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Review

European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics: Update 2022

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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 for 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 with dermatoscopy. If a melanoma is suspected, a histopathological examination is always required. Sequential digital dermatoscopy and full body photography can be used in high-risk patients to improve the detection of early melanoma. Where available, confocal reflectance microscopy can also improve clinical diagnosis in special cases. Melanoma shall be classified according to the 8th version of the American Joint Committee on Cancer classification. Thin melanomas up to 0.8 mm tumor thickness do not require further imaging diagnostics. From stage IB onwards, examinations with lymph node sonography are recommended, but no further imaging examinations. From stage IIC onwards whole-body examinations with computed tomography (CT) or positron emission tomography CT (PET-CT) in combination with brain magnetic resonance imaging 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 define 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 optimal requirements, but further studies may be considered. This guideline is valid until the end of 2024.
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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). Paul Lorigan (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.

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 guideline. Special emphasis has been placed on imaging diagnostics and follow-up examinations. These European Guidelines are not intended to replace national guidelines that take into account the national specificities of health care systems. Rather, they are intended to support the development of national guidelines.

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 November 2021 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, for example, *melanoma [ti] AND (radiotherapy [ti] OR irradiation [ti] OR stereotactic [ti])*.

All diagnostic and treatment recommendations summarized 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 2020.

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 in part reimbursed 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 be also amelanotic. Even thin tumors can metastasize but over 85% of melanomas will not metastasize. Melanomas account for 90% of the deaths associated with cutaneous tumors. In this guideline, we concentrate on the treatment of cutaneous melanoma [2–9].

3. Epidemiology and etiology

The incidence of melanoma is increasing worldwide in white populations, especially where fair-skinned people have excessive sun exposure. 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 a very high incidence is observed, 50–60 per 100,000. In recent years, there has been a dramatic increase in incidence in individuals over the age of 60, especially, in men in parts of Europe but the incidence in many parts of Europe continues to increase for all age groups, and is predicted to continue to increase for decades [10]. The commonest phenotypic risk factor is skin that tends to burn in the sun, and inherited melanocortin-1 receptor (*MC1R*) variants are the most important underlying genotypic risk factors. 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 [11–14]. The inheritance of melanoma is in most cases caused by variants in common lower risk susceptibility genes, but 5%–10% of melanomas appear in melanoma-prone families who are likely to carry mutations in high penetrance susceptibility genes [15,16]. The most important exogenous factor is exposure to UV irradiation, particularly intermittent high sun exposure [17–19].

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 have been traditionally distinguished into four major clinicpathological subtypes: superficial spreading melanoma (SSM) (41%), 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) [20–24]. Of note, clinicpathological subtypes are not included as prognostic factors in the current 8th edition of the American Joint Committee on Cancer (AJCC) staging system for melanoma [25].

SSM begins with an intraepidermal horizontal or radial growth phase, appearing first as a macular lesion

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

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

[a] 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 a large or very large effect size.
[b] As always, a systematic review is generally better than an individual study.

that slowly evolves into a plaque, often with multiple colors and pale areas of regression. A characteristic histological feature of in situ melanoma is the presence of a dermo-epidermal horizontal component with pagetoid spread of malignant melanocytes throughout the epidermis. For invasive SSM and NM a vertical growth phase of the tumor is observed with malignant melanocytes into the dermis. However, NM is a primarily nodular, exophytic brown–black, or red–pink in amelanotic tumors, often eroded or bleeding tumor, which is characterized by a predominant aggressive vertical growth phase. When present, the epidermal lateral component is limited to up to three rete ridges at maximum. NM is associated with greater Breslow thickness, and its early clinical features not conforming to the well-established warning signs of ABCD, make early detection difficult especially if not pigmented [26–28].

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 body-areas of elderly individuals [29]. LMM is characterized histologically by a lentiginous proliferation of atypical melanocytes at the dermo-epidermal junction, confluence, formation of nests in the dermis, and a perifollicular localization of melanocytes.

ALM has typically a palmoplantar (volar) or subungual localization. In its initial intraepidermal phase (which may be protracted), there is irregular, poorly circumscribed pigmentation; later a vertical growth leads to a nodular component.

Desmoplastic melanoma 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 [30]. 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 decision about diagnostic staging and treatment [31].

Amelanotic/hypomelanotic melanoma is defined as a form of melanoma with no or little pigment on macroscopic or dermoscopic evaluation or as melanoma that lacks melanin in the cytoplasm of tumor cells on histological examination [32]. Amelanotic melanoma is more frequent in the nodular and desmoplastic histological subtypes, and more frequently localized on the ear, nose, and face [33].

In the updated WHO classification of skin tumors (4th edition, 2018), melanoma is classified based on the likely pathogenesis and the degree of its association with sun-exposure (Table 3) [24]. For melanomas arising on sun-exposed skin, further classification is based on the degree of cumulative sun damage (CSD) as assessed by the degree of solar elastosis on biopsy specimen. Low-CSD melanoma includes SSM and a subset of NM, and high-CSD melanoma includes LMM, desmoplastic melanoma and a subset of NM. Melanomas arising on non-sun exposed areas include spitzoid melanoma, acral melanoma, mucosal melanoma (genital, oral, sinonasal), melanoma arising in congenital naevus, melanoma arising in blue naevus, uveal melanoma, nodular as well as nodular and nevoid melanoma [24]. Distinct molecular signatures have been identified in tumors at different anatomical locations, which have different levels of UV exposure. Melanoma of "low-UV radiation exposure/CSD" is mainly located on the trunk and extremities and frequently carries a *BRAF* mutation, which is present in approximately 45% of cutaneous melanomas. Melanoma of "high-UV radiation exposure/CSD" is located mainly in the head and neck region and is more likely to have *NRAS* and other RAS

Table 2
Grades of recommendation

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

Table 3
Classification of melanomas including epidemiological, clinical, pathological, and common genetic features. Adapted from [24].

Type of UV radiation 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 UV radiation exposure (or variable/ incidental)	Spitzoid melanoma	*HRAS, ROS1, NTRK1, NTRK3, ALK, RET, MET, BRAF* *CDKN2A* *TERT*
	Acral melanoma Mucosal melanoma (genital, oral, sinonasal)	*NRAS, KIT, NF1, SPRED1, BRAF, CCND1, ALK, ROS1, RET, NTRK1* *CDKN2A, CDK4, TP53,* *SWI/SNF* *TERT*
	Uveal melanoma	*GNAQ, GNA11, CYSLTR2, PLCB4* *BAP1* *SF3B1, ElF1AX*
	Melanoma arising in congenital naevus	*NRAS*
	Melanoma arising in blue naevus	*GNAQ, GNA11, CYSLTR2* *BAP1, SF3B1, ElF1AX*

CSD = Cumulative sun damage; SSM: superficial spreading melanoma; LMM: lentigo maligna melanoma.

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 *C-KIT* mutations (Table 3) [29,34–36].

Pediatric melanoma is addressed separately. It is classified as prepubertal (congenital and childhood) melanoma occurring before the age of 10–12 years, or post-pubertal (adolescent) melanomas in patients of 10–19 years old. WHO classification of skin tumors describes four major histopathological subtypes of pediatric melanoma [24].

- De novo melanoma
- Melanoma arising in a congenital naevus
- Spitzoid tumors and spitzoid 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, and nodal or distant metastases. Metastatic melanomas of unknown primary occur in about 3% of the melanoma patients. Genetic investigations showed that these melanomas of unknown primary almost always arise from the skin [37]. Therefore, it is not useful to search for the primary tumor in mucosal membranes, eyes, or other organs.

5. Eighth AJCC melanoma classification and potential new biomarkers

About 90% of melanomas are diagnosed as primary tumors without any evidence of metastasis at the time of diagnosis. The tumor-specific 10-year-survival for such tumors is 75%–95%. The most important histological prognostic factors for primary melanoma are:

- Vertical tumor thickness (Breslow's depth) as measured on histological specimen with an optical micrometer scale, and defined as histologic depth of the tumor from the granular layer of the epidermis to the deepest point of invasion.
- Presence of histologically defined 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 [38].
- Mitotic rate (number of mitosis/mm^2) appears as an independent prognostic factor in several population studies [39] but it is no longer used for sub-classification of thin melanomas in the 8th revision of the AJCC staging system (see below) [25].
- Level of invasion (Clark's level) is no longer part of the AJCC staging system.

Apart from the factors above, prognosis is also poorer with increased age, in male patients and truncal/head and neck tumors compared to melanomas on the limbs [40,41]. Personalized risk prediction is possible using tools available online such as: https://www.melanomarisk.org.au/.

Melanomas can metastasize 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 [42,43]. In contrast to macrometastases, micrometastases are clinically recognizable neither by palpation, nor by imaging techniques.
- Clinically or radiologically recognizable regional lymph node metastases (macrometastases).

Distant metastases have a very poor prognosis in untreated patients, although there is considerable variation depending on progression of the tumor, which can be clinically defined by the number of organs involved, presence of brain metastases, and serum levels of lactate dehydrogenase (LDH) (see Tables 6 and 7).

In 2017, the AJCC issued the 8th TNM classification for staging of melanoma [25]. This new system forms the cornerstone for classifying melanomas and is summarized in Tables 4–7. This classification has been criticized, as the survival of equivalent stages differs significantly from the 7th to the 8th TNM classification, and may affect translation of results obtained in clinical trials from one version to the other. Moreover, survival curves published with the 8th TNM classification have been criticized. In two large European cohorts of AJCC version 7 versus the AJCC version 8 cohort, the melanoma-specific survival (MSS) rates at 5 years for stage III melanoma were 67% versus 77%, and at 10

Table 4
T classification of primary tumor for melanoma.

T category	Tumor thickness	Additional prognostic parameters
Tis		Melanoma in situ, no tumor invasion
Tx	No information	Tumor thickness cannot be determined[a]
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

[a] 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	
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+	
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+	
N3a	≥4 LN+, clinically occult	No
N3b	≥4 LN+, of which ≥ 1clinically detected	No
N3c	≥ 2 LN+, clinically detected or not	Yes

LN+ denotes lymph node with melanoma deposit.

years were 56% versus 69%, respectively. This is particularly true for stages IIIA and IIIB: for stage IIIA, the MSS rates at 5 years were 80% versus 93%, and at 10 years were 71% versus 88%; for stage IIIB, the MSS rates at 5 years were 75% versus 83%, and at 10 years were 61% versus 77% [44].

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

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

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

The clinical appearance of melanoma varies according to the melanoma subtype. Typical macroscopic features, as summarized in the ABCD rule, include asymmetry of the lesion, irregular borders, variability in colors and diameter

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	IIIC
T3b/T4a	Any N ≥ N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC

larger than 5 mm. Ulceration and a nodular component might develop with the evolution of the tumor. In terms of history of the lesion, melanoma is almost always growing and changing shape and/or colors. The sensitivity of clinical diagnosis by experienced dermatologists is difficult to assess but estimated to be around 70% [45]. Less frequently, melanoma might be hypo- or amelanotic, rendering its recognition particularly challenging. Nodular melanoma may lack the aforementioned diagnostic features. In this case the EFG rule, standing for Elevated Firm and Growing, is relevant for prompting excision of a potentially aggressive melanoma [46].

The clinical 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).

The clinical diagnosis of melanoma is based on: (1) total body visual skin examination for the detection of lesions displaying one or more of the aforementioned ABCDE criteria; (2) intra-individual comparative analysis, which is searching for the lesion that is not alike the others in the same patient (ugly duckling sign) [47]; (3) assessment of the evolution of lesions in case there is available documentation.

Recommendation 2:

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

Dermatoscopy should always be used in the clinical assessment of skin tumors. Training in dermatoscopy is mandatory since the technique becomes more beneficial with increasing experience. 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% [48].

Melanoma is dermatoscopically characterized by an asymmetry of structures and multiple colors. Characteristic dermatoscopic features of melanoma include atypical pigment network, irregular brown–black dots/globules/clods, irregular streaks (lines), irregular blotch/hyperpigmented areas, white shiny streaks/lines and regression structures. Additional criteria, for example, blue–white veil and polymorphic vessels are common in invasive melanoma [49–53].

Amelanotic melanoma lacks most of the aforementioned dermatoscopic criteria and is characterized by a polymorphic vascular pattern and white shiny streaks/lines [54–57].

Finally, a parallel ridge pattern and irregular diffuse pigmentation are the main dermatoscopic features of acral melanoma, although any of the aforementioned melanoma criteria might be present [58–62].

The prototypical dermatoscopic progression model for LMM on the face includes four sequential patterns, that are annular–granular pattern, asymmetrically pigmented follicular openings, rhomboidal structures [63,64], whilst the importance of additional features such as increased vascular network and red rhomboidal structures have been linked to the development of tumor-induced neo-vascularization [65].

Subungual melanoma manifests as a pigmented nail band, dermatoscopically characterized by irregular lines in terms of thickness and color and expansion of the pigmentation on the periungual skin (Hutchinson and micro-Hutchinson sign) [66].

Mucosal melanoma is dermatoscopically characterized by multiple colors, including various combinations of brown, black, blue, red, white, and gray [67].

Dermatoscopy should be applied on all lesions and not only on clinically suspicious ones. This is because dermatoscopy has the potential to uncover the morphologic asymmetry of melanoma before it becomes clinically recognizable and reveal clues that are strongly suggestive of melanoma.

Clinical and dermatoscopic photographic documentation of the primary tumor before excision is recommended.

In the scenario where dermatoscopy is not available, but the clinical suspicion is high, excision should not be delayed.

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.
Level of evidence: 1b	Guideline adaptation [68,69] De novo literature research for nail, acral, and mucosal melanomas [65–67,70–73] Consensus rate: 100%

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.
Level of evidence: 2b	De novo literature research [79–81] Consensus rate: 95%

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.
Level of evidence: 2b	De novo literature research [82–85] Consensus rate: 90%

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 was shown to increase 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]. Reflectance confocal microscopy 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. Here the evidence suggests that reflectance confocal microscopy may be both more sensitive and specific in comparison to dermatoscopy. This technology also allows the diagnosis of amelanotic melanoma and helps to better distinguish the limits of the tumor [88,90].

Recommendation 6:

Reflectance confocal microscopy	Evidence-based statement
Level of recommendation C	Reflectance confocal microscopy can be used for further evaluation of clinically/ dermatoscopically equivocal skin lesions.
Level of evidence: 2b	De novo literature research [86–89] Consensus rate: 100%

Electrical impedance spectroscopy has been certified as class-2A medical device for the assessment of melanocytic lesions. In a prospective clinical trial, the reported sensitivity and specify for melanoma diagnosis were 97.7% and 33.1%, respectively. This technique maybe useful as a complementary tool in clinical practice [91].

Artificial intelligence-based algorithms have been tested in multiple reader studies for the classification of skin tumors. In the experimental setting, they showed a remarkable accuracy for melanoma diagnosis, comparable to that of experienced dermatologists. However, although numerous Artificial intelligence-based apps are available, there is no evidence on their use in the clinical practice [92–94].

6.2. Histopathologic diagnosis

Whenever a suspicious skin lesion is surgically excised, histological examination is mandatory. Difficulties in the clinical diagnosis of melanoma can also be encountered on the histological level. The specimen should be entrusted to a dermatopathologist experienced in the interpretation of pigmented skin lesions. The histopathological report should include the following information [95].

1. Diagnosis and clinic-pathological subtype (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^2 (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
6. Lateral and deep excision margins

Besides these absolutely necessary histological 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
- Presence of lymphatic emboli
- Vascular or perineural involvement

In some instances, when the histological diagnosis is unclear, immunohistochemistry 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).

6.3. Molecular analysis

BRAF^{V600} mutational analysis is required for treatment decision in patients with distant metastasis or non-resectable regional metastasis, and, considering the approval of BRAF and MEK inhibitors in the adjuvant setting, in resected high-risk stage III melanoma patients. In the metastatic setting, *BRAF*^{V600} mutation testing should be performed in metastatic tissue, either distant or regional. If sampling of the metastatic tissue is

not feasible, the analysis can be performed on samples obtained from the primary tumor since a high concordance rate in the *BRAF* status exists between primary and metastatic melanoma lesions [96,97].

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. A 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 [98,99].

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 wild type, additionally analyzed for c-*KIT* mutations. Clinical benefit has been demonstrated for c-KIT inhibitors in selected patients [100].

The molecular classification of melanoma included a *NF1*-mutant melanoma subtype. However, *NF1* mutational analysis is not routinely performed since it currently lacks direct clinical implications [101,102].

Comprehensive screening of multiple genes in melanoma by next generation sequencing is still considered as a research tool rather than a technique to be used in everyday practice. However, limiting the analysis to currently actionable genes (i.e., *BRAF, NRAS*, and *KIT*) in one single experiment seems cost and time effective in the diagnostic setting. The importance of multi-gene analysis in melanoma is expected to increase in the future, as more pharmacologically actionable oncogenic mutations will be discovered, and additional targeted treatments become available [97,102].

Mutation rates vary considerably among different cancer entities, and likewise within a single cancer entity. Tumor mutational burden (TMB) is defined as the number of somatic mutations per megabase of genes studied. TMB has been successfully used to predict response to immune checkpoint inhibitors in patients with melanoma, lung cancer, and other solid cancers. The higher the TMB or mutation rate in a cancer cell, the more likely it is to be recognized as foreign by the immune system, thus improving the efficacy of immunotherapy [103]. In the Keynote-158 study, it was shown that treatment with pembrolizumab was successful in adult and pediatric patients with solid tumors with high TMB. TMB-high was set at TMB $\geq$ 10 mut/Mb for formalin-fixed paraffin embedded tumor tissue samples from patients tested using the Foundation Medicine Foundation One CDx assay [104]. The results of this study led to the approval of pembrolizumab using TMB-high as a positive predictive biomarker [105]. In cutaneous melanoma, a prospective biomarker study showed that response and overall survival of patients treated with a combination of ipilimumab and nivolumab were positively associated with a high-TMB value. High TMB was defined as $\geq$23.1 mut/Mb. All patients with high TMB achieved an objective response, whereas the response rate for patients with lower TMB was <25% [106]. Estimation of TMB varies between different gene panels, with panel size, gene content, and other factors contributing to variability. To promote reproducibility and comparability between assays, a statistical calibration software tool has been developed and made publicly available [107].

Gene expression profiling (GEP) testing is designed to improve patients' stratification by providing prognostic information on melanoma recurrence and metastatic risk and is based on expression patterns of a selected panel of genes in the primary tumor. Multiple GEP platforms are currently available for cutaneous melanoma (the 31-GEP panel Decision-Dx Melanoma™, Melagenix™, the clinical-pathological-GEP Merlin test) and increasingly used by healthcare professionals, despite current guidelines do not recommending their routine use [108]. Several studies suggest GEP testing will be able to improve staging and guide interventions such as sentinel lymph node biopsy, surveillance imaging intensity, and adjuvant therapy. However, while GEP tests have been successfully implemented in other malignancies, additional data are required in melanoma to address if they provide independent prognostic information in addition to known clinicopathologic factors before they can be integrated into clinical decision-making [109].

Liquid biopsies detecting circulating tumor cells, tumor DNA, mRNA, or extracellular vesicles in peripheral blood samples that may integrate signals from all metastatic foci and repeated serially during the course of treatment might be useful as predictive biomarkers [110]. They can confirm 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 is expected in the near future.

Recommendation 7:

BRAF status	Evidence-based statement
Level of recommendation B	BRAF status should be available in stage III/IV patients and can be proposed in stage IIB-C.
Level of evidence:	Consensus rate: 100%

6.4. Staging examinations according to AJCC stages

Staging depends on clinical examination and, in case of primary melanoma, on histological characteristics. Physical examination of the entire body and accessible mucosal membranes should be performed looking for tumor satellites and in-transit metastases and for second melanoma due to its increased risk [111]. All lymph node areas should be carefully examined with particular attention to the draining regional lymph node basin.

Patients with pT1a melanomas with negative physical examination and no symptoms need no further imaging nor SLNB. 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 35% and specificity of 94% [112]. The presence of lymph node metastasis can be confirmed for all clinically or radiologically suspicious lymph node using fine-needle aspiration cytology or ultrasound-guided core needle biopsy [113–115]. Noteworthy, ultra-sound shall not be considered as a substitute for sentinel lymph node biopsy. A positive node with ultrasound with fine-needle aspiration cytology can prevent futile SLNB surgery and allow patients to access neo-adjuvant trial participation.

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) [116–118].

Imaging aiming to detect distant metastasis includes computed tomography (CT) with intravenous contrast of the thorax and abdomen or positron emission tomography scans (PET CT); brain metastasis are better detected using brain magnetic resonance imaging (MRI) with intravenous contrast than with CT scan. Such work up is generally recommended in all stage III patients. However, its significance in stage III patients with micrometastasis only (N1a or N2a) remains debatable since distant metastasis are detected in less than 2% of these patients [119]. The positivity is higher in clinically palpable lymph node and ranges from 4% to 16% [120,121]. A recent Cochrane meta-analysis estimated the sensitivity of distant work up to 30%–47% and specificity to 73%–88% [112].

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 [122]. Such work up 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 serum LDH should be assessed.

Recommendation 8:

Lymph node ultrasound in primary melanoma	Evidence based recommendation
Level of recommendation B	Ultrasound of the loco-regional lymph nodes and in-transit area should be done for the initial workup in all primary melanomas pT1b and higher.
Level of evidence: 2a	De novo literature research [112] Consensus rate: 80%; 4 abstentions

7. 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 searching 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 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 act as a point of contact and patients should be encouraged to contact them if they are anxious and need support. Specialized services may also be engaged if the patient has issues of loss of income whilst 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 counselling services in some countries.

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/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. Whilst 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 a safe advice: it raises anxiety, is difficult to adhere to and limits quality of life.

8. Melanoma in pregnancy

Melanoma is the most common cancer encountered during pregnancy and represents 31% of all malignancies [123]. Whilst 29% of women may have a melanoma during their reproductive period, only 0.9% will have their melanoma diagnosed during a 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 [124,125]. Although anecdotal cases of aggressive melanoma during pregnancy have been reported in the past, O'Meara *et al.* and Lens *et al.* [126,127] showed that pregnancy did not affect melanoma survival in two large population-based studies in the United States of America 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 [123]. 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 a 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. However, the majority of recurrences will occur after a two-year period and therefore it is of great importance to discuss with the patient the risk and its change along the time [125].

In terms of the contraceptive pill and hormone replacement (HRT), there is also no evidence that they confer an increased risk of melanoma [125,128]. 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 [129]. 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 contra-indicated in pregnancy, but the blue dye should be avoided as it carries a small risk of allergic reaction. 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. In case a woman has an indication for adjuvant therapy, she should still be able to access it, even if the window of twelve weeks after SLNB has been exceded due to pregnancy. 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 post-partum. 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 [128]. Immunotherapy and targeted therapies are usually not considered safe for the fetus and therefore these agents are used only in exceptionally rare circumstances. Women in the first or second trimester who are eligible for immunotherapy are usually advised to terminate their pregnancy, as are those, whose life is imminently threatened by their disease as treatment should not be delayed. The effects of immunotherapy unlike chemotherapy seem to have increased toxicity in the third trimester because of the increase in immunoglobulins in the placenta towards the end of the pregnancy. Yet, women need to be presented with the risks of continuing a pregnancy if already on immunotherapy or is due to start soon. Women need to be aware that although reports of immune checkpoint inhibitor therapy are rare during pregnancy, immunotherapy can lead to miscarriages, stillbirth, premature delivery, pregnancy complications especially in the third trimester of pregnancy and possibility of autoimmune diseases in the fetus. These decisions will obviously depend on the stage of pregnancy and the wishes of the mother. If the woman has already been on immunotherapy for a while and becomes pregnant but with a good response to treatment, it is possible to discuss the interruption of immunotherapy as the response may be prolonged even after stopping treatment. Pregnant women can still have MRI 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.

9. Follow-up

9.1. 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 primary prevention, both for the patient and their first-degree relatives.
4. Providing education of the patient and their family on skin self-examination to promote 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 [130,131].
7. Recognize and treat cutaneous side effects related to systemic treatment [132–134].

No randomized trials are currently available comparing different follow-up schemes in melanoma patients and different follow-up schemes have been proposed on an international level [135]. An example of follow-up schedule examinations in melanoma by stage is presented in Table 8.

General practitioners in follow-up examinations: In many European countries, follow-up is mainly performed by dermatologists, but in some countries, dermatologists do not have the capacity to handle this workload due to their small numbers (Anglo-Saxon type of dermatology). In these countries, general practitioners have taken over a good part of the follow-up care and have undergone special training for this purpose. General practitioners with a focus on skin cancer care should also be trained in dermatoscopy. Close interdisciplinary collaboration with dermatologists is recommended.

Multiple primary melanomas are observed in 5%–8% of melanoma patients. Thus, melanoma patients have a significantly increased risk of developing a new primary melanoma. Patients with multiple primary melanomas have an older age and are more often male. Subsequent primary melanomas are diagnosed at a median of 3 years and are more often in situ and thinner than the initial tumors. The risk of subsequent melanoma decreased from 2% in the first year after diagnosis to a stable rate of approximately 1% during the 15-year follow-up period [136,137]. A German study analyzed a cohort of 2253 patients from the German Central Malignant Melanoma Registry with prospectively documented follow-up found that 146 patients (6.5%) developed multiple primary melanomas, of whom 39 had synchronous melanoma within the first 30 days after initial diagnosis and 107 developed multiple primary melanomas later. Thirty percent of these patients were diagnosed with in situ melanoma and 56% had tumor thickness $\leq$ 1 mm. In general, multiple primary melanomas did not affect the patient's overall prognosis due to early diagnosis [111].

Patient-managed surveillance: To improve early detection of multiple primary melanomas, patient-managed surveillance should be used as a complementary strategy for follow-up after treatment of primary melanoma. This requirement is based on the recognition that patients and their partners self-detect many subsequent new primary or recurrent melanomas prior to a routinely scheduled clinic visit. Skin self-examination is often recommended in clinical guidelines, but patients are usually inadequately informed about it. The patient-led model may include education in skin self-examination (face-to-face or via an Internet platform and/or smartphone application), capturing images of the lesions of interest (smartphone applications), and use of teledermatology. A recently published prospective study demonstrated that skin self-examination can be used effectively in patient care [138].

Frequency and extent of follow-up: The frequency and extent of follow-up examinations depend on primary tumor stage and presence of additional risk factors (i.e., multiple nevi, family and personal history of melanoma, history of sunburns etc.) [139,140]. 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 [141,142].

The first 5 years following excision of the primary 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/

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	
Year	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	–	3–6 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								

in-transit, and regional nodal recurrences are detected by patients or physicians [143]. Ultrasound of the lymph-nodes appears the best method to detect sub-clinical nodal disease compared to palpation, CT scan and PET CT [144,145]. Ultrasound-based follow-up did not increase the survival of melanoma patients in stage IB-IIA [146]. However, performing 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 are suitable for the detection of metastases. Brain MRI at T4b deserves further discussion, considering ultimate clinical benefit in terms of management and therapeutic options for asymptomatic patients [147].

In a 10 years single center prospective study of 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 re-currences 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 that is no longer recommended [148]. In the same cohort, six-monthly CT scan of the chest, abdomen and pelvis was a cost-effective technique for recurrence screening 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 [149].

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 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 treatment efficacy.
2. In the setting of a 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.

Recommendation 9:

Follow-up duration	Consensus-based recommendation
GCP	Stage specific follow-up for detection of recurrence and new primaries should be performed for at least 5 years.
	Consensus rate: 100%

Recommendation 10:

Follow-up duration	Consensus-based recommendation
GCP	Follow-up for detection of new primaries and other skin cancers should be performed for at least 10 years.
	Consensus rate: 85%

9.2. Recommendations for structured follow-up

The classical follow-up schedules are variable across Europe, ranging in frequency from 2 to 4 times per year for 5–10 years, with limited data to support 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 3–6 months for the first two to five years, whereas for the next years to 10th year period follow-up 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.

Proposed follow-up schedule may be adapted if additional risk factors such as high-nevus count, personal or family history of melanoma and non-melanoma skin cancer or cancer prone syndromes are present.

Recommendation 11:

Follow-up schedule	Consensus-based recommendation
GCP	Stage specific follow-up examinations are recommended. A proposal is presented in Table 8. More intensive follow-up examinations may be considered.
	Consensus rate: 100%

10. Consensus-building process and participants

The guidelines published here originate from contributors who were previously involved in the development of respective national guidelines. These national guidelines were written by different specialties involved melanoma management (dermatology, medical oncology, surgical oncology, radiotherapy, pathology, and others).

These European Guidelines are not intended to replace national guidelines that take into account the national specificities of health care systems. Rather, they are intended to support the development of national guidelines.

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 organized 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 26th of November 2021 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 three years.

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