous lesions as amelanotic melanoma or better distinguish the limits of the tumor [88,90].

#### Recommendation 6

Confocal laser microscopy	Evidence based statement
Level of recommendation C	Confocal laser microscopy can be used for further evaluation of clinically/dermatoscopic equivocal skin lesions.
Level of evidence: 2b	<i>De novo</i> literature research [86–89] Consensus rate: 100%

### 6.2. 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: [91].

1. Diagnosis and clinic-pathologic type (SSM, NM, LMM, ALM); when there is uncertainty about malignancy, it should be clearly stated in the report conclusion.
2. Tumor thickness in mm (Breslow depth).
3. Presence or absence of ulceration.
4. number of mitoses per mm<sup>2</sup> (in hot spots).
5. Microsatellites (if present), defined as any discontinuous nest of intra-lymphatic metastatic cells of >0.05 mm in diameter clearly separated by normal dermis or

subcutaneous fat from the invasive component of the tumor by a distance of at least 0.3 mm.

### 7. Lateral and deep excision margins

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

- ◆ Growth phase (horizontal or vertical)
- ◆ Presence or absence of established regression
- ◆ Presence or absence of tumor-infiltrating lymphocytes (TIL) 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, Melan-A, HMB45 and SOX10 for the confirmation of the melanocytic nature of the tumor, HMB45 as an additional feature of malignancy when there is an inverted positive gradient, MIB-1 as a proliferation marker).

#### 7.1. Molecular diagnosis

Mutational analysis is required to determine the *BRAF*<sup>V600</sup> mutation status in patients with distant metastasis or non-resectable regional metastasis to identify those who are eligible to receive treatment with combined BRAF and MEK inhibitors, and in resected high-risk stage III melanoma patients in the adjuvant setting. *BRAF*<sup>V600</sup> mutation testing should be performed on metastatic tissue, either distant or regional, or on primary tumor if sampling of the metastatic tissue is not feasible. A clinically meaningful discrepancy rate in the BRAF status indeed may exist between primary and metastatic melanoma lesions [92]. Mutational analysis for BRAF of the primary lesion is not recommended for patients with cutaneous melanoma but without evidence of the disease, unless required to guide consideration of clinical trials for adjuvant therapy.

*NRAS* mutations are identified in 15%–20% of melanoma samples and are mutually exclusive with BRAF mutations, with few exceptions of patients with both BRAF and NRAS mutations. A positive NRAS mutation also serves to reassure that a BRAF mutation has not been missed. An NRAS-targeted approach for patients with NRAS mutations has so far shown limited efficacy; however, additional NRAS inhibitors and combined treatment strategies are currently under clinical investigation for these patients [93,94].

*c-KIT*-mutant melanoma represents a rare subset (1–3%), most commonly arising from mucosal, acral, and chronically sun-damaged skin. Since the positivity rate of *c-KIT* mutations is low, acral and mucosal melanomas should initially be tested for *BRAF* and *NRAS*

mutations, and if the wild type, additionally analyzed for *c-KIT* mutations. Clinical benefit has been demonstrated for *c-KIT* inhibitors in selected patients [95].

A recent molecular classification of melanoma included an *NF1*-mutant melanoma subtype. However, *NF1* mutational analysis is not routinely performed since it currently lacks direct clinical implications [96,97].

Genetic profiling of melanoma tissues using next-generation panel sequencing might help in identifying genetic alterations, which can be targeted by drugs, thus assisting clinicians with clinical decision making and management. However, real-world performance data in a standardised diagnostic setting are still limited [97].

Increasing evidence has recently been reported on the clinical relevance of liquid biopsy detecting circulating tumor cells, circulating tumor DNA, and circulating RNA in peripheral blood samples that may integrate signals from all metastatic foci and can be repeated serially during the course of treatment [98]. Liquid biopsy results might be useful as predictive biomarkers enabling the determination of baseline mutational status, with a high level of concordance with tissue mutational status, assessing the suitability for targeted therapies, monitoring of treatment response and resistance to targeted therapy. Translation of liquid biopsy into clinical use for melanoma patients might be expected in the near future.

## 7.2. Staging examinations according to AJCC stages

Staging depends on clinical examination, and in the case of primary melanoma, on histological characteristics. Physical examination of the entire body and accessible mucosal membranes should be performed looking for second melanoma (increased risk) [99] but mostly for tumor satellites and in-transit metastases. All lymph node areas should be carefully examined with particular attention to the regional lymph node basin.

Patients with pT1a melanomas with normal physical examination and no symptoms need no further imaging nor sentinel lymph node biopsy. Ultrasound of the loco-regional lymph nodes shall be done for patients in stage IB and higher. A recent Cochrane meta-analysis showed that its use in primary staging had a sensitivity of 60% and specificity of 97% [100]. The presence of lymph node metastasis can be confirmed for all clinically or radiologically suspicious lymph nodes using fine-needle aspiration cytology (FNAC) or Ultrasound-guided core needle biopsy [101–103]. Noteworthy, ultrasound shall not be considered as a substitute for sentinel lymph node biopsy.

In primary melanoma without clinically or radiologically positive lymph node, sentinel node biopsy is the most important prognostic factor in primary tumors with Breslow >1 mm (discussed below) [104–106].

Imaging aim to detect distant metastasis includes computed tomography with intravenous contrast of the thorax and abdomen or positron emission tomography scans (PET CT); brain metastasis is better detected using brain MRI with intravenous contrast than CT scan. Such workup is generally recommended in all stage III patients. However, its significance in stage III patients with micrometastasis only (N1 or 2a) remains debatable since distant metastasis is detected in less than 2% of these patients [107]. The positivity is higher in clinically palpable lymph node and ranges from 4 to 16% [108,109]. A recent Cochrane meta-analysis estimated the sensitivity and specificity of distant workup to 30%–47% and 73%–88%, respectively [100].

The rate of positivity is much lower in stage II patients. A recent review showed a sensitivity for PET CT ranging from 0 to 67% and specificity 77–100% and concluded that it is not beneficial [110]. Such workup can, however, be considered for the poor prognosis stage IIC.

Stage IV patients need careful total body imaging using CT or PET CT and brain MRI.

No routine blood test is recommended except for stage IV patients for whom plasma LDH should be assessed.

### Recommendation 7

Lymph node ultrasound in primary melanoma	Evidence based recommendation
<b>Level of recommendation A</b>	Ultrasound of the loco-regional lymph nodes shall be done for the initial workup in all primary melanomas pT1b and higher.
<b>Level of evidence: 2a</b>	<i>De novo</i> literature research [100] Consensus rate: 90%

## 8. Communication with the patient

When discussing a melanoma diagnosis with the patient, it is important to give tailored advice and prognostic information. Too often, the patient has already been on the internet and is extremely anxious because of frightening information they have discovered online. Many patients can be reassured that their prognosis is excellent and that the chance of recurrence is small. Clinicians should avoid saying that if the patient had come a few months later, he/she would be in a more difficult situation. Such statements are not evidence-based, as melanoma progression can be very slow, particularly for thin melanomas, and increased anxiety leads to patients viewing any other pigmented lesions as dangerous precursors. This may lead to the patient regularly asking for biopsies of healthy naevi. Ideally, all patients should be given as accurate a prognosis as possible unless they express the view that they would rather not be told. If possible, discussing melanoma diagnosis, especially of high-risk tumors or progression of the disease, should

take place with a relative as patients are often too anxious to remember many facts. Many melanoma clinics now have a clinical nurse specialist who can spend more time with patients after the delivery of bad news to help them digest this information and to answer any further questions they may have. The clinical nurse specialist also acts as a point of contact, and patients should be encouraged to contact them if they are anxious and need support. Specialised services may also be engaged if the patient has issues of loss of income while on treatment. Liaisons with community nurses and local services may need to be arranged, and clinicians should be familiar with the social circumstances of their patients. Relatives may also access counseling services in some countries.

A family history of melanoma and other cancers should be documented, and patients and their relatives may need to be referred to a cancer genetics clinic for an open discussion around genetic risk. The presence of the atypical mole syndrome phenotype also means that if the clinician looking after a patient is not a dermatologist, the patient may need alternate follow-ups between the dermatologist and the oncologist/plastic surgeon, if feasible. First-degree relatives of patients with melanoma should have regular dermatology screening, and this should be presented as an important screening opportunity.

Sun exposure following a melanoma diagnosis is a controversial area. While it is clear that patients should be safe in the sun and avoid sunburn and excessive sun exposure, too often melanoma patients are told they should avoid any future sun-exposure. This is not safe advice; it raises anxiety, is difficult to adhere to, and limits the quality of life.

## 9. Melanoma in pregnancy

Melanoma is the most common cancer encountered during pregnancy and represents 31% of all malignancies [111]. But while 29% of women may have a melanoma during their reproductive period, only 0.9% will have their melanoma diagnosed during pregnancy. Various epidemiological studies have looked at the effects of pregnancy on melanoma risk and conflicting results have been published. However, current evidence suggests that pregnancy does not affect melanoma risk, with over 5500 melanoma cases in females studied in a pooled analysis of 10 case–control studies [112,113]. Although anecdotal cases of aggressive melanomas during pregnancy have been reported in the past, O’Meara *et al.* and Lens *et al.* [114,115] showed that pregnancy did not affect melanoma survival in two large population-based studies in the United States and Sweden, respectively. Another large study in Norway with a median follow-up of over 10 years supported these findings as melanoma survival was comparable

between pregnant women and control women [111]. So, at present, there is enough evidence showing that pregnancy does not affect melanoma risk and does not affect melanoma survival.

When discussing future pregnancies in women after the diagnosis of melanoma with favorable prognosis, there is no need to defer the pregnancy. However, the clinician will need to take age and family circumstances into account and advise the patient accordingly. In high-risk melanomas, the advice is usually to wait two years after a melanoma diagnosis as the risk of relapse is the greatest during that period, but individual factors may affect this advice [113].

In terms of the contraceptive pill (OCP) and hormone replacement (HRT), there is also no evidence that they confer an increased risk of melanoma [113,116]. A recent Finnish study suggests that caution should apply for women on HRT with unopposed progesterone, but most women receiving HRT have combined continuous or interrupted opposition of the estrogen with progesterone [117]. Women having estrogen-only HRT may have had hysterectomy and oophorectomy for various reasons, which may be a confounding factor for melanoma risk.

Sentinel node biopsies are not contraindicated in pregnancy, but the blue dye should be avoided as it carries a small risk of an allergic reaction. Technetium is safe to use. Before the introduction of adjuvant treatments, it was thought that sentinel node biopsy should be avoided in pregnant women, as it simply completed staging and offered no therapeutic advantage. However, if the patient is toward the end of their pregnancy and possibly eligible for adjuvant treatment, sentinel node biopsy should be discussed with the patient. If a lymphadenectomy is needed for palpable lymph nodes, the best timing for surgery is the third trimester or postpartum. As such, depending on gestation at diagnosis of stage III disease, it is preferable to wait, as general anesthesia can be detrimental for a developing fetus [116]. Immunotherapy and targeted therapies are usually not considered safe for the fetus, and therefore, specific agents are used only in exceptionally rare circumstances. Women in the first or second trimester are usually advised to terminate their pregnancy, as are those whose life is imminently threatened by their disease as treatment should not be delayed. Pregnant women can still have MRIs instead of CT scans for surveillance of high-risk tumors. Women should be advised to ensure the use of adequate contraception when treated with immunotherapy or targeted therapy.

## 10. Follow-up

### 10.1. General principles

Follow up after melanoma diagnosis aims the following goals:

1. Identifying recurrent disease (local, distant) at the earliest stage;
2. Offering psychosocial support;
3. Providing education on prevention, for the patient and his first-degree relatives;
4. Providing education of the patient and his family on skin self-examination to promote the early detection of melanoma;
5. Administering and monitoring adjuvant therapy, where appropriate;
6. Improve early detection of subsequent secondary melanoma and non-melanoma skin cancers; [118,119].
7. Recognise and treat cutaneous side-effects related to adjuvant or palliative treatment [120–122].

No randomised trials are currently available comparing different follow-up schemes in melanoma patients, and different follow-up schemes have been proposed on an international level [123]. An example of follow-up schedule examinations in melanoma by stage is presented in Table 8.

**Frequency and extent of follow-up:** The frequency and extent of follow-up examinations depend on the primary tumor stage and presence of additional risk factors (i.e. multiple nevi, family, and personal history of melanoma, history of sunburns, etc.) [124,125]. The following examinations are recommended:

1. careful evaluation of reported symptoms;
2. physical examination of the scar and surrounding skin;
3. physical examination of the lymph nodes;
4. total skin clinical and dermatoscopic examination, including the genitals, oral mucosa, and scalp;
5. Blood testing for LDH and S-100 [126,127].

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 regular follow-up beyond 5 years. There is evidence that most local, satellite/in-transit, and regional nodal recurrences are detected by patients or physicians [128]. Ultrasound of the lymph-nodes appears the best method to detect sub-clinical nodal disease compared to palpation, CT scan, and PET CT [129,130]. The ultrasound-based follow-up did not increase the survival of melanoma patients in

stage IB-IIA [131]. However, performing an ultrasound for assessing lymph node metastasis in patients with AJCC T1b stage and above is advisable according to the most recent international guidelines. In patients with stage T4b, CT, or PET, CT is suitable for the detection of metastasis. Brain MRI at T4b deserves further discussion, considering the ultimate clinical benefit in terms of management and therapeutic options for asymptomatic patients [132].

In a single-center prospective study of 10 years in 290 consecutive melanoma patients, it was observed that intensive monitoring was appropriate for early detection of recurrence in stage IIB, IIC, and III melanoma. In contrast to previous studies, 17.8% of recurrences were detected by the patient, 23.7% by the physician, and 56.7% by imaging tests. This increase in the number of metastases detected by imaging tests can be explained by the more frequent use of CT and MRI, which have higher sensitivity and specificity than chest X-ray [133]. In the same cohort, six-monthly CT scan of the chest, abdomen, and pelvis was a cost-effective technique for the early detection of metastases in the first 4 years of follow-up in patients with AJCC stage IIC and III melanoma, and in the first 3 years in patients with AJCC stage IIB melanoma. In addition, brain MRI was shown to be cost-effective only in the first year of follow-up in patients with AJCC stage IIC and III melanoma [134].

For patients with high-risk melanoma (resected stage IV or stage III melanoma), the timing between follow-up visits and requested radiographic imaging examinations should be discussed by a multidisciplinary team and depends on whether patients receive therapy or not.

In non-resected stage IV melanoma or patients with suspected but not verified metastases, surveillance depends on the setting:

1. in an active treatment setting, imaging and surveillance aims to assess the treatment efficacy;
2. in the setting of suspected metastatic disease, surveillance aims to assess the evolution over time;
3. In patients with distant metastases, follow-up should be discussed case by case according to the willingness of the patient and the medical considerations of the treating physician.

Table 8

Example of follow-up schedule examinations in melanoma by stage.

Stage	Clinical-dermatological examination			Lymph node sonography		Laboratory examination: LDH, S-100		CT neck, thorax, abdominal, pelvic or PET-CT – MRI head	
	1 to 3	4 to 10	>10	1 to 3	4 to 10	1 to 3	4 to 10	1 to 3	4 to 10
IA	6 m	12 m	12 m	–	–	–	–	–	–
IB-IIB	3–6 m	6 m	12 m	6 m	–	–	–	–	–
IIC-IIIC	3 m	6 m	12 m	3–6 m	–	3–6 m	–	6 m	–
IIID	3 m	6 m	12 m	3–6 m	–	3–6 m	–	3–6 m	–
IV NED (resected, CR under therapy)	3 m	6 m	12 m	3–6 m	–	3–6 m	–	3 m	–
IV (M1a – M1d) (distant metastasis)	Individually, depends on examinations, therapy, and symptoms; otherwise staging every 12 weeks								

## Recommendation 8

Follow-up duration	Consensus-based recommendation
GCP	Stage-specific follow-up for detection of recurrence should be performed for at least 5 years. Follow-up for the detection of new primaries and other skin cancers should be performed at least 10 years. Consensus rate: 90%

## 10.2. 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 limited data to support the different schedules.

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 two to five years, whereas for the next years to 10th year period attendance every 6 months seems to be adequate. In patients with thin cutaneous melanoma ( $\leq 0.8$  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. A proposal for a structured stage-based follow-up schedule is given in [Table 8](#).

## Recommendation 9

Follow-up schedule	Consensus-based recommendation
GCP	Stage-specific follow-up examinations are recommended. A proposal is presented in <a href="#">Table 8</a> . More intensive follow-up examinations may be considered. Consensus rate: 100%

## 11. 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 specialties involved in the management of melanoma patients (dermatology, medical oncology, surgical oncology, radiotherapy, pathology, and others).

These guidelines were prepared 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 a first-round, medical experts who participated in their national guideline

development processes were involved. In a second round, the EORTC selected experts from different specialties to contribute to these guidelines. This process was first organised in 2008/2009, and the update was developed by the same groups in 2012 and 2016. The formal recommendations were discussed and agreed upon at the consensus conference on the 23rd of September 2019 in Rome by the Guideline Group, represented by 20 European experts. 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 two years.

## Conflict of interest statement

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