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Guidelines

# European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics - Update 2024

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ABSTRACT

This guideline was developed in close collaboration with multidisciplinary experts from the European Association of Dermato-Oncology (EADO), the European Dermatology Forum (EDF) and the European Organization for Research and Treatment of Cancer (EORTC). Recommendations for the diagnosis and treatment of melanoma were developed on the basis of systematic literature research and consensus conferences. Cutaneous melanoma (CM) is the most dangerous form of skin tumor and accounts for 90 % of skin cancer mortality. The diagnosis of melanoma can be made clinically and must always be confirmed by dermoscopy. If melanoma is suspected, a histopathological examination is always required. Sequential digital dermoscopy and whole-body photography can be used in high-risk patients to improve the detection of early-stage melanoma. If available, confocal reflectance microscopy can also improve the clinical diagnosis in special cases. Melanoma is classified according to the 8th version of the American Joint Committee on Cancer classification. For thin melanomas up to a tumor thickness of 0.8 mm, no further diagnostic imaging is required. From stage IB, lymph node sonography is recommended, but no further imaging examinations. From stage IIB/C, whole-body examinations with computed tomography or positron emission tomography CT in combination with magnetic resonance imaging of the brain are recommended. From stage IIB/C and higher, a mutation test is recommended, especially for the BRAF V600 mutation. It is important to perform a structured follow-up to detect relapses and secondary primary melanomas as early as possible. A stage-based follow-up regimen is proposed, which in the experience of the guideline group covers the optimal requirements, although further studies may be considered. This guideline is valid until the end of 2026.

## 1. Introduction

### 1.1. Societies in charge

This guideline was developed on behalf of the European Association of Dermato-Oncology (EADO), the European Dermatology Forum (EDF) and the European Organization for Research and Treatment of Cancer (EORTC). Claus Garbe in collaboration with Teresa Amaral coordinated the authors' contributions as part of the EADO Guideline Program in Oncology (GPO). Mario Mandala in collaboration with Paul Lorigan (EORTC, senior authors) were responsible for the interdisciplinary quality of the guideline.

### 1.2. Disclaimer

Medicine is subject to a continuous development process. Therefore, all statements, including those on diagnostic and therapeutic procedures, can only reflect the state of scientific knowledge at the time this guideline went to press. The treating physician who refers to the recommendations of this guideline must consider scientific progress since the guideline was published.

### 1.3. Scope

This guideline has been written to assist the clinician in the diagnosis, follow-up and prevention of melanoma. Recent diagnostic strategies have been included in this guideline. Special emphasis has been placed on imaging diagnostic and follow-up examinations. These European Guidelines are not intended to replace national guidelines that consider 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, treatment, and prevention. 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 Nobember 2024 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 summarized in specific tables are evaluated based on 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. The authors paid their own travel expenses for participation in the consensus conferences. Accommodation costs 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. [2–9] In this guideline, we concentrate on the prevention, diagnosis, and follow-up of cutaneous melanoma.

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## 3. Epidemiology and etiology

The incidence of melanoma is increasing worldwide in white populations, especially where fair-skinned people have excessive sun exposure. The International Agency for Research on Cancer (IARC, Lyon, France) calculated 325,000 new cases of melanoma worldwide for 2020 (174,000 male, 151,000 female) and 57,000 deaths (32,000 male, 25,000 female). There are large geographical variations. Fair-skinned people have the highest incidences increasing in recent decades. Age-standardized rates (world standard) show the highest incidence rates in Australia/New Zealand with 42 cases per 100,000 persons/year for males and 31 cases per 100,000 persons/year for females. In Western Europe there were 19 cases for men and women and in North America 18 cases for men and 14 cases for women per 100,000 persons/year. Melanoma is rare in populations of color in African and Asian countries with incidence rates mostly less than 1 case/100,000 persons/year [10].

The increase in incidence rates is particularly visible in a long-term analysis. Melanoma in Denmark has been registered since 1943 and the increase in incidence rates from 1943 to 2016 (age-standardized for the European standard population in 2013) showed an increase of 1.1 to 46.5 in men and 1.0 to 48.5 in women. A further increase to 60.0 in men and 73.0 in women per 100,000 persons/year is predicted by 2036. In New Zealand, melanoma has been registered since 1948 and the increase from 1948 to 2016 is from 2.7 to 81.0 for men and from 3.8 to 54.7 for women. After that, a slight decrease is predicted. Similar increases are reported in the USA, where melanoma has been registered in the Surveillance, Epidemiology, and End Results (SEER) Program since 1975 [11]. This huge increase in incidence is due to a change in lifestyle after World War II with sunny holidays and increased sun exposure during leisure time. Approximately 95 % of melanomas are due to UV exposure [12]. There are no other known causal factors for the development of melanoma. A comparison between the incidence and mortality of melanoma is available in Fig. 1.

The most important risk factor for the development of cutaneous melanoma is the total number of benign melanocytic nevi on the entire integument. With high numbers, such as 100 nevi and more, the risk of developing melanoma increases by a factor of 8 to 10. The presence of larger, atypical melanocytic nevi is the second most important risk factor. With 5 or more such lesions, the relative risk increases approximately 6-fold [13]. The risks are multiplicative to each other. Many solar lentigines are associated with an approximately 3-fold increase in risk. Additional risk factors include skin type, actinic damage, a family history of melanoma and other phenotypic factors.[14,15] The individual risk of developing melanoma can be easily estimated, particularly based on pigmented moles, and can vary between a factor of 1 and a factor of up to 150, based on the number of nevi, the presence of atypical nevi and of actinic lentigines.

**Table 2**
Grades of recommendation.

| Grade of recommendation | Description | Syntax |
|---|---|---|
| A | Strong recommendation | shall |
| B | Recommendation | should |
| C | Recommendation pending | may/can |

## 4. Prevention

For several decades a causal relationship between ultraviolet (UV) radiation and melanoma has been established and further supported based on a large body of evidence from epidemiological, genetic and animal model studies [16]. The entire UV radiation spectrum has been classified as a group 1 carcinogen by the World Health Organization

**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 reviewof 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 reviewof 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 reviewof randomized trials or *n*-of−1 trials | Randomized trialor 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 reviewof 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 trialor (exceptionally) observational study with dramatic effect | Non-randomized controlled cohort/ follow-up study (post-marketing surveillance) provided there are enough 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 trialor (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 based on 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.

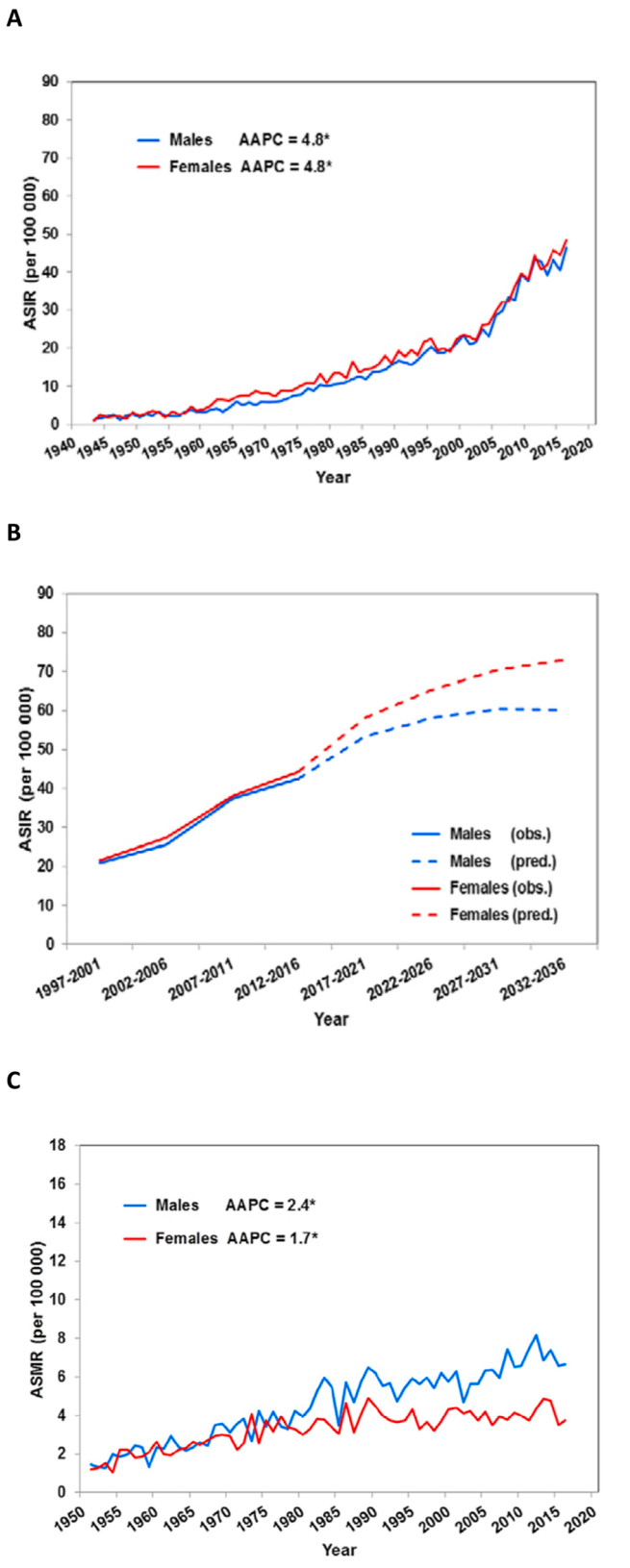


**Fig. 1.** Observed and predicted incidence rates and mortality rates in Denmark, age-standardized (EU-27 + EFTA Standard Population, 2013). Average annual percentage change of melanoma (AAPC) (A) incidence rates of melanoma in Denmark 1943 – 2016 and AAPC. (B) Incidence rates of melanoma in Denmark, projected until 2036. (C) Mortality rates of melanoma in Denmark 1951 – 2016 and AAPC.
(Adapted from [11].

[17]. Worldwide the percentage of melanomas attributed to UV is estimated at around 75 % but in Oceania, the US and most parts of Europe the population-attributable factor is higher mounting up to 96–97 % [11]. These data indicate that most melanomas are preventable.

Adequate UV protection implies avoiding intentional exposure to solar or artificial UV for sunbathing or tanning, using photoprotective measures outdoors for a UV index higher than 3, and staying indoors for a UV index of 8 and above. Photoprotective measures consist of the combination of seeking shade, physical protection through clothing, including a sun hat with wide brim and sunglasses, and applying sunscreens with broad spectrum UVA, UVB and blue light, and high SPF (30−50) for areas of skin that cannot be protected by clothes [18].

Sunscreens should not be used as replacement of protection with clothes, nor for intentional sunbathing. Studies have repeatedly found a reduced risk of sunburns, development of nevi in children and melanoma with protection by clothes as compared to sunscreens [19]. A community-based prospective randomized trial in Australia observed a lower number of melanomas after a 10-year follow-up in the sunscreen group that had used sunscreen on the head and arms during daily life [20].

Still, sunscreen use does not offer protection in conditions of intentional sun exposure. [19,21] In these conditions, the use of sunscreen may actually promote risk behavior by increasing sun exposure duration and intensity. [22] Sunbed use is associated with increased melanoma risk, especially when started before the age of 35, with a RR of 1.75 (IC95: 1.35–2.26) for melanoma. [23] Intentional UV exposure during sunbathing activities, tanning and sunbed use may therefore be considered unhealthy behavior.

These photoprotective measures apply to the public as well as to specific risk groups such as children, outdoors workers and persons with a history of or with a high risk for skin cancer. Babies under the age of 6 months should not be exposed to direct sunlight. Currently, there is not enough evidence to make recommendations for the photoprotection of skin of color.

Primary prevention of skin cancer has a positive return on investment. [24,25] Policymakers have a responsibility to communicate UV protection messages to the public and strictly regulate sunbed use at a national level. They should facilitate broad communication on daily UV index and the creation of outdoor shade facilities at public places such as schools and recreational areas.

## 5. 8th AJCC melanoma staging

In 2017, the American Joint Committee on Cancer (AJCC) issued the 8th TNM classification for the staging of cutaneous melanoma [26]. This AJCC v8 edition forms the cornerstone for staging cutaneous melanoma and is summarized in Tables 4–7.

About 90 % of melanomas are diagnosed as primary tumors without any evidence of metastasis at the time of diagnosis. The tumor-specific

**Table 3**
T classification of primary tumor for cutaneous melanoma.

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

[c] Tumor thickness or information on ulceration not available or unknown primary tumor

**Table 4**
N classification of the regional lymph nodes for cutaneous 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 N1b | 1 LN+ , clinically occult1 LN+ , clinically detected | NoNo |
| 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 | $\geq$ 4 LN+ , or any in-transit, satellite, and/or microsatellite metastasis with 2 −3 LN+ | |
| N3a | $\geq$ 4 LN+ , clinically occult | No |
| N3b | $\geq$ 4 LN+ , of which $\geq$ 1clinically detected | No |
| N3c | $\geq$ 2 LN+ , clinically detected or not | Yes |

LN+ denotes lymph node with melanoma deposit

**Table 5**
M classification of distant metastases for cutaneous 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 |

**Table 6**
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 $\geq$ N1 | M0 | IIIC |
| T4b | N1a-N2c | M0 | IIIC |
| T4b | N3a/b/c | M0 | IIID |
| Any T, Tis | Any N | M1 | IV |

**Table 7**
Classification of melanomas including epidemiological, clinical, pathological, and common genetic features.

| Type of UV radiation exposure/ CSD | Subtype of melanoma | Affected genes |
|---|---|---|
| Low-CSD melanoma | SSM | *BRAF V600E/K or NRASCDKN2ATP53SWI/SNFTERT* |
| High-CSD melanoma | LMM | *NF1, NRAS, BRAF, KITCDKN2ATP53SWI/SNFTERT* |
| | Desmoplastic melanoma | |
| Low to no UV radiation exposure (or variable/ incidental) | Spitzoid melanoma | *HRAS, ROS1, NTRK1, NTRK3, ALK, RET, MET, BRAFCDKN2ATERT* |
| | Acral melanoma | *NRAS, KIT, NF1, SPRED1, BRAF,* |
| | Mucosal melanoma (genital, oral, sinonasal) | *CCND1, ALK, ROS1, RET, NTRK1CDKN2A, CDK4, TP53, SWI/ SNFTERT* |
| | Uveal melanoma | *GNAQ, GNA11, CYSLTR2, PLCB4BAP1SF3B1, ElF1AX* |
| | Melanoma arising in congenital naevus | *NRAS* |
| | Melanoma arising in blue naevus | *GNAQ, GNA11, CYSLTR2BAP1, SF3B1, ElF1AX* |

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

10-year-survival rate for such tumors is 85–95 %. The most important histological prognostic factors for primary melanoma 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 top of the granular layer of the epidermis or, if the surface overlying the entire dermal component is ulcerated, from the base of the ulcer 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 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. [27]
- Mitotic rate (number of mitosis/mm$^2$) appears as an independent prognostic factor in several population studies [28] but it is no longer used for sub-classification of thin melanomas in the 8th revision of the AJCC staging system. [26]

Apart from the factors above, the prognosis is also poorer with increased age, in male patients and truncal/head and neck tumors compared to melanomas on the limbs. [29,30].

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. Locoregional 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. [31,32] In contrast to macrometastases, micrometastases are not clinically recognizable neither by palpation, nor by imaging techniques.
- Clinically or radiologically recognizable regional lymph node metastases (macrometastases).

The progression of the tumor can be defined by the number of organs involved, the presence of brain metastases, and serum levels of lactate dehydrogenase (LDH) (see Tables 6 and 7). The AJCC v8 edition has

been criticized, as the survival of equivalent stages differs significantly from the 7th to the 8th TNM classification and affects the translation of results obtained in clinical trials from one version to the other. Moreover, survival curves published with the 8th TNM classification have also been questioned. In 2 large European cohorts of AJCC v7 versus the AJCC v8 cohort, the melanoma-specific survival (MSS) rates at 5 years for stage III melanoma were quite different - 67 % versus 77 %, and at 10 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 % [33]. Similar findings has been published for stage I and II melanoma. The MSS rates at 10 years were 90 %−91 % versus 94 % in stage IB; 81 %−83 % versus 88 % in stage IIA; 72 %−80 % versus 82 % in stage IIB; and 56 %−65 % versus 75 % in stage IIC, respectively.

Personalized risk prediction is possible using nomogram tools available online such as: https://www.melanomarisk.org.au/.

The WHO melanoma subtypes may have prognostic and predictive features, although they are not included as prognostic factors in the AJCC v8 [26]. Pure desmoplastic cutaneous melanoma has a lower risk of lymph node metastasis and better MSS compared with superficial spreading melanoma (SSM) [34]. Acral lentiginous melanoma (ALM) has unfavorable survival compared to other subtypes [35]. Population-based and retrospective studies have shown that nodular melanoma (NM) was an independent predictor of sentinel lymph node metastasis in very thin melanomas and had an independent association with worse survival independently of stage and in thin tumors. [36–39].

Patients with pT1a melanomas with negative physical examination and no symptoms do not need further imaging nor sentinel lymph node biopsy (SLNB). Ultrasound of the loco-regional lymph nodes and in transit areas shall be done for patients with stage IB melanoma and higher. A recent Cochrane meta-analysis showed that its use in primary staging had a sensitivity of 35 % and specificity of 94 % [41]. The presence of lymph node metastasis can be confirmed for all clinically or radiologically suspicious lymph nodes using fine-needle aspiration cytology or ultrasound-guided core needle biopsy. [42–44] Noteworthy, ultra-sound shall not be considered as a substitute for SLNB. A positive node in ultrasound with fine-needle aspiration cytology can prevent futile SLNB surgery and allow patients to access neo-adjuvant trial participation or perioperative treatment. [45,46].

In primary melanoma without clinically or radiologically positive lymph node, SLNB is currently the most important prognostic factor in primary tumors with Breslow $>$ 1 mm (discussed below). [47–49].

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 metastases are better detected using brain magnetic resonance imaging (MRI) with intravenous contrast than with a CT scan. Such workup is generally recommended in all stage III patients but also in patients with stage IIB and IIC who are candidates for adjuvant treatment. Based on the recent analysis of more than 25000 patients from Denmark, the risk of relapse is similar between stages IIIB and IIC and between stages IIIA and IIB warranting distant metastasis surveillance in these patients. [50].

Specifically for PET-CT a recent publication from Denmark showed that the sensitivity, specificity, false positive and false negative rates in stage IIB, IIC and IIIA patients were 100 %, 94.7 %, 100 % and 74.4 %, respectively. The authors concluded that routine PET-CT has a high sensitivity and specificity when used in high-risk melanoma surveillance [51].

Patients with stage IV should undergo total body imaging using CT or PET CT and brain MRI.

No routine blood test is recommended, except serum LDH for patients with stage IV melanoma.

Recommendation 1.

| Stage classification | Consensus based recommendation |
|---|---|
| **GCP** | The classification into prognostic stages shall be performed according to the 8$^{th}$ edition of the AJCC staging system |
| | Consensus rate: 100% (19/19) |

## 6. 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 tumor satellites and in-transit metastases and for second melanoma due to its increased risk [40]. All lymph node areas should be carefully examined with particular attention to the draining regional lymph node basin.

Recommendation 2 [41].

| 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** | [41] |
| | Consensus rate: 90 %; (19/21) 2 abstentions |

## 7. Diagnostic approach

### 7.1. 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 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 is estimated to be around 70 % [52]. Less frequently, melanoma might be hypo- or amelanotic, rendering its recognition particularly challenging. Nodular melanoma (NM) may lack the previously mentioned diagnostic features. In this case, the EFG rule, standing for Elevated, Firm and Growing, is relevant for prompting the excision of a potentially aggressive melanoma [53].

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: a) total body visual examination of the skin for the detection of lesions displaying one or more of the aforementioned ABCDE criteria; b) Intra-individual comparative analysis, which is searching for the lesion that is not alike the others in the same patient (ugly duckling sign) [54]; c) Assessment of the evolution of lesions in case there is available documentation.

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 % [55].

Melanoma is dermatoscopically characterized by an asymmetry of structures and multiple colors – Figs. 2 and 3**.** 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 e.g., blue-white veil and polymorphic vessels are common in invasive melanoma. [56–60].

Amelanotic melanoma lacks most of the mentioned dermatoscopic criteria and is characterized by a polymorphic vascular pattern and white shiny streaks/lines. [61–64].

A parallel ridge pattern and irregular diffuse pigmentation are the main dermatoscopic features of acral melanoma (ALM), although any of the previous melanoma criteria might be present. [65–69].

The prototypical dermatoscopic progression model for lentigo maligna melanoma (LMM) on the face includes four sequential patterns, that are annular-granular pattern, asymmetrically pigmented follicular openings, rhomboidal structures, [70,71] 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. [72].

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) [73].

Mucosal melanoma is dermatoscopically characterized by multiple colors, including various combinations of brown, black, blue, red, white, and gray [74].

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.

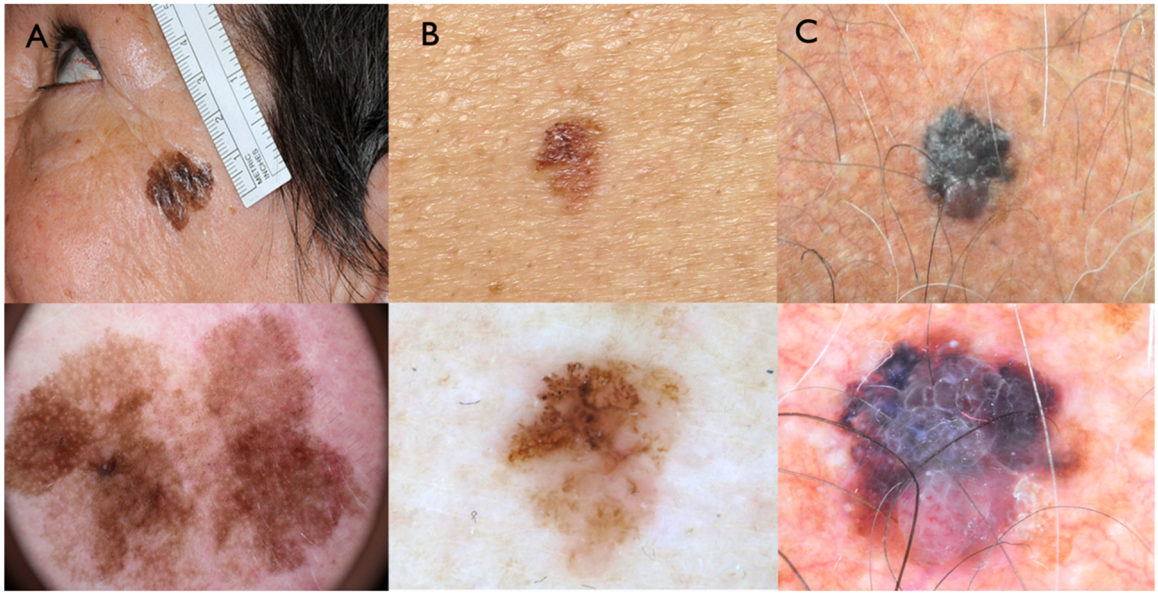


**Fig. 2.** Clinical and dermatoscopic images of different subtypes of melanoma. A) Lentigo maligna melanoma on the face appearing as a brown flat pigmented lesion. Dermoscopy exhibits a brown pseudo network with irregular pigmentation of the follicular openings; B) Superficial spreading melanoma on the dorsum of 5 mm in diameter and asymmetry of colors (brown and pink). The dermoscopic image shows asymmetry in colors and structures, multicomponent pattern and atypical globules and pigment network; C) Nodular melanoma on the upper anterior trunk with a nodular aspect and bluish and pink coloration and 5 mm in diameter. Dermatoscopy shows asymmetry in colors and structures, blue and pinkish coloration with globules and polymorphous vessels. White lines are also present.

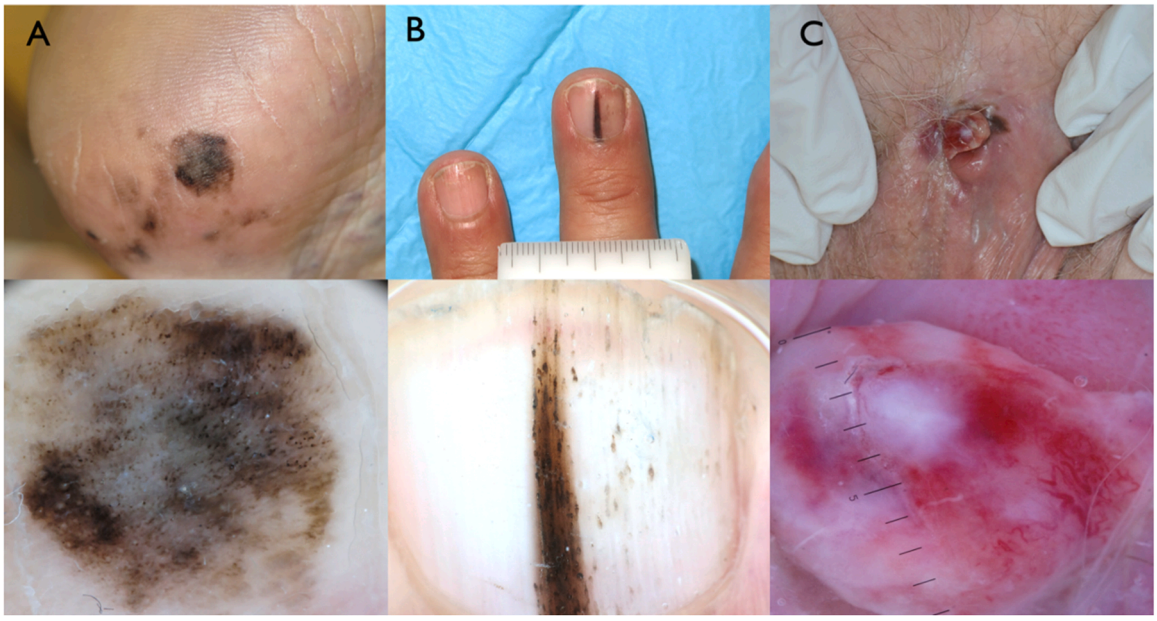


**Fig. 3.** Clinical and dermatoscopic images of different subtypes of melanoma. A) Acral lentiginous melanoma in situ of the sole. This early lesion exhibits asymmetrical and black, grey, and brown pigmentation. In the dermatoscopic examination a characteristic pattern ridge pattern is indicative of melanoma; B) Acral lentiginous melanoma of the nail. The clinical presentation consists of a dark brown melanonychia with a triangular shape. Dermatoscopy exhibits irregular bands of brown pigmentation with globules and dots. The extension of the lesion with globules beyond the melanonychia in the nail plate is visible in this image; C) Mucosal melanoma in the genitalia. In the dermatoscopic examination of the amelanotic nodule red, pink, and whitish color and multiple polymorphous atypical vessels are seen. At the periphery of the nodule a brown homogeneous area corresponds to a macular pigmented area in the clinical image.

Recommendation 3.

| Clinical diagnosis | Consensus based statement |
|---|---|
| GCP | If a melanoma is clinically suspected, it shall be confirmed by histopathology. |
| | Consensus rate: 100% (19/19) |

Recommendation 4 [72–80].

| 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 [75, 76]<br>De novo literature research for nail, acral and mucosal melanomas [72-74, 77-80] |
| | Consensus rate: 100% (19/19) |

Sequential 2D or 3D whole-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 whole-body photography [81]. 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 [82].

Recommendation 5 [81].

| 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** | [81] |
| | Consensus rate: 100% (19/19) |

Recommendation 6 [82].

| 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** | [82] |
| | Consensus rate: 100% (19/19) |

In addition to dermatoscopy, new non-invasive methods have been introduced in the clinical setting to increase the diagnostic accuracy of equivocal lesions. Reflectance confocal microscopy was shown to increase diagnostic specificity in equivocal dermatoscopic melanocytic lesions both in prospective studies, [83–85] and in two recent meta-analyses. [86] Reflectance confocal (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. Here the evidence suggests that reflectance confocal microscopy may be both more sensitive and specific in comparison to dermatoscopy. A recent randomized clinical trial that tested the hypothesis that RCM reduces unnecessary lesion excision, showed that, among the 3165 participants, RCM was associated with remarkable number needed to excise reduction of 43.4 % (5.3 vs 3.0), when compared with standard therapeutic care only. Of lesions referred to follow-up after RCM, 1.8 % with delayed melanoma diagnoses were thinner than 0.5 mm confirming a safety profile of the technology [87]. This technology also allows the diagnosis of amelanotic melanoma and helps to better distinguish the limits of the tumor. [85,88].

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 specificity for melanoma diagnosis were 97.7 % and 33.1 %, respectively [89]. This technique may be useful as a complementary tool in clinical practice.

Recently non-invasive tape stripping tests have been introduced for the non-invasive diagnosis of “clinically ambiguous lesions” and not “definitive melanomas”. In one study it was shown that dermatologists’ mean biopsy sensitivity and specificity improved from 95.0 % to 98.6 % ($p = 0.01$) and from 32.1 % to 56.9 % ($p < 0.001$), respectively, when tape stripping was incorporated into their decision on when or when not to biopsy [90]. A recent meta-analysis was made to examine the test’s accuracy of tape stripping, and the authors concluded that some of the studies show high sensitivity and specificity [91]. However, most of the studies included were conducted in the United States and additional studies are needed in Europe and Australia/New Zealand to assess regional differences. No randomized controlled trials have yet been

Recommendation 7 [83–87].

| Reflectance confocal microscopy | Evidence based statement |
|---|---|
| **Level of recommendation B** | Reflectance confocal microscopy should be used for further evaluation of clinically/dermatoscopically equivocal skin lesions, when available. |
| **Level of evidence: 1b** | De novo literature research [83-87] |
| | Consensus rate: 100% (23/23) |

made to find the difference between tape stripping and no tape stripping and how it affects the patient's prognosis.

Artificial intelligence (AI) aided diagnostic has been evaluated in melanoma with a high performance in reader studies [92]. AI can help in the detection of new lesions, identification of changes and providing risk scores in a melanocytic lesion. In a recent prospective study, it was shown that an AI-based algorithm increased the accuracy of melanoma diagnosis for dermatologists and these results conducted to its certification as a medical device in Europe [93]. In a recent multicenter, prospective, diagnostic, clinical trial, a mobile phone-powered AI technology was accurate for the diagnosis of suspicious pigmented skin cancer in patients presenting to a specialist setting [94]. However, an AI algorithm that was superior in experimental studies was significantly inferior to specialists in a real-world scenario, suggesting that caution is needed when extrapolating the results of experimental studies to clinical practice. Several artificial intelligence-based apps are available for consumers [95]. However, there is no evidence of their use in this population. [96,97].

### 7.2. Histopathologic diagnosis

Whenever a suspicious skin lesion is surgically excised, histological examination is mandatory. To be able to assess the architecture of the melanocytic lesion, the melanoma should always be completely excised if possible. Difficulties in the diagnosis of melanoma can also occur at the histopathological level. The specimen should be entrusted to a dermatopathologist experienced in the interpretation of pigmented skin lesions. The histopathological synoptic report should include the following information:[98–100].

1. Diagnosis and clinic-pathological subtype (SSM, NM, lentigo maligna melanoma (LMM), ALM, desmoplastic melanoma). When there is uncertainty about malignancy it should be clearly stated in the report conclusion.
2. Tumor thickness in mm (Breslow's depth).
3. Clark (anatomic) Level I-V.
4. Presence or absence of ulceration.
5. Presence or absence of established regression.
6. 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.
8. Mitoses per $mm^2$ (in hot spots), when available.

Immunohistochemistry is being increasingly used, especially when the diagnosis is not clear. [101,102] There is no certain marker for malignancy, but the melanocytic nature and architecture of the lesion can be better assessed. The following markers are preferred in the diagnosis of melanoma:

1. **S100 protein**: S100 is a calcium-binding protein found in melanocytes and is often strongly positive in melanoma cells.
2. **Melan-A (MART-1)**: Melan-A is a melanocyte-specific marker and is usually strongly positive in melanoma cells.
3. **HMB-45**: HMB-45 is another melanocyte-specific marker and is often positive in melanoma cells. It stains the cytoplasm of melanocytes and melanoma cells.
4. **Tyrosinase**: Tyrosinase is an enzyme involved in melanin synthesis and is expressed in melanocytes and melanoma cells. It is another useful marker for melanoma diagnosis.
5. **SOX10**: SOX10 is a transcription factor involved in the development of melanocytes and is expressed in melanoma cells.
6. **MITF** (Microphthalmia-associated transcription factor): MITF is a transcription factor involved in melanocyte differentiation and is often expressed in melanoma cells.
7. **Ki-67**: Ki-67 is a marker of cellular proliferation and can be used to assess the proliferative activity of melanoma cells

### 7.3. 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 clinic-pathological subtypes: SSM (41 %), NM (16 %), LMM (2.7 %−14 %) and ALM (1 %−5 % in non-Hispanic White population and higher rates in Asian or African American population). [103–107] Of note, clinic-pathological subtypes are not included as prognostic factors in the current 8th edition of the AJCC staging system for melanoma. [26].

SSM begins with an intraepidermal horizontal or radial growth phase, appearing first as a macular lesion 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. [38,108,109].

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 [110]. 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 [111]. 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 [112].

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 [113]. Amelanotic melanoma is more frequent in the nodular and desmoplastic histological subtypes, and more frequently localized on the ear, nose, and face [114].

In the 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 7) [107]. 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 melanomas include SSM and a subset of NM and high-CSD melanomas include LMM, desmoplastic melanoma and a subset of NM. Melanomas arising on non-sun exposed areas include Spitzoid melanoma, acral melanoma, mucosal melanoma (genital, oral, sino nasal), melanoma arising in congenital naevus, melanoma arising in blue naevus, uveal melanoma, nodular as well as nodular and nevoid melanoma [107]. 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 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 7). [110,115–117].

Paediatric melanoma is addressed separately. It is classified as prepubertal melanoma (congenital and childhood) 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 paediatric melanoma [107]:

- 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, in-transit metastases, nodal or distant metastases. Metastatic melanomas of unknown primary occur in about 3 % of patients with melanoma. Genetic investigations showed that these melanomas of unknown primary almost always arise from the skin [118]. Therefore, it is not useful to search for the primary tumor in mucosal membranes, eyes, or other organs.

## 8. Molecular analysis and other biomarkers

The multidimensional analysis from The Cancer Genome Atlas Network identified four different genomic subtypes of cutaneous melanoma: mutant BRAF, mutant NRAS, mutant NF1, and triple wild type (WT) [119].

Testing for *BRAFV600* mutations in stage III and IV melanoma is a core element as BRAF V600 mutational status is required for treatment decisions in stage III and IV melanoma patients, given the possibility of BRAF/MEK inhibitor combination therapy in the adjuvant and metastatic setting. [120,121]. Non-core elements agreed by experts that may be clinically important but not yet validated or regularly used in patient management include: 1) TILs, b) MHC-I and -II, c) tumor mutational burden, d) PD-L1 immunohistochemistry, e) IFN-γ gene signature, and f) melanoma WHO subtypes (other than desmoplastic) [34].

Hotspot mutations in V600 codon of *BRAF* and Q61 codon of *NRAS*, as well as loss of function mutation of *NF1*, lead to deregulation of the mitogen-activated protein kinase (MAPK) pathway, the driving tumorigenic signal in cutaneous melanoma. Triple WT melanoma can also harbor constitutional activation of the MAPK signaling, via deregulation of alternative pathways, such as *c-KIT* amplifications and mutations. [119,122,123].

Activating *BRAF V600* mutations are found in approximately 40–50 % of melanoma diagnoses, with *V600E* being the most common (80 %), followed by *V600K* (15 %) and *V600R/M/D/G* (5 %) [124]. *BRAFV600* mutations are associated with sensitivity to BRAF as well as MEK inhibitors. [125] Conversely, *BRAF* mutations in exons 11 and 15 may not display sensitivity to either BRAF or MEK inhibition. [126].

Molecular testing shall be performed on metastatic tissue, either distant or regional metastasis. If sampling of the metastatic tumor is not feasible, the mutational analysis can be performed on the primary tumor sample since high concordance rate exists between the primary and the metastatic tissue. [127,128] Broader next-generation-sequencing (NGS) panels should be preferred over *BRAFV600* single gene testing, as the molecular results might guide future treatment strategies and patient enrollment in clinical trials.

Activating *NRAS* mutations are found in 15–20 % of melanoma patients, and they most commonly occur at hotspots Q61 (90 %) and G12 (5 %) [128]. The randomized open-label phase III clinical trial investigating binimetinib versus dacarbazine in advanced *NRAS* mutant melanoma patients (NEMO trial), showed that MEK inhibitors have limited efficacy in *NRAS* mutant melanoma patients. [129] Novel targeted agents blocking upstream or downstream effectors of RAS proteins (pan RAF, ERK, FAK inhibitors), as well as combinatorial regimens are currently under investigation in the patients with NRAS mutant melanoma. [130].

*C-KIT* mutations are found in 1–3 % of chronically sun-damaged cutaneous melanoma, and up to 10–15 % of acral and mucosal melanoma [131]. C-KIT mutations may occur at several hotspots across the gene, and they have shown different sensitivity to KIT inhibitors: c-KIT exon 11 and 13 mutations have the greatest sensitivity to KIT inhibitors; conversely, c-KIT exon 17 mutations display minimal or no sensitivity to KIT inhibitors. Also, *c-KIT* amplifications appear to have minimal or no sensitivity to KIT inhibitors. [132,133] There are no approved KIT inhibitor therapies for c-KIT mutant melanoma. Imatinib and nilotinib have shown limited clinical benefit in selected clinical trials. Broad spectrum KIT/multikinase inhibitors are currently being investigated in c-KIT mutant metastatic melanoma. [132–135].

As mentioned before, the molecular classification of melanoma includes a *NF1*-mutant melanoma subtype. However, NF1 mutational analysis is not routinely performed since it currently lacks direct clinical implications [136].

The use of broad NGS panels may uncover other uncommon genetic drivers of melanoma: fusions in *NTRK1*, *NTRK2*, *NTRK3* genes are rare (<1 %) in melanoma. These are more common (25 %) in spitzoid melanoma [137]. Larotrectinib and entrectinib have been approved by the U.S. Food and Drug Administration for NTRK gene fusion-positive unresectable and/or metastatic solid tumors which have progressed to standard therapies and/or for which there are no other treatment options.[138,139].

Tumor mutational burden (TMB) is defined as the number of non-synonymous 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 [140]. The Keynote-158 study showed 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 [141]. The results of this study led to the approval of pembrolizumab using TMB-high as a positive predictive biomarker [142]. In cutaneous melanoma, a prospective biomarker study showed that response and overall survival (OS) of patients treated with a combination of ipilimumab and nivolumab were positively associated with a high TMB value (≥23.1 mut/Mb) [143]. Estimation of TMB varies between different gene panels, with panel size and gene content. Whole-exome sequencing (WES) is the only approach to definitively assess somatic tumor TMB. Nevertheless, targeted NGS was shown to correlate with the WES results and immune checkpoint inhibitors response. To promote reproducibility and comparability between assays, a statistical calibration software tool has been developed and made publicly available [144].

Programmed death ligand 1 (PD-L1) is a co-inhibitory molecule which is expressed on T and B cells, macrophages, and dendritic cells, as well as tumor cells upon interferon-gamma stimulation [145]. Conflicting data exists on whether melanoma expressing PD-L1 is more likely to respond to immune checkpoint inhibitors, suggesting that PD-L1 expression alone is a poor predictive biomarker of efficacy outcomes. [146,147] The 3- and 5-year follow-up analysis of the CheckMate 067 trial consistently reported superiority of the combinatorial regimen (nivolumab plus ipilimumab) and nivolumab monotherapy versus ipilimumab alone, regardless of PD-L1 status patient stratification.[148,149] Recently, the combination nivolumab plus relatlimab was approved by EMA as a first-line treatment for advanced melanoma

(unresectable or metastatic) in patients with tumor cell PD-L1 expression < 1 % [150]. As a result, PD-L1 testing is a companion diagnostic for this treatment in the EU.

The use of several antibody clones for immunohistochemical (IHC) detection of PD-L1, the different thresholds to define meaningfully elevated PD-L1 expression, and the subcellular PD-L1 localization (membranous versus cytoplasmatic) add further complexity to the interpretation of PD-L1 results and hinder the utility of this biomarker for clinical decision-making [147].

A recent prospective multicenter translational study (ADOREG/TRIM; CA209–578) investigated the correlation between PD-L1 expression and outcomes to immunotherapy outcomes in patients with melanoma [151]. Placke et al. demonstrated a stronger correlation with immunotherapy efficacy outcomes for lymph-node metastases expressing PD-L1 than for primary tumors or distant organ metastases expressing PD-L1. Another population-based study showed no benefit with combo IO vs anti PD-1 alone in advanced melanoma patients with PD-L1 > 1 % [152].

Gene expression profile (GEP) platforms involve testing the expression patterns of a selected panel of genes in the primary tumor. The aim is to improve patients' stratification by providing information on risk of recurrence [151]. Several assays are being evaluated. An 11- GEP assay was shown to independently predict prognosis and risk for melanoma-specific survival in patients with stage I-III melanoma [153]. Another GEP incorporating information on the expression of 8 genes combined with two clinicopathological variables age and Breslow thickness, was able to identify subgroups of patients with stage I/II melanoma with distinct risk profiles [154]. In addition, a 31-GEP immune assay is commercially available in the USA [155]. Finally, an immunohistochemistry-based, 7-biomarker signature prognosticated survival in patients with stage I-IIA melanoma [156]. These results may support the use of GEP for predicting risk of recurrence, as well as the probability of SLN positivity. However, validation studies on prospectively collected melanoma patient cohorts are needed to establish the prognostic role of GEP in guiding clinical decision-making. [157–160].

Liquid biopsy encompasses testing patients' peripheral blood for the detection of circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), tumor-derived extracellular vesicles (EV), and circulating free microRNA (miRNA) [161]. The advantage of liquid biopsy over tissue biomarkers is to allow for real-time, repetitive, minimally invasive and longitudinal monitoring of tumor burden and heterogeneity. Liquid biopsy offers several applications in the cancer patient population: a) early tumor diagnosis; b) assessment of minimal residual disease (MDR); c) longitudinal disease monitoring along anticancer treatments; d) uncovering tumor heterogeneity and early treatment resistance [162].

CtDNA is the most widely studied among liquid biopsy biomarkers. In the translational analysis of the CheckMate 915 study, Long et al. demonstrated that pre-treatment ctDNA levels were significantly associated with increased risk of recurrence (HR: 1.87, 95 % confidence interval [CI]: 1.48–2.36) in surgically resected stage IIIB-D/IV melanoma patients, regardless of the treatment arm (ipilimumab plus nivolumab versus nivolumab alone) [163]. Also, a recent meta-analysis of 19 studies confirmed that baseline detection of ctDNA was significantly associated with the risk of disease progression in metastatic melanoma patients (HR: 2.10, 95 % CI: 1.71–2.59) [164].

There are increasing efforts to incorporate ctDNA analysis in prospective clinical trial designs to refine treatment strategies. The CaCTUS trial (NCT03808441) is investigating the role of ctDNA in guiding a switch between targeted therapy and immunotherapy in patients with advanced *BRAF*-mutated melanoma [165]. Also, the DETECTION phase II/III clinical trial (NCT04901988) is exploring the role of ctDNA longitudinal monitoring in fully resected stage IIB/IIC melanoma patients for early detection of molecular relapse followed by either standard follow-up or nivolumab treatment.

Recommendation 8.

| 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. |
| | Consensus rate: 100% (22/22) |

## 9. Familial melanoma

An estimated 5–12 % of melanomas are diagnosed in a familial setting. Familial melanoma is defined as a family in which either 2 first-degree relatives or 3 or more melanoma patients on the same side of the family (regardless of degree of relationship) have been diagnosed with melanoma. The pattern of heritability is consistent with autosomal dominant inheritance with incomplete penetrance.

Germline susceptibility has been associated with high and intermediate penetrance alleles in known melanoma predisposition genes such as *CDKN2A, CDK4, POT1, BAP1, ACD, TERT, TERF2IP, MC1R* and *MITF*. [166–169] *CDKN2A* is the major high penetrance susceptibility gene with germline mutations identified in 10–40 % of melanoma families, depending on the stringency of selection criteria and geographic origin of the families. *CDKN2A* mutation penetrance varies between geographic areas, according to the incidence rate of melanoma in the population. A positive *CDKN2A* mutation status has been associated with a high number of affected family members, multiple primary melanomas, pancreatic cancer and other smoking-related cancers, and earlier age of melanoma onset. Pathogenic variants in the other established high-risk genes are rare, and less characterized. *CDK4* variants occur in exon 2 and have been associated with early diagnosis. Variants in telomere-linked genes (*TERT, POT1, ACD, TERF2IP*) are reported in families with a high density of additional tumors. Families carrying germline *BAP1* mutations have an increased risk of uveal melanoma, mesothelioma, renal cell carcinoma and atypical intradermal melanocytic tumors. Other recently identified susceptibility genes, such as *GOLM1, EBF3, POLE* and *NEK11*, need additional validation.

The inheritance of melanoma is unexplained for half of suspected hereditary melanoma cases and has been related to multiple low-to-intermediate risk alleles and/or shared environmental exposure [166]. The major known low-to-intermediate risk genes are involved in melanogenesis (*MC1R, MITF, OCA2, SLC45A2, TYR, TYRP1*), DNA synthesis, immunity pathways, cell-cell junction and transcriptional regulation (*ATM, HLA* locus, *CDH1, FOXD3, SOX10*). Variants in *MC1R* are the most common and established genetic trait that predisposes to cutaneous melanoma. Carriers of *MC1R RHC* (red hair color) alleles are more vulnerable to UV damage, and subsequent melanoma risk. Coinheritance of *MC1R RHC* variants and *CDKN2A* pathogenic variants is associated with higher risk and younger age of onset of melanoma.

Genetic testing for melanoma susceptibility genes is recommended in

families with melanoma after selection of the appropriate candidate and adequate counseling of the patient. Eligibility for genetic testing depends on geographic melanoma incidence rate, and the recommended genetic assessment criteria are more stringent in very high-incidence countries as Australia than in moderate-incidence areas such as Northern Europe and North America and in low-incidence countries as Southern Europe. [170–172] Genetic testing for the *CDKN2A* gene has been available for more than two decades. However, the use of multi-gene panels for hereditary melanoma testing has been increasingly implemented in clinical practice, increasing the likelihood of identifying pathogenetic variants. [173] Multi-gene testing is especially relevant in the presence of a family history of other cancers, as some melanoma predisposition genes can be related to a hereditary multi-tumor cancer syndrome, facilitating a personalized testing approach. [171].

Individuals from families with melanoma should receive genetic counselling to be informed about the inclusion criteria for genetic testing, the likelihood of an inconclusive result, the genetic risk for melanoma and other cancers and the questionable role of medical management. All patients and relatives from melanoma kindreds, regardless of mutation status, should be informed about the risks associated with UV exposure, skin self-examination and surveillance by physicians.

## 10. Melanoma in pregnancy

Melanoma is the most common cancer encountered during pregnancy and represents 31 % of all malignancies [174]. Whilst 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. [175,176] Although anecdotal cases of aggressive melanomas during pregnancy have been reported in the past, O'Meara et al and Lens et al [177,178] 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. [174] So, at present, the evidence shows that pregnancy does not affect the risk of melanoma recurrence and does not affect MSS. Therefore, when discussing future pregnancies in women after the diagnosis of a melanoma with favorable prognosis, there is no evidence that future pregnancies should be delayed because of increased risk of recurrence in pregnant women. However, in high-risk melanomas, the patient needs to consider what the risk of recurrence is and what would happen if they did become pregnant. Given the highest risk of recurrence is in the first 2–3 years and considering that many patients will receive adjuvant therapy, a consideration is often to wait two years after a melanoma diagnosis as the risk of relapse is the greatest during that period. However individual factors may affect this decision. Furthermore, depending on the stage of the disease and the treatment given, there is still a real risk of recurrence after 2 years, and this too needs to be considered. [176,179].

There is no evidence that the oral contraceptive pill or hormone replacement (HRT), there is also no evidence that they confer an increased risk of melanoma. [176,180] 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 a progesterone. [181] 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 biopsy is not contra-indicated in pregnancy, but the blue dye should be avoided as it carries a small risk of allergic reaction. SLN should be avoided in the 1st trimester due to the theoretical teratogenic effect of the radioactivity. When performed, it is best practice to have a urinary catheter in situ to no have radioactivity accumulate near the fetus. In the third trimester, SLN should be performed with neonatal care available on site. SLN biopsy remains one of the most accurate staging systems. In most countries however, it is not required to access adjuvant therapy for resected Stage IIb and IIc melanoma, though it still gives more accurate data on the potential absolute benefit.

If a lymphadenectomy is needed for palpable lymph nodes, the best timing for surgery is the third trimester or post-partum, as general anesthesia can be detrimental for a developing fetus [180]. However, decisions around the timing for surgery are complex, and need to be individualized and made in discussion with the patient.

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. Immunotherapies seem to have increased toxicity in the third trimester because of the increase in immunoglobulins in the placenta towards the end of the pregnancy. The use of systemic therapy is associated with potential toxicity and the risks and benefits need to be considered carefully, taking in to account the mothers' wishes.

Pregnant women can 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.

## 11. Follow-up

### 11.1. General principles

Follow-up after melanoma diagnosis has the following aims:

1. Identifying recurrent disease (local, distant) at the earliest stage.
2. Improve early detection of subsequent secondary melanoma and non-melanoma skin cancers; [182,183]
3. Providing education on primary prevention, both for the patient and their first-degree relatives.
4. Recognize and treat side effects related to systemic treatment, when appropriate. [184–186]
5. Offering psychosocial support.
6. Providing education of the patient and their family on skin self-examination to promote early detection of melanoma.

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 [187]. 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 cannot handle this workload due to their small numbers. In these countries, general practitioners have taken over a good part of the follow-up care and have undergone special training for this purpose [188]. General practitioners with a focus on skin cancer care should also be trained in dermatoscopy. Close interdisciplinary collaboration with dermatologists is highly 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

**Table 8**
Example of follow-up schedule examinations in melanoma by stage.

| Stage | Clinical-dermatological examination | | | Lymph node sonography | | 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-IIA | 3 –6 m | 6 m | 12 m | 6 m | - | 6 m | - | | - |
| IIB-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) | Individual follow-up. Otherwise staging every 8 –12 weeks is recommended[d] | | | | | | | | |

[d] Standard of Care for Clinical Studies

melanoma decreased from 2 % in the first year after diagnosis to a stable rate of approximately 1 % during the 15-year follow-up period. [189,190] One study found that 6.5 % of patients 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 were diagnosed with in situ melanoma and 56 % had tumor thickness $\leq$ 1 mm. Multiple primary melanomas did not affect the patient's overall prognosis [40].

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 before 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 the use of teledermatology. A recently published prospective study demonstrated that skin self-examination can be used effectively in patient care [191].

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.). [13,192] 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. [193,194]

The first 5 years following the excision of the primary are most important, as 90 % of all metastases occur during this time. Metastasis do however occur after 5 years of melanoma diagnosis and indicates the relevance of a regular follow-up, and the need to guarantee rapid and easy access to a reference center after the initial 5-year period. There is evidence that most local, satellite/in-transit, and regional nodal recurrences are detected by patients or physicians [195]. Ultrasound of the lymph-nodes appears the best method to detect sub-clinical nodal disease compared to palpation, CT scan and PET CT. [196,197] Ultrasound-based follow-up did not increase the survival of melanoma patients in stage IB-IIA. [198] 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. For T3b/T4a an individualized discussion about performing regular CT or PET-CT should be recommended. Patients with stage IIB melanoma have metastasis detection rates similar to stage IIC and imaging monitoring detected metastases continuously throughout the first 3 years of follow-up. [199] If patients undergo adjuvant ICI therapy, which is now approved after stage IIB melanoma diagnosis (T3b/T4a) these imaging techniques are necessary to monitor the further course of the disease. [147] In patients with stage T4b, CT or PET CT are suitable for the detection of metastases. Brain MRI at T4b deserves further discussion, considering the ultimate clinical benefit in terms of management and therapeutic options for asymptomatic patients. [200].

In a 10-year 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 recurrences 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 [199]. 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 [201].

For patients with high-risk melanoma (stage III or resected stage IV 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.

Recommendation 9.

| Follow-up duration | Consensus based recommendation |
|---|---|
| **GCP** | Stage specific follow-up for detection of recurrence should be performed for at least 5 years. The screening to detect new primaries and other skin cancers should be performed for at least 10 years. |
| | Consensus rate: 95% (20/21) 1 abstains |

### 11.2. 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 to 10 years, with limited data to support different schedules.

Patients with melanoma in situ in the absence of additional risk factors (e.g. no nevi, no family history) should be instructed to perform self-detection of local recurrence. In particular, patients should be advised to seek consultation in case of newly developing re-pigmentation at the border of the scar.

In stage I to IIA 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. In contrast, 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. 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. For all melanoma patients a rapid and fast access to the referral center should be guaranteed in case of any changes in the overall situation since the last follow-up visit (i.e., newly developing subcutaneous nodule(s), pigmentation changes, new palpable nodes or other symptoms not clearly correlated to a definable disease.

Recommendation 10.

| 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% (21/21) |

## 12. Communication with the patient

When discussing a melanoma diagnosis, 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 nurse specialist who can spend more time with patients to help them with 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 for 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.

## 13. 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 in melanoma management (dermatology, medical oncology, surgical oncology, radiotherapy, pathology, and others).

These European Guidelines are not intended to replace national guidelines that consider 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 Association of Dermato-Oncology (EADO), the European Dermatology Forum (EDF), 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, 2016 and 2022. The formal recommendations were discussed and agreed upon at the consensus conferences on the 3rd of November 2023 and on 8th November 2024 in Rome by the Guideline Group represented by 20 + European experts. Professor Claus Garbe and Dr Teresa Amaral, MD, PhD, 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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The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Amaral reports personal fees for advisory board membership from Delcath and Philogen; personal fees as an invited speaker from BMS, Neracare, Novartis and Pierre Fabre; personal fees for a writing engagement from CeCaVa and Medtrix; institutional fees as local principal investigator (PI) from Agenus Inc., AstraZeneca, BioNTech, BMS, HUYA Bioscience, Immunocore, IO Biotech, MSD, Pfizer, Philogen, Regeneron, Roche and University Hospital Essen; institutional fees as coordinating PI from Unicancer; institutional research grants from iFIT and Novartis; institutional funding from MNI - Naturwissenschaftliches und Medizinisches Institut, Neracare, Novartis, Pascoe, Sanofi and Skyline-Dx; non-remunerated membership of the American Society of Clinical Oncology (ASCO) and the Portuguese Society for Medical Oncology; and a role as clinical expert in the area of medical oncology for Infarmed. Dr. Arenberger reports personal fees from BMS, personal fees from MSD, personal fees from Novartis, personal fees from Sanofi, outside the submitted work. Dr Basset-Seguin has nothing to disclose. Dr. Bastholt reports personal fees for advisory boards from Bristol Myers-Squibb, Pierre Fabre, Merck MSD, Novartis and Roche, outside the submitted work. Dr. Bataille has nothing to disclose. Dr. Brochez has nothing to disclose.

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