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Guidelines

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S3-Guideline "Diagnosis, therapy and follow-up of melanoma" – short version

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1. Information on this short version

1.1. Publisher

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1.2. Financing of the guideline

This guideline was supported by the German Cancer Aid within the context of the German Guideline Program in Oncology (GGPO).

1.3. Medical society in overall charge

German Society of Dermatology (DDG)

2. Introduction

2.1. Target patient group

The aim of the S3-guideline melanoma contains recommendations on diagnosis, therapy and follow-up of cutaneous melanoma in its primary, limited locoregional and metastatic stages. Mucosal and uveal melanomas are not considered. Questions on early recognition have been considered in the S3-guideline on prevention of skin cancer.

2.2. Objectives and formulation of questions

The aim of the S3-guideline melanoma is to provide physicians in office and clinical practice in the field of oncology an accepted, evidence-based decision-making aid for the selection and performance of suitable measures for diagnostics, therapy and follow-up of cutaneous melanoma. The systematic presentation of study results with respect to benefits and risks are intended to support physicians as well as patients in their decision-making.

The basis of the recommendations is a review of available evidence according to the criteria of evidence-based medicine, the adaptation of available evidence-based international guidelines as well as in the event of lack of evidence on the basis of good clinical practice. All recommendations were evaluated by interdisciplinary representatives and consented.

The guideline should set quality standards and thus in the long term improve care of melanoma patients.

2.3. Addressees and duration of validity

The S3-guideline melanoma is directed at dermatologists, family physicians, internists, general practitioners, gynecologists, surgeons, oncologists, radiologists and radiation therapists in inpatient and outpatient settings and other medical specialties involved in the diagnosis and treatment of patients with cutaneous melanoma. The guideline is also directed at affected patients and their family members. Further, it should serve as orientation for health insurance providers and political decision makers.

The maximum duration of validity stipulated by the AWMF is five years. A modular update in yearly intervals is planned.

In 2015 an update of the entire guideline is planned with a designation of new mandate holders. Contact person for the update: Dr. Annette Pflugfelder, Department of Dermatology, University of Tübingen, annette.pflugfelder@med.uni-tuebingen.de

2.4. Fundamentals of the methodology

Remark: A detailed description of the methodology is found in a separate document which is available on the site of the AWMF (*http://www.awmf.org/leitlinien/detail/ll/032-024OL.html*).

2.5 Evidence base

The recommendations were developed on the basis of key questions that were agreed upon at the start in a kick-off meeting by the mandate holders.

Evidence-based recommendations: Statement of evidence level (quality level of evidence) as well as grade of recommendation (inclusion of the clinical evaluation) and strength of consensus.

Basis: adaptation of source guidelines or systematic search of the literature *de-novo*.

Non-evidence-based recommendations: A smaller share of recommendations was not evidence-based but based on GCP (Good Clinical Practice), strength of consensus, no level of evidence, no grade of recommendation.

Oxford levels of evidence

Level	Therapy/prevention, etiology/side effects
1a	Systematic review (SR) (with homogeneity of randomized, controlled studies (RCTs)
1b	Individual RCT (with narrow confidence interval)
1c	All or none
2a	SR (with homogeneity) of cohort studies
2b	Individual cohort study (including poor quality RCT; e.g. < 80 % follow-up)
2c	Outcome research, ecological studies
3a	SR (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal or based on physiology or bench research or "first principles"

Grades of recommendation

Grade of recommendation	Description	Syntax
A	Strong recommendation	Shall
B	Recommendation	Should
0	Open recommendation	May

AWMF rules envision designation of grades or recommendation by the guidelines authors within the context of a formal consensus process. Accordingly, a multi-step nominal group process moderated by the AWMF was performed.

3. Consented and voted recommendations and statements

3.1. Epidemiology

Melanoma is the skin cancer with the highest rate of metastasis and is responsible for more than 90 % of all deaths due to skin cancer. Therefore, early recognition and the best possible treatment are important. According to the Robert Koch Institute the number of deaths in the year 2008 was 2,500; the number of new melanomas in 2008 was estimated at 17,800 [1].

3.2. Diagnosis and therapy in primary care

Classification

No.	Recommendation	EG	LoE	Sources
3.2.1.	The AJCC classification of 2009 should be the standard for reporting the histopathology of melanoma	GCP		

Tumor thickness (Breslow depth) is the most important prognostic factor in the primary stage of melanoma. The tumor thickness classes were newly defined in the AJCC classification of 2001 (≤1.0 mm, 1.01–2.0 mm, 2.01–4.0 mm, >4 mm). In contrast to the previous classifications in the current classification of 2009 besides tumor thickness and ulceration the mitosis rate is included in primary melanomas of ≤1 mm [2].

Based on present study data a general recommendation for measuring the mitosis rate can be made. It could be shown that the mitosis rate has a particularly strong prognostic value in thin melanomas of tumor thickness ≤1 mm [3] (Table 1, 2, 3, 4).

Clinical diagnosis

No.	Recommendation	EG	LoE	Sources
3.2.2.a	Examination of the patient without aids is suitable for making a clinical working diagnosis	GCP		

Whole-body examination includes the complete inspection of the skin including adjoining and visible mucous membranes as well as palpation of the lymphatic drainage basins and lymph nodes (see also: S3-guideline "Early detection and prevention of skin cancer").

No.	Recommendation	EG	LoE	Sources
3.2.2.b	For the diagnosis of pigmented skin lesions, dermatologists shall offer dermatoscopy and be trained in the field of dermatoscopy	A	1b	Guidelines adaptation: [4]

Table 1 T-classification of the primary tumor in melanoma.

T classification	Tumor thickness	Additional prognostic parameters
Tis		Melanoma in situ, no tumor invasion
Tx	No statement	Stage cannot be determined*
T1	< = 1.0 mm	a: without ulceration, mitoses < 1/mm2 b: with ulceration or mitosis rate/mm2 ≥ 1
T2	1.01–2.0 mm	a: without ulceration b: with ulceration
T3	2.01–4.0 mm	a: without ulceration b: with ulceration
T4	> 4.0 mm	a: without ulceration b: with ulceration

*Lack of determination of tumor thickness and/or ulceration or unknown primary tumor; # The mitosis rate is measured in the H&E section.

Table 2 N-classification of regional lymph nodes in melanoma.

N-classification	Number of lymph nodes (LN) with metastases	Extent of lymph node metastasis
N1	1 LN	a: only micrometastasis/es (clinically occult)+ b: only macrometastasis/es (clinically detectable)
N2	2–3 LN	a: only nodal micrometastasis/es+ b: only nodal macrometastasis/es c: satellite or in-transit metastasis/es *without* regional lymph node metastases
N3	≥4 LN or matted lymph nodes or satellite or in-transit metastases *with* regional lymph node involvement	

+The detection of micrometastasis is in the new AJCC classification now also the detection of one single cell that reacts positively immunochemically. These cases should be specially marked.

Table 3 M-classification of distant metastases in melanoma.

M-classification	Type of distant metastasis	LDH
M1a	Metastases in skin, subcutaneous tissue or lymph nodes beyond the regional lymph nodes	Normal
M1b	Pulmonary metastasis/es	Normal
M1c	Distant metastasis/es of other location	Normal
	or	
	distant metastasis/es of any location with elevated lactate dehydrogenase (LDH) levels	Elevated

Iliac lymph nodes are also classified as M1a.

Table 4 Stage classification of melanoma.

Stage	Primary tumor (pT)	Regional lymph node metastases (N)	Distant metastases (M)
0	In situ tumors	None	None
IA	≤ 1.0 mm, no ulceration	None	None
IB	≤ 1.0 mm with ulceration or mitosis rate/mm² ≥ 1	None	None
	1.01–2.0 mm, no ulceration	None	None
IIA	1.01–2.0 mm with ulceration	None	None
	2.01–4.0 mm, no ulceration	None	None
IIB	2.01–4.0 mm with ulceration	None	None
	> 4.0 mm, no ulceration	None	None
IIC	> 4.0 mm with ulceration	None	None
IIIA	Any tumor thickness, no ulceration	Micrometastases (clinically occult) in up to 3 lymph nodes	None
IIIB	Any tumor thickness with ulceration	Micrometastases (clinically occult) in up to 3 lymph nodes	None
	Any tumor thickness, no ulceration	Up to three nodal macrometastases	None
	Any tumor thickness, no ulceration	No, but satellite and/or in-transit metastases	None
IIIC	Any tumor thickness with ulceration	Up to three nodal macrometastases or satellite or in-transit metastasis/es *without* regional lymph node metastases	None
	Any tumor thickness ± ulceration	Four or more nodal macrometastases or matted lymph nodes or satellite and/or in-transit metastases *with* regional lymph node metastases	None
IV			Distant metastases

Sequential digital dermatoscopy

No.	Recommendation	EG	LoE	Sources
3.2.2.1.a	During the course of observation, sequential digital dermatoscopy can improve early recognition of melanomas that lack specific dermatoscopic criteria of malignancy.	B	2b	Guidelines adaptation: [4]
3.2.2.1.b	Whole-body photography represents one possibility for early recognition of melanoma in collectives at risk.	-	3b	Guidelines adaptation: [4]

Primary excision

No.	Recommendation	EG	LoE	Sources
3.2.3.	When melanoma is suspected clinically, primary complete excision with small safety margins shall be performed.	GCP		

Prerequisite for the following histologic confirmation of the diagnosis of melanoma is an evaluation of the entire tumor. In the excision a lateral safety margin of about 2 mm is recommended, at the base, the excision should extend into the fatty tissue. A shave excision is not recommended when melanoma is suspected. In special situations, especially in large, extensive tumors in the face or on acral skin where a primary diagnostic excision is difficult, a biopsy or partial excision may be performed [5–7].

Safety margin in primary excision

No.	Recommendation	EG	LoE	Sources
3.2.3.1.a	When melanoma is excised with intent to cure, a radical excision with adequate safety margins at the tumor edge shall be performed in order to prevent local recurrences.	A	1a	Systematic search of the literature *de-novo*: [8]

Stage	Tumor thickness (Breslow depth)	Safety margin
pT1, pT2	≤ 1–2 mm	1 cm
pT3, pT4	2.01– > 4.0 mm	2 cm

3.2.3.1.b	The final decision for a deviation from the safety margins should be made by the surgeon in agreement with the informed patient, also depending on the special anatomic location of the tumor and taking the results of staging diagnostics into consideration.	GCP		
3.2.3.1.c	At the base, the excision should be performed down to the fascia.	B	2b	Systematic search of the literature *de-novo*: [9]

Safety margin for melanoma in situ

No.	Recommendation	EG	LoE	Sources
3.2.3.2.	For in situ melanomas complete excision with a lateral safety margin of 5 mm shall be performed.	GCP		

Micrographically controlled surgery is helpful to insure complete excision [10-12].

Excision with 3D-histology

No.	Recommendation	EG	LoE	Sources
3.2.3.3.	In melanomas (e.g. lentigo maligna melanoma, acral melanomas) in special anatomic locations, such as border sites in the face, on ears, fingers and toes, reduced safety margins may be used. Retrospective studies have demonstrated that with use of 3D-histology (micrographically controlled surgery) there is no increase in local recurrences or decreased overall survival. As data are limited for this situation, the surgeon should make the decision together with the informed patient.	GCP		

Amputations in subungual melanomas should be reserved for advanced cases with bone or joint involvement [12-14, 14-16].

Procedure in the event of R1- or R2-resection

No.	Recommendation	EG	LoE	Sources
3.2.3.4	In the R1- and R2 situation (microscopically or macroscopically detected residual tumor) the primary tumor region shall always undergo re-excision if an R0-situation can be achieved. When surgery cannot achieve an R0-resection, other therapy modalities in order to achieve local tumor control (e.g. hyperthermic limb perfusion, radiotherapy, cryosurgery) should be employed. In the R1- and R2-situation of the lymphatic path of metastasis as well as the lymph nodes of the locoregional lymphatic drainage basin, re-excision should be strived for. When inoperable, other therapy measures should be considered. In R1- and R2-resection of distant metastases (stage IV) an individual approach shall be determined by an interdisciplinary tumor conference.	GCP		

Radiotherapy of the primary tumor

No.	Recommendation	EG	LoE	Sources
3.2.4.a	In lentigo maligna melanomas not suitable for surgical therapy due to size, location and/or age of the patient, primary radiotherapy should be employed. Good tumor control rates can be achieved with this.	B	4	Systematic search of the literature *de-novo*: [17–19]
3.2.4.b	In inoperable primary tumors with R1- or R2-resection, radiotherapy with the goal of local control may be employed.	0	4	Systematic search of the literature *de-novo*: [20–22]
3.2.4.c	In desmoplastic melanomas that have not been resected with adequate safety margins (<1 cm or R1/R2, respectively), postoperative radiotherapy should be performed to secure local tumor control.	B	3b	Systematic search of the literature *de-novo*: [23–25]

Histopathologic examination of the primary tumor

No.	Recommendation	EG	LoE	Sources
3.2.5.	Histological staging according to the valid TNM classification (tumor thickness [Breslow depth], ulceration, mitosis rate in tumor thickness < 1 mm) is obligatory. Determination of the tumor type according to the WHO classification is desirable. Histopathologic special features, such as possible association with a melanocytic nevus, a regression zone, morphologic peculiarities (e.g. desmoplastic melanoma areas) and vascular invasion should be included on a facultative basis as far as present.	GCP		

Clinically and histologically the WHO classification differentiates four melanoma types: lentigo maligna melanoma, superficial spreading melanoma, nodular melanoma, and acral lentiginous melanoma. Beyond this, rare histological variants exist, such as spitzoid melanoma and nevoid melanoma as well as desmoplastic or neurotropic melanoma.

The location of the melanoma on the skin is of significance for determining the type and for the definition of the regional lymph nodes. Perineural invasion (Pn classification) as well as blood vessel (V classification) and/or lymph vessel invasion (L classification) should be included in the report. The lateral and deep resection margins should be evaluated for lack of or presence of melanoma (residual tumor [R] classification).

Micrometastases and in-transit metastases in the primary excision are considered in the N status.

Results of immunohistologic studies on melanocytic differentiation (e.g. S100B protein, HMB45, melan A) shall also be communicated.

Initial staging diagnostics up to stage IIB

Besides physical examination of the entire body which includes inspection of the entire skin surface and adjoining and visible muca membranes as well as palpation of the lymphatic drainage basins and lymph nodes, the following examinations are recommended (Table 5).

A particular problem with imaging such as MRI, CT, abdominal ultrasound and chest x-ray in the tumor stages I to IIB is the difficult-to-quantify rate of false-negative and false-positive findings. While false-negative findings provide a false sense of security and thus might even delay timely diagnosis, false-positive lead to further tests that contribute to insecurity of the patient and add unnecessary burdens.

Initial staging diagnostics – whole-body CT

No.	Recommendation	EG	LoE	Sources
3.2.6.1.	Whole-body CT shall not be performed as standard in asymptomatic patients with the primary diagnosis of melanoma.	A	1a	Systematic search of the literature *de-novo*: [26–29]

Table 5 Overview of the recommendations on examination methods in the initial staging diagnostics for melanoma patients up to stage IIB.

Examination method	Recommendations on staging diagnostics in asymptomatic patients in diagnosis of the primary tumor up to stage IIB	Grade of recommendation	Level of Evidence
Cranial MRI	No	A	3b
Cross-sectional imaging (whole-body without head*)	No	A	1a
Chest x-ray	No	A	2b
Abdominal ultrasound	No	B	2b
Lymph node sonography	Yes (stage IB and above)	A	1a
Skeletal scintigraphy	No	A	3b
Tumor marker S100	Yes (stage IB and above)	0	1a
Tumor marker LDH	No	B	2b

*PET/CT, CT, MRT (whole-body).

Initial staging diagnostics – cranial MRI

No.	Recommendation	EG	LoE	Sources
3.2.6.2.	Cranial MRI shall not be performed as standard in asymptomatic patients with the primary diagnosis of melanoma.	A	3b-	Systematic search of the literature *de-novo*: [30, 31]

Initial staging diagnostics- chest x-ray

No.	Recommendation	EG	LoE	Sources
3.2.6.3.	Chest x-ray shall not be performed as standard in asymptomatic patients with the primary diagnosis of melanoma.	A	2b	De novo investigation: Systematic search of the literature *de-novo*: [27, 32–36]

Initial staging diagnostics – lymph node sonography

No.	Recommendation	EG	LoE	Sources
3.2.6.4.	Locoregional lymph node sonography shall be performed in patients with the primary diagnosis of melanoma of tumor stage IB or higher.	A	1a	Systematic search of the literature *de-novo*: [37]

Initial staging diagnostics – abdominal ultrasound

No.	Recommendation	EG	LoE	Sources
3.2.6.5.	Abdominal ultrasound should not be performed as standard in patients with the primary diagnosis of melanoma.	B	2b	Systematic search of the literature *de-novo*: [33, 38–40]

Initial staging diagnostics – S100B, MIA, LDH

No.	Recommendation	EG	LoE	Sources
3.2.6.6.a	S100B may be measured in asymptomatic patients with the primary diagnosis of melanoma.	0	1a	Systematic search of the literature *de-novo*: [41]
3.2.6.6.b	Due to insufficient data, at present no statement can be made if MIA has the same prognostic value as S100B in the primary diagnosis of melanoma.		2b-	Systematic search of the literature *de-novo*: [42–45]
3.2.6.6.c	Serum LDH should not be determined in patients with the primary diagnosis of melanoma.	B	2b	Systematic search of the literature *de-novo*: [32]

Initial staging diagnostics – PET/CT

No.	Recommendation	EG	LoE	Sources
3.2.6.7.	PET and PET/CT shall not be performed routinely as initial staging procedures up to stage IIA/IIB.	A	1a	Systematic search of the literature *de-novo*: [27, 29, 46]

Initial staging diagnostics – skeletal scintigraphy

No.	Recommendation	EG	LoE	Sources
3.2.6.8.	Skeletal scintigraphy shall not be performed as standard in the initial staging workup in patients up to stage IIA/IIB.	A	3b	Systematic search of the literature *de-novo*: [34, 39, 47–49]

Sentinel lymph node biopsy
Indications for sentinel lymph node biopsy

No.	Recommendation	EG	LoE	Sources
3.2.7.1.a	In order to facilitate staging, sentinel lymph node biopsy shall be performed at a tumor thickness of 1.0 mm and above and in the absence of evidence for locoregional or distant metastasis.	A	1a	Systematic search of the literature *de-novo*: [50–56]
3.2.7.1.b	In the event of additional risk factors for a positive sentinel lymph node, sentinel lymph node biopsy should be performed even in thinner primary tumors (0.75–1 mm); these include ulceration and/or increased mitosis rate.	B	1a	Systematic search of the literature *de-novo*: [50–56]

Regression of the primary tumor does not correlate with sentinel lymph node positivity in studies [52, 57, 58] or correlates with a low rate of positive sentinel lymph nodes [54, 69].

Methods for detection of the sentinel lymph node

No.	Recommendation	EG	LoE	Sources
3.2.7.2.	Lymph drainage pathways should be located with preoperative lymphoscintigraphy and sentinel lymph nodes be detected intraoperatively using a manually held gamma probe. Further methods may be employed as a supplement.	GCP		

The further methods that may facilitate localizing and finding the sentinel lymph nodes include:

- Static single-photon emission computed tomography/ computed tomography (SPECT/CT) [60, 61].
- Gamma camera (intraoperatively) [62, 63].
- 3D-navigation devices (currently still being tested) [64].
- Injection of a dye capable of passing into the lymph (e.g. patent blue V) at the tumor site (immediately preoperatively) [65, 66]; this is seen critically by several centers due to the risks (such as anaphylactic reaction, permanent tattoo, pain during injection) [67].

Evaluation and technical processing of sentinel lymph nodes

No.	Recommendation	EG	LoE	Sources
3.2.7.3.	The sentinel lymph nodes shall be evaluated by a histopathologist experienced in the evaluation of primary tumors of melanomas. The technical processing of the sentinel lymph node shall correspond to national or international protocols.	GCP		

Various protocols have been proposed that envision extensive processing of the sentinel lymph node in order to detect small metastases [68–72]. A minimal requirement in consensus recommendations after dividing the sentinel LN in half is making and examining at least four tissue sections per half. In very small sentinel LN it may be even less.

Staining should be with hematoxylin-eosin (H&E) and immunohistochemical stains; the most common markers are HMB-45, S-100 and melan A/ MART-1. A cocktail of these markers may also be employed.

Histological report of the sentinel lymph node

No.	Recommendation	EG	LoE	Sources
3.2.7.4.	The following information shall be included in the histological report on the sentinel LN: 1. Detection of nevus or melanoma cells 2. In the case of melanoma cells, statement of prognostically significant parameters 3. Largest diameter of the micrometastasis	GCP		

In case of the detection of melanoma cells in the sentinel lymph node, it has to date not been clearly defined which parameters of the tumor burden or how the distribution of tumor cells in the lymph node must be stated in the histological report. Parameters are emerging that possess prognostic relevance or can predict the involvement of further non-sentinel lymph nodes in the affected lymph node regions. Among these are:

- the length of the large melanoma cell conglomerate [73–76], report in tenths of a millimeter
- the maximal depth of penetration of melanoma cells in the lymph node parenchyma with respect to the lymph node capsule [74, 77, 78]
- the infiltration of the lymph node capsule [74, 79] or perforation of the capsule
- lymphangiosis, i.e. the presence of tumor cells in lymphatic vessels outside of the sentinel lymph node [75, 76, 80]
- the location of melanoma cells in the lymph node, e.g. subcapsular versus parenchymal

Tumor burden in the sentinel lymph node

No.	Recommendation	EG	LoE	Sources
3.2.7.5.	The detection of micrometastases in the sentinel lymph node is associated with a significantly poorer prognosis. The prognosis correlates with the tumor burden and the location of the melanoma cells in the sentinel lymph node. At present it is an open question which parameters as measures of tumor burden and tumor cell location are most meaningful.		2b	Systematic search of the literature *de-novo*: [2, 74, 81, 82]

3.3. Information and communication

The physician's patient briefing

No.	Recommendation	EG	LoE	Sources
3.3.1.	Information serves participative decision-making and shall be oriented on the current information wishes of the patient. Patients shall be encouraged to communicate their current information needs to their physician, which information is at that time important for them and how comprehensive and detailed this shall be. The information shall be comprehensive, understandable and truthful and be given multiple times during the course of treatment. Here, particularly the patient's ability to cope must be taken into consideration. The informing physician shall make sure that the information is understood by the patient. Relatives/attachment figures should be included in the information process with the consent of the patient.	GCP		

Contents of the patient briefing

No.	Recommendation	EG	LoE	Sources
3.3.2.	Patients shall receive comprehensive and appropriate information on diagnostics, therapy, follow-up, and social medical questions. The form and extent of the information depend particularly on the stage of the disease, the point of time in the medical treatment as well as the preferences of the patient. Here information shall be given particularly on the benefits and risks associated with the medical measures.	GCP		

Communication with melanoma patients and relatives

No.	Recommendation	EG	LoE	Sources
3.3.3.	All members of the oncological team should receive communication training in order to improve patient compliance, satisfaction and coping with the disease as well as to strengthen satisfaction with work from the viewpoint of the treatment team.	GCP		

3.4. Diagnostics and therapy in the event of locoregional metastasis

The stage of locoregional metastasis (AJCC 2009 stage IIIA, IIIB and IIIC) encompasses a clinically and prognostically very heterogenous patient group. The 5-year survival lies between 23 % and 87 % [81]. The majority of patients develop lymph node or in-transit metastases only during the course after successful primary excision.

As in the tumor-free stage III a large share of patients are healed and as a definitive effect on survival has not been shown to date for surgical or medical adjuvant measures, the use of adjuvant therapies must be carefully balanced with respect to benefits and side effects.

No.	Recommendation	EG	LoE	Sources
3.4.	Therapy recommendations for patients in stage III or above should be made within the context of interdisciplinary tumor conferences.	GCP		

Staging diagnostics

No.	Recommendation	EG	LoE	Sources
3.4.1.	Patients in stage IIC have a higher risk of recurrence that is comparable to micrometastasis in stage III. Patients in stage IIC shall therefore be treated like patients in stage III with respect to the diagnostic approach.	GCP		

Table 6 Overview of the recommendations on examination methods in stage IIC and III.

Examination method	Recommendations on staging diagnostics in patients with suspected or proven locoregional metastasis**	Grade of recommendation	Level of Evidence
Cranial MRI	Yes	GCP	–
Cross-sectional imaging (whole-body without head*)	Yes	B	1a
Chest x-ray	No	B	2b
Abdominal ultrasound	No	B	2b
Lymph node sonography	Yes	A	1a
Tumor marker S100B	Yes	A	1a
Tumor marker LDH	Yes	0	1b

*PET/CT, CT, MRT (whole-body), **patient stadium IIc and III

Besides a complete physical examination that includes inspection of the entire skin and adjoining and visible mucous membranes as well as palpation of the lymphatic drainage basins and lymph nodes the following examinations are recommended (Table 6).

Abdominal ultrasound in locoregional metastasis

No.	Recommendation	EG	LoE	Sources
3.4.1.1.	Abdominal ultrasound should not be performed as standard in patients with suspected or proven locoregional metastasis of a melanoma	B	2b	Systematic search of the literature *de-novo*: [33, 34]

Chest x-ray in locoregional metastasis

No.	Recommendation	EG	LoE	Sources
3.4.1.2.	A chest x-ray should not be performed as standard in patients with suspected or proven locoregional metastasis of a melanoma.	B	2b	Systematic search of the literature *de-novo*: [33, 34, 36]

Lymph node sonography in locoregional metastasis

No.	Recommendation	EG	LoE	Sources
3.4.1.3.	Locoregional lymph node sonography shall be performed in patients with suspected or proven locoregional metastasis of a melanoma.	A	1a	Systematic search of the literature *de-novo*: [29, 33, 37]

Cross-sectional imaging in locoregional metastasis

No.	Recommendation	EG	LoE	Sources
3.4.1.4.	Cross-sectional imaging modalities are today standard in staging diagnostics in stage III and higher for melanoma. Here it has been shown that PET/CT is superior to other modalities in diagnostic accuracy.		1a	Systematic search of the literature *de-novo*: [29]

For the practical performance of cross-sectional imaging the practical and economic availability of the respective imaging method must be taken into consideration, so that as an alternative to PET/CT whole-body MRI or whole-body CT may also be employed.

Cranial MRI in locoregional metastasis

No.	Recommendation	EG	LoE	Sources
3.4.1.5.	MRI possesses the highest diagnostic accuracy for the detection of brain metastases of melanoma.	GCP		

S100B, LDH, MIA in locoregional metastasis

No.	Recommendation	EG	LoE	Sources
3.4.1.6.a	S100B shall be determined in patients with suspected or proven locoregional metastasis.	A	1a	Systematic search of the literature *de-novo*: [41, 83]
3.4.1.6.b	LDH may also be employed as an additional prognostic marker in patients with suspected or proven locoregional metastasis.	0	1b	Systematic search of the literature *de-novo*: [84]
3.4.1.6.c	The significance of MIA especially in patients with suspected or proven locoregional metastasis is unclear	2b-	1b	Systematic search of the literature *de-novo*: [44, 45, 85]

Lymphadenectomy

The terms lymphadenectomy and lymph node dissection are used synonymously in this guideline.

Elective lymphadenectomy

No.	Recommendation	EG	LoE	Sources
3.4.2.1.	Elective (prophylactic) lymphadenectomy is not recommended for melanoma, independent of the Breslow depth of the primary tumor.	A	1a	Guidelines adaptation: [4]

Therapeutic lymphadenectomy

No.	Recommendation	EG	LoE	Sources
3.4.2.2.a	Therapeutic lymphadenectomy shall be performed when lymphogenic metastasis is detected (cytologic or histologic confirmation, lymph node sonography, CT, PET/CT) without indication of distant metastases (stage IIIB and IIIC).	GCP		
3.4.2.2.b	Patients with a lymph node recurrence in a lymphatic drainage basin already operated on without indications of distant metastases should depending on surgical feasibility undergo lymph node dissection or resection of lymph node metastases.	GCP		

Lymphadenectomy in the event of micrometastases in the sentinel lymph node

No.	Recommendation	EG	LoE	Sources
3.4.2.3.a	When micrometastases are present in the sentinel lymph node a complete lymph node dissection should be offered. The decision for complete lymph node dissection in sentinel lymph nodes with a minimal tumor burden and/or subcapsular location must be made together with the patient and should take further risk factors such as tumor thickness, ulceration, tumor mitosis rate, number of positive sentinel lymph nodes and anatomic site of the primary tumor into consideration	B	2b	Systematic search of the literature *de-novo*: [74, 81, 82, 86]
3.4.2.3.b	Weighted scores including several histologic and/or clinical risk factors may be employed to assess the risk of metastases in non-sentinel lymph nodes, but require further clinical validation before a general recommendation.	0	2b	Systematic search of the literature *de-novo*: [74, 77, 86]

Extent of the lymph node dissection

No.	Recommendation	EG	LoE	Sources
3.4.2.4.	Before a lymph node dissection staging imaging diagnostics and/or histologic confirmation of the lymph node metastasis e.g. with fine needle puncture should have been performed. Preoperatively, if indicated, lymphoscintigraphy may be performed for surgical planning. Due to the considerable risk of local lymph node recurrences, a radical lymph node dissection shall be performed. This applies to the femoral triangle lymph nodes in the inguinal region. In the axillary region the dissection of the typical lymph node stations I–III is only recommended for primary tumors whose lymphatic drainage is to this site. In the head and neck area a differentiated approach on the basis of the anatomic drainage pathways and preoperative diagnostics is required.	GCP		

Region	Extent	Enlargement
Head and neck area	Modified radical neck dissection	Superficial (lateral, nerve-sparing) parotidectomy Posterolateral neck dissection (retroauricular, suboccipital lymph nodes, lateral neck triangle, parts of the levels II–IV dorsal to V. jugularis interna)
Axillary (upper limb, trunk)	Level I–III, depending on the site of the primary tumor	
Inguinal (lower limb, trunk)	Femoral triangle lymph nodes	Iliac and obturator lymph nodes

Adjuvant radiotherapy after lymphadenectomy

No.	Recommendation	EG	LoE	Sources
3.4.3.a	To improve tumor control in the lymph node region, postoperative adjuvant radiotherapy should be performed when at least one of the following criteria is fulfilled • 3 affected lymph nodes • capsule penetration • lymph node metastasis > 3 cm	B	1b	Systematic search of the literature *de-novo*: [87–96]
3.4.3.b	To improve tumor control in the lymph node region, postoperative radiotherapy should be performed after resection of a lymphatic recurrence.	GCP		
3.4.3.c	If there is an indication for radiotherapy of the lymphatic drainage basin, radiotherapy shall be performed with 50–60 Gy in conventional fractionated doses (5 x 1.8–2.5 Gy/week).	A	2b	Systematic search of the literature *de-novo*: [87-95, 97]
3.4.3.d	A positive effect of postoperative radiotherapy of the regional lymphatic drainage basin on survival time has not yet been proven.		2b	Systematic search of the literature *de-novo*: [87, 92, 93, 95, 98, 99]

Adjuvant medical therapy

Adjuvant chemotherapy

No.	Recommendation	EG	LoE	Sources
3.4.4.1.	Dacarbazine shall not be administered in the adjuvant therapy of melanoma.	A	1a	Guidelines adaptation: [100, 101]

Adjuvant vaccination therapy

No.	Recommendation	EG	LoE	Sources
3.4.4.2.	Vaccination therapy shall not be administered in the adjuvant therapy of melanoma outside of clinical studies.	A	1b	Guidelines adaptation: [100]

Adjuvant limb perfusion

No.	Recommendation	EG	LoE	Sources
3.4.4.3.	Adjuvant limb perfusion with melphalan shall not be administered in the adjuvant therapy of melanoma.	A	1b	Guidelines adaptation: [100]

Adjuvant immunostimulation

No.	Recommendation	EG	LoE	Sources
3.4.4.4.a	Adjuvant therapy with the unspecific immunostimulant levamisole shall not be administered.	A	1a	Guidelines adaptation: [100, 101]
3.4.4.4.b	Adjuvant therapy with the unspecific immunostimulant BCG shall not be administered.	A	1b	Guidelines adaptation: [100, 101]

Adjuvant mistletoe therapy

No.	Recommendation	EG	LoE	Sources
3.4.4.5.	Adjuvant therapy with mistletoe preparations shall not be administered.	A	1b	Systematic search of the literature *de-novo*: [102–105]

Adjuvant interferon therapy

No.	Recommendation	EG	LoE	Sources
3.4.4.6.a	Patients in the AJCC 2009 tumor stage IIB/C and IIIA–C shall be offered adjuvant therapy with interferon.	A	1a-	Systematic search of the literature *de-novo*: [106–111]
3.4.4.6.b	Patients in the AJCC 2009 tumor stage IIA may be offered a low-dose adjuvant interferon therapy.	0	1b	Systematic search of the literature *de-novo*: [112, 113]
3.4.4.6.c	The individual therapy regimen should be discussed with the patient by carefully balancing expected benefit by possible side effects and reduction of quality of life.	GCP		
3.4.4.6.d	Pegylated interferon prolongs recurrence-free survival in comparison to untreated control patients in stage III.		2b	Systematic search of the literature *de-novo*: [114]
3.4.4.6.e	In patients with high-risk melanomas, the possibility of participation in a clinical study should be assessed.	GCP		
3.4.4.6.f	Patients with a high risk of metastasis may subjected to follow-up only, provided that an adjuvant therapy with IFN-alpha has been discussed with them beforehand.		1a-	Systematic search of the literature *de-novo*: [106–111]

Table 7 Overview of randomized studies on interferon-alpha in different dosages.

Study	Pat.	Overall survival	p	Recurrence-free survival	p
Low-dose IFN-alpha					
Pehamberger, AMCG, 1998	311	Not sign., HR n.r.	-	Sign., HR n.r.	<0.2
Garbe, DeCOG, 2008	444	Sign., HR = 0.62	0.0045	Sign., HR = 0.69	0.018
Kleeberg, EORTC 18871, 2004	484	Not sign., HR = 0.96	0.72	Not sign., HR = 1.04	0.71
Hancock, UKCCCR, 2004	674	Not sign., OR = 0.94	0.6	Not sign., OR = 0.91	0.3
Cascinelli, WHO, 2001	444	Not sign., HR n.r.	0.72	Not sign., HR n.r.	0.5
Cameron, SMG, 2001	95	Not sign., HR n.r.	> 0.2	Not sign., HR n.r.	-
Kirkwood, E1690, 2000	642	Not sign., HR = 1.04§	0.813	Not sign., HR = 1.19§	0.171
Grob, FCGM, 1998	489	Not sign., HR n.r.	0.059	Sign., HR n.r.	0.035
Middle-dose IFN-alpha					
Hansson, Nordic trial, 2011	855	Not sign., HR = 0.91	0.642	Sign., HR = 0.80	0.030
Eggermont, EORTC 18952, 2005		Not sign.,		Not sign.,	
	832	HR = 1.00	0.96	HR = 0.95*	0.59
	835	HR = 0.85	0.11	HR = 0.83*	0.05
High-dose IFN-alpha					
Kirkwood, E1690, 2000	642	Not sign., HR = 1.0§	0.995	Not sign., HR = 1.28§	0.054
Kirkwood, E1684, 1996/2004		Update:		Update: Sign.,	
	287	Not sign., HR = 1.22§	0.18	HR = 1.38§	0.02
		Initially: sign., HR n.r.	0.0237	Initially: sign., HR n.r.	0.0023
Creagan, NCCTG, 1995	262	Not sign., HR = 0.9	0.53	Not sign., HR = 0.83	0.37
Pegylated IFN-alpha					
Eggermont, EORTC 18991, 2008	1256	Not sign., HR = 0.98	0.78	Sign., HR = 0.82	0.01

Abbreviations: sign. = significant (= study showed a significant benefit for interferon alpha), n.r.= not reported, HR = Hazard Ratio, OR = Odds Ratio; *Eggermont et al. 2005: 3 treatment arms: 13 months and 25 months interferon alpha versus observation; HR in the column "recurrence-free survival" refers to survival without distant metastases. §Kirkwood et al.: HR > 1 = IFN alpha superior; based on risk not to suffer the event (unlike other trials HR <1 = IFN alpha superior; based on risk to suffer the event).

The studies on interferon therapy were performed in varying dosages, tumor stages and with varying therapy duration. Due to the change of the melanoma classification of the AJCC, the studies are not directly comparable with respect to the patient cohorts examined. The meta-analyses demonstrate no significant difference between the different interferon dosages, regimens and duration of the interferon therapy. This means that no concrete interferon regimen recommendation can be made (Table 7).

Surgical therapy in locoregional metastases

No.	Recommendation	EG	LoE	Sources
3.4.6.	Surgical therapy of locoregional metastases shall be performed when – with lack of indications of distant metastasis – there is a possibility of macroscopic and microscopic complete removal (R0-resection) of the metastases.	GCP		

The recommendation applies to cutaneous and subcutaneous locoregional metastases (in-transit and satellite metastases).

Radiotherapy in locoregional metastases

Nr.	Recommendation	EG	LoE	Sources
3.4.7.	Local radiotherapy may be employed in satellite and in-transit metastases with the goal of local tumor control.	0	4	Systematic search of the literature *de-novo*: [115–119]

Algorithm in locoregional metastases (Figure 1)

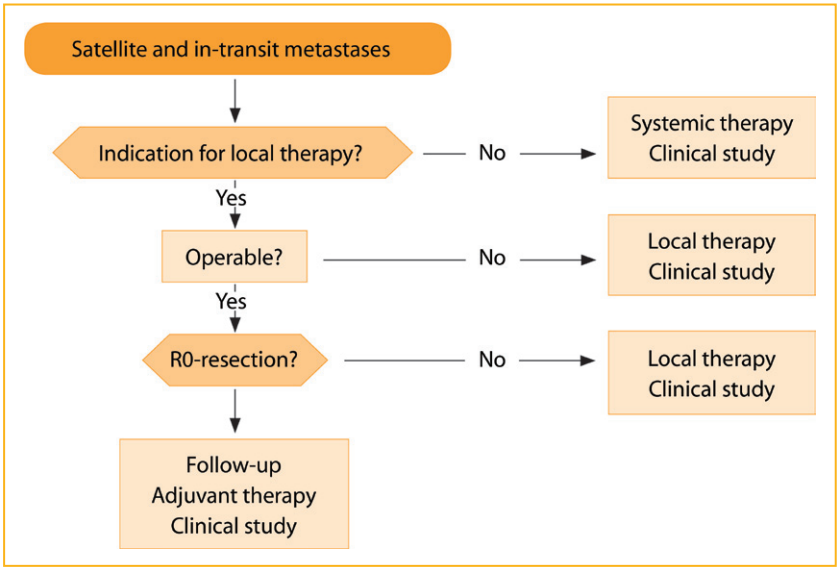

Figure 1 Algorithm on locoregional metastases. **Local therapy** options: intralesional IL-2 therapy, radiotherapy, intratumoral electrochemotherapy, local immunotherapy with DNCB or DCP, isolated limb perfusion, CO_2 laser ablation.

Medical procedures in locoregional metastases

No.	Recommendation	EG	LoE	Sources
3.4.8.a	Patients with satellite and in-transit metastases should be treated within the context of clinical studies if possible.	GCP		
3.4.8.b	In patients with satellite and in-transit metastases various local procedures can be employed with the highest response rates being reported for the intratumoral injection of interleukin-2, intratumoral electrochemotherapy with bleomycin or cisplatin and the local immunotherapy with DNCB or DCP.	o	4	Systematic search of the literature *de-novo*: [120–129]

Limb perfusion in locoregional metastases

No.	Recommendation	EG	LoE	Sources
3.4.9.	In patients with multiple, rapidly recurrent skin and subcutaneous metastases (satellitosis, in-transit metastases, local metastases) that are limited to the arm or leg, the indication for isolated limb perfusion should be examined, when the metastases cannot be controlled by other measures (e.g. repeated excision, CO_2 laser ablation).	GCP		

3.5. Diagnostics and therapy in the stage of distant metastasis

Algorithm initial stage IV (Figure 2)

Staging diagnostics in stage IV

Besides a whole-body examination that includes complete inspection of the skin including adjoining and visible mucous membranes as well as palpation of the lymphatic drainage basin and lymph nodes, the following examinations are recommended (Table 8).

Abdominal ultrasound in distant metastasis

No.	Recommendation	EG	LoE	Sources
3.5.2.1.	Abdominal ultrasound may be performed in patients with suspected or proven distant metastases. The method is, however, inferior to MRI, CT and PET or PET/CT with respect to the detection of distant metastases.	o	3b	Systematic search of the literature *de-novo*: [130–132]

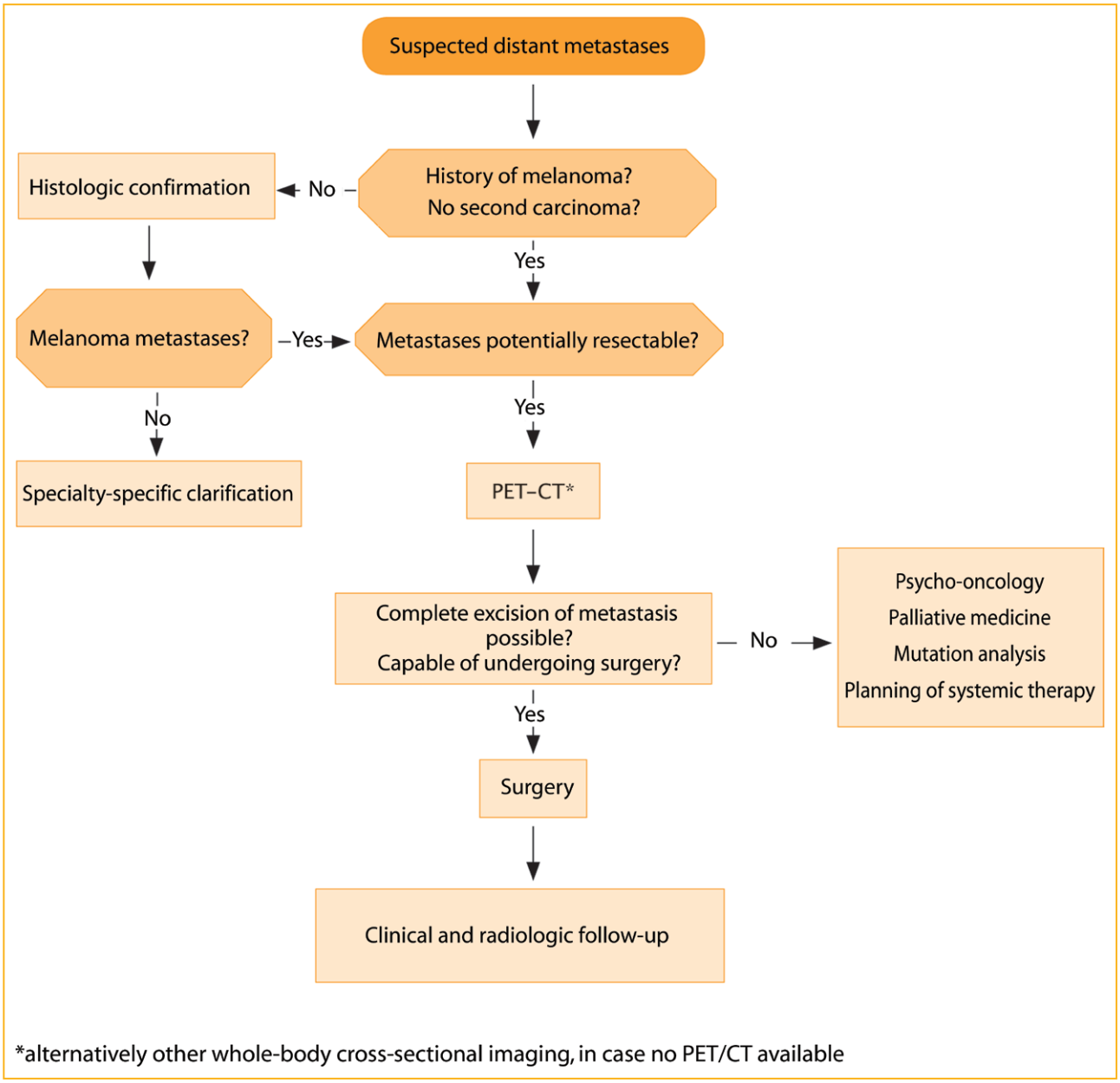

Figure 2 Algorithm on diagnostics and indication for surgery in suspected distant metastases alternative other whole-body diagnostics with cross-sectional imaging in case PET/CT is not available.

Lymph node sonography in distant metastasis

No.	Recommendation	EG	LoE	Sources
3.5.2.2.	Locoregional lymph node sonography may be performed in patients with suspected or proven distant metastases of a melanoma.	0	1a	Systematic search of the literature *de-novo*: [29, 37]

Table 8 Overview of recommendations on examination methods in stage IV.

Examination method	Recommendations on staging diagnostics in patients with suspected or proven distant metastases	Grade of recommendation	Level of Evidence
Cranial MRI	Yes	GCP	–
Cross-sectional imaging (whole-body without head*)	Yes	B	1a
Abdominal ultrasound	Yes	0	3b
Lymph node sonography	Yes	0	1a
Skeletal scintigraphy	Yes	GCP	–
Tumor marker S100B	Yes	A	1a
Tumor marker LDH	Yes	A	1b

*PET/CT, CT, MRT (whole-body)

Cross-sectional imaging in distant metastasis

No.	Recommendation	EG	LoE	Sources
3.5.2.3.	Cross-sectional imaging methods are today the standard in the staging diagnostics of melanoma of stage III and above. Here it has been shown that PET/CT is superior to the other methods in diagnostic accuracy.		1a	Systematic search of the literature *de-novo*: [29]

For the practical performance of cross-sectional imaging the practical and economic availability of the respective imaging method must be taken into consideration, so that as an alternative to PET/CT, whole-body MRI or whole-body CT may also be employed.

Cross-sectional imaging studies in melanoma patients in stage IV under therapy should be repeated in regular intervals, i.e. depending on therapeutic agent every 6–12 weeks.

Cranial MRI in distant metastasis

No.	Recommendation	EG	LoE	Sources
3.5.2.4.	For the detection of brain metastases, MRI possesses the greatest diagnostic accuracy.	GCP		

Skeletal scintigraphy in distant metastasis

No.	Recommendation	EG	LoE	Sources
3.5.2.5.	In patients with advanced disease with bone pain, skeletal scintigraphy may be employed in addition for clarification of skeletal metastasis.	GCP		

S100B and LDH in distant metastasis

No.	Recommendation	EG	LoE	Sources
3.5.2.6.	S100B shall be measured in patients with suspected or proven distant metastases.	A	1a	Systematic search of the literature *de-novo*: [41, 133]
3.5.2.7.	LDH as part of the current AJCC classification shall be measured in patients with suspected or proven distant metastases.	A	1b	Systematic search of the literature *de-novo*: [2, 134, 135]

According to the current AJCC classification [2] LDH is to be measured regularly after entrance into stage IV.

Diagnostics in metastasis of occult melanoma

No.	Recommendation	EG	LoE	Sources
3.5.3.	In the event of cutaneous, lymph node or distant metastases of an unknown primary melanoma, a search for an extracutaneous primary melanoma is not recommended.	GCP		

A clinical ophthalmologic, otorhinologic and colonoscopic examination searching for a primary tumor of the eye, the internal ear or possibly the intestinal tract usually does not discover a tumor [136]. Even if no primary tumor is detected, the identified lymph node or distant metastases should be treated properly according to the guidelines. Prior staging diagnostics also shall be performed according to the standards in melanoma stage III or IV [137, 139].

Molecular pathology diagnostics

No.	Recommendation	EG	LoE	Sources
3.5.4.	When BRAF and c-KIT mutations are detected, therapeutically specific inhibitors are available. In stage IIIB or above mutations (c-KIT only in ALM and mucosal melanoma) should be tested.	GCP		

Since targeted medications may become available for N-RAS mutations in the future, the corresponding tests also should be performed here. An activating N-RAS mutation can be detected in about 15 % of melanomas [140].

Surgical therapy of distant metastases

No.	Recommendation	EG	LoE	Sources
3.5.5.	Every patient with metastases of a melanoma requires an interdisciplinary decision on an indication for surgical therapy. The resection of distant metastases should be considered if technically Ro-resection is possible and ▸ no unacceptable functional deficit is expected ▸ positive predictive factors for the local procedure exist (low number of metastases, long duration of the metastasis-free interval) ▸ other therapy modalities are exhausted or less promising.	B	2b	Systematic search of the literature *de-novo*: [141–143]

Medical therapy in stage IV

Adjuvant medical therapy after excision of metastasis

No.	Recommendation	EG	LoE	Sources
3.5.6.1.	A general recommendation on adjuvant therapy after excision of metastasis cannot be given due to lack of data.	GCP		

The median survival time for patients with metastatic melanoma in stage IV is estimated at eight months (±2 months) [2] with great individual variations. There exists a general consensus that surgical therapy is the treatment of choice for melanoma metastases, when complete surgical removal (R0-resection) of the metastases is possible.

Therapy with signal transduction inhibitors (BRAF inhibitor)

Mutations in BRAF are detected in 40–60 % of melanomas [144]. Of these mutations 90 % lead to an amino acid exchange of valine (V) through glutamate (E) (BRAFV600E). Rarer are other mutations sensitive to BRAF inhibitors such as BRAFV600K. These result in constitutive activation of the RAF-MEK-ERK signal transduction pathway that is relevant to tumor development and progression of melanoma.

Algorithm medical therapy in stage IV (Figure 3)

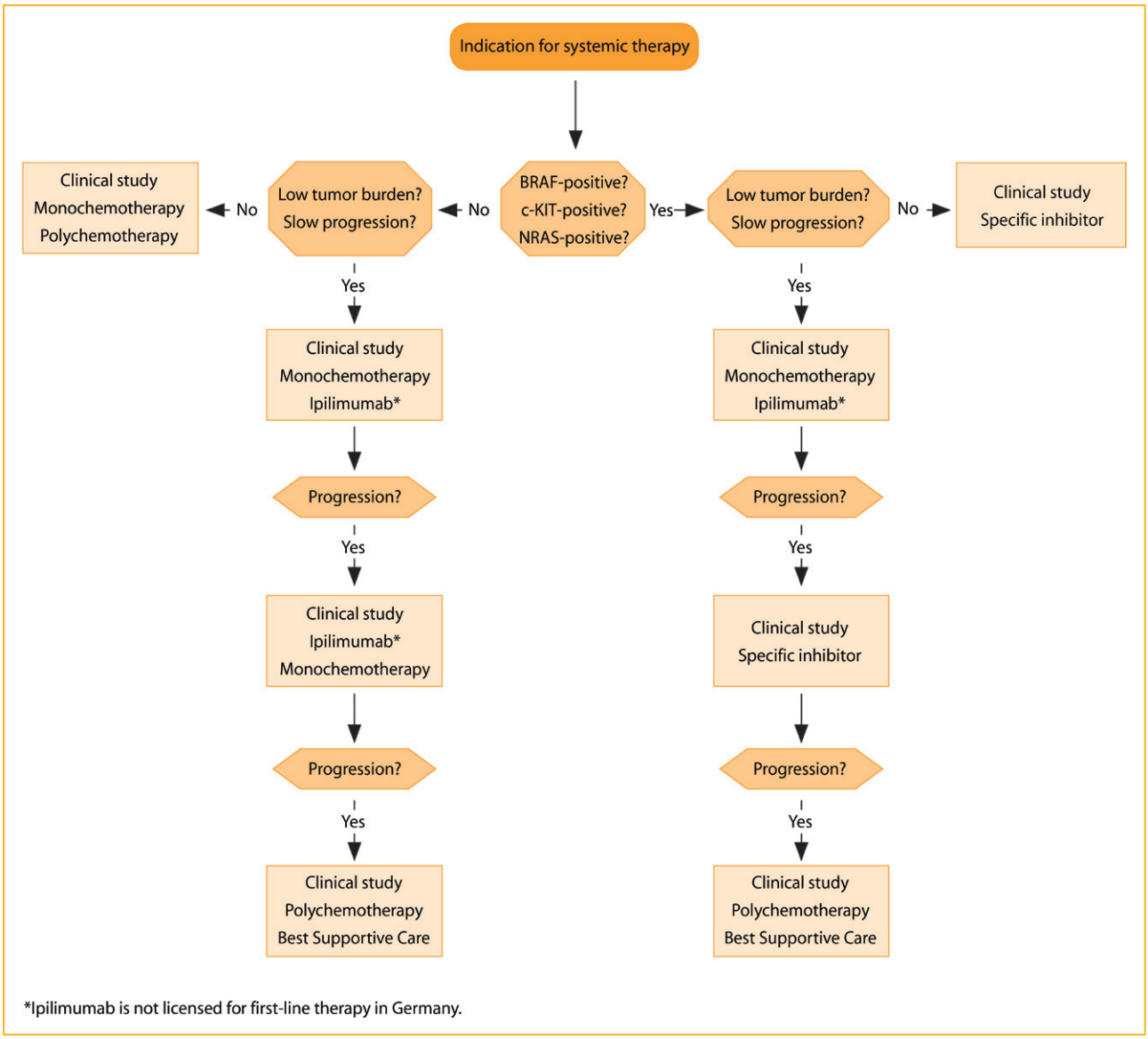

Figure 3 Algorithm on the indication for systemic therapy in stage IV as well as non-resectable stage III.

No.	Recommendation	EG	LoE	Sources
3.5.6.3.	In BRAF inhibitor-sensitive BRAF mutation, therapy with a BRAF inhibitor shall be performed.	A	1b	Systematic search of the literature *de-novo*: [145, 146]

It is remarkable that particularly melanoma patients with a high tumor burden (M1c) profit from treatment with a BRAF inhibitor. The duration of response is nonetheless limited due to the development of resistance mechanisms and lasts about 5–7 months.

In the event of few lung metastases, frequently a very good response to chemotherapy is seen, alternatively ipilimumab is available. In case of low tumor burden, slow dynamics and few clinical symptoms, these therapy options may be considered primarily.

BRAF inhibitors are contraindicated in melanoma patients with wild-type BRAF. The recommended dose for the already licensed vemurafenib is 960 mg twice daily. A dose reduction of more than 50 % is not recommended.

The most common side effects of BRAF inhibition (>30 %) are arthralgia, exanthema, alopecia, fatigue, photosensitivity, nausea, pruritus, papillomas and squamous cell carcinomas, frequently of the keratoacanthoma-type.

Therapy with signal transduction inhibitors (c-KIT inhibitor)

No.	Recommendation	EG	LoE	Sources
3.5.6.4.	In a c-KIT inhibitor-sensitive c-KIT mutation, the option of therapy with a c-KIT kinase inhibitor shall be examined.	GCP		

Observations from phase II studies to date suggest that patients with a c-KIT aberration may respond to treatment a c-KIT kinase inhibitor [147, 148]. Patients with a c-KIT mutation in exon 11 or in exon 13 responded best to imatinib (400 mg daily). A c-KIT mutation is found uncommonly, most often in acral-lentiginous and mucosal melanomas. The most common side effects of c-KIT kinase inhibitors are edema, fatigue, diarrhea, inappetence, nausea, neutropenia and elevated liver parameters. Overall the side effects are usually mild to moderate.

Immunotherapy in stage IV

No.	Recommendation	EG	LoE	Sources
3.5.6.5.	In melanoma patients with non-resectable metastases, the option of immunotherapy with ipilimumab shall be examined.	A	1b	Systematic search of the literature *de-novo*: [149, 150]

Ipilimumab is a human IgG1 monoclonal antibody that blocks the cytotoxic T-lymphocyte associated antigen (CTLA-4) on the T cell, which normally down-regulates previously activated T cells negatively. Through blockade of CTLA-4, the activation and proliferation of T cells, autoimmunity and antitumor immunity is augmented.

Four cycles of ipilimumab 3 mg/kg i.v. over 90 min every three weeks is recommended. As ipilimumab can induce severe immune-mediated side effects, compliance of the patient is a must. Particularly cutaneous (exanthems), gastrointestinal (colitis), hepatic (hepatitis), endocrine (hypopituitarism) and neurological side effects develop. Detailed guidelines have been developed for the management of side effects that can be consulted in the prescribing information. As the response to ipilimumab can manifest in a delayed fashion up to twelve weeks and even months after initiation of therapy, the assessment of the tumor response to ipilimumab should be made only after completion of the four cycles of therapy.

Monochemotherapy

No.	Recommendation	EG	LoE	Sources
3.5.6.6.a	Monochemotherapy with dacarbazine is an established systemic therapy and may be offered to melanoma patients with non-resectable metastases.	0	1b	Systematic search of the literature *de-novo*: [145, 149, 151–166]
3.5.6.6.b	The efficacy of temozolomide and fotemustine is equivalent to that of dacarbazine.		1b	Systematic search of the literature *de-novo*: [152, 159, 161]

Table 9 Overview of monochemotherapies for metastatic melanoma.

Medication	Dosage
Dacarbazine	800–1200 mg/m² i.v. day 1 every 3–4 weeks or 250 mg/m² i.v. day 1–5 every 3–4 weeks
Temozolomide	15–200 mg/m² orally day 1–5 every 4 weeks
Fotemustine	100 mg/m² i.v. day, 1, 8 and 15 then 5 week pause, then every 3 weeks

Source: S2-guideline Melanoma, 2007.

In randomized clinical studies the chemotherapeutic agents dacarbazine, temozolomide, carboplatin, cisplatin, paclitaxel, vindesine, detorubicin and fotemustine have been investigated as single substances, but without a placebo-control arm. For none of the substances could significant prolongation of survival time be demonstrated. The alkylating cytostatic agent dacarbazine (DTIC) has been employed most often and is considered standard or reference therapeutic agent for patients with metastatic melanoma. An objective response has been reported in 5–12 % of patients in current phase III studies, with only individual patients with a lasting response. Temozolomide is an oral alkylating cytotoxic agent with the same active metabolite and a similar favorable side effect profile as dacarbazine. In phase III studies temozolomide and dacarbazine have displayed equivalent efficacy [152, 161]. Frequent side effects of dacarbazine and temozolomide are loss of appetite, nausea and vomiting as well as leukocytopenia, thrombocytopenia and anemia. In a phase III study fotemustine was equivalent to dacarbazine with respect to survival and response [159] (Table 9).

Polychemotherapy

No.	Recommendation	EG	LoE	Sources
3.5.6.7.a	Polychemotherapy is associated with higher response rates; median overall survival is not significantly altered.		1a	Systematic search of the literature *de-novo*: [164, 166–172]
3.5.6.7.b	Patients with tumor progression during previous systemic therapy or initially rapid tumor progression may be offered polychemotherapy.	GCP		

Overview of various polychemotherapy regimens for metastatic melanoma (Table 10).

Biochemotherapy

No.	Recommendation	EG	LoE	Sources
3.5.6.8.	Biochemotherapy consisting of polychemotherapy in combination with interferon-alpha and interleukin-2 should no longer be employed, as high toxicity is opposed by uncertain advantages with respect to survival.	A	1a	Guidelines adaptation: [173]

Quality of life in the stage of distant metastasis

No.	Recommendation	EG	LoE	Sources
3.5.6.9.	Insufficient indications exist that medical tumor therapy in the metastatic stage has a positive effect on the quality of life.		1b	Systematic search of the literature *de-novo*: [160, 165, 174–187]

Table 10 Overview of diverse chemotherapy regimens for metastatic melanoma.

Regimen	Dosage
CarboTax regimen	Carboplatin AUC6 i.v., paclitaxel 225 mg/m² i.v. Day 1 every 3 weeks, starting with cycle 5, dose reduction (C AUC5/P 175 mg/m²)
GemTreo regimen	Gemcitabine 1000 mg/m² i.v. Treosulfan 3500 mg/m² i.v. Days 1 and 8 every 4 weeks
DVP regimen	DTIC 450 mg/m² i.v. Vindesine 3 mgm² i.v. Cisplatin 50 mgm² i.v. Days 1 and 8 every 3–4 weeks
BHD regimen	BCNU (carmustine) 150 mg/m² i.v. day 1 every 8 weeks Hydroxyurea 1500 mg/m² orally day 1 every 8 weeks DTIC 150 mg/m² i.v. days 1–5 every 4 weeks
BOLD regimen	Bleomycin 15 mg i.v. days 1 and 4 every 4 weeks Vincristine 1 mg/m² i.v. days 1 and 5 every 4 weeks CCNU (lomustine) 80 mg/m² orally day 1 every 4 weeks DTIC 200 g/m² i.v. days 1–5 every 4 weeks

Source: S2-guideline Melanoma, 2007. AUC = area under the curve, d1q21 = d days of drug administration, q cycle duration.

Radiotherapy of distant metastases

Radiotherapy – fractionation

No.	Recommendation	EG	LoE	Sources
3.5.7.1.	Conventional fractionation regimens show equal efficacy with respect to local tumor control in comparison to higher individual doses (>3 Gy).		1b	Systematic search of the literature *de-novo*: [188]

Radiotherapy of spinal cord, skin, subcutaneous tissues and lymph nodes

No.	Recommendation	EG	LoE	Sources
3.5.7.2.a	In patients with acute signs and symptoms due to epidural compression in the spinal cord, radiotherapy may be performed for local symptom control.	0	4	Systematic search of the literature *de-novo*: [189]
3.5.7.2.b	In the stage of distant metastasis, metastases in the skin, subcutaneous tissue or lymph nodes that are inoperable due to number, size or location may undergo radiotherapy with the aim of improving quality of life, prevention of pain and improvement of local tumor control.	0	4	Systematic search of the literature *de-novo*: [116, 119, 190–197]
3.5.7.2.c	The cumulative doses in radiation of metastases in the skin, subcutaneous tissue or lymph nodes should be at least 30 Gy. A smaller tumor size is associated with significantly better response rates, so that the indication for radiotherapy should be made early.	B	4	Systematic search of the literature *de-novo*: [119, 189, 191, 192, 194, 198, 199]

The general state of data on the indication for radiation therapy in stage IV (distant metastasis) of melanoma is on the whole insufficient. No systematic, randomized multicenter studies exist on this subject. The above recommendations were drawn from mostly retrospective case series with a level of evidence according to Oxford of maximally 4.

It must be emphasized that the radiation of distant metastases of melanoma, especially skin, soft tissue, lymph node and bone metastases, result in good local control rates and palliative effects. An effect on overall survival has not yet been demonstrated.

Therapy of bone metastases

Medical therapy of bone metastases

No.	Recommendation	EG	LoE	Sources
3.5.8.1.a	Patients with osseous metastases should receive amino bisphosphonates* or a RANK ligand inhibitor**.	GCP		
3.5.8.1.b	Due to the risk of mandibular osteonecrosis, taking the general health and prognosis into consideration, dental and maxillary surgery evaluation and, if indicated, therapy should be provided before initiating therapy.	GCP		

*ibandronate, pamidronate, risedronate, zoledronic acid, **denosumab.

No specific data for melanoma exist. The recommendations are based on the guideline of the American Society of Clinical Oncology clinical practice guideline update (ASCO) on "Bone modifying substances" in metastatic breast cancer.

Radiotherapy in bone metastases

No.	Recommendation	EG	LoE	Sources
3.5.8.2.	In patients with osseous metastasis, radiotherapy should be performed to improve clinical signs and symptoms and to prevent local complications.	B	4	Systematic search of the literature *de-novo*: [190, 193, 196, 198–201]

In at least two-thirds of cases of osseous metastasis, radiation therapy a distinct palliative effect with respect to pain can be achieved. Therefore, this therapy should be performed when clinical signs are present or there is a danger or fracture. In asymptomatic metastases not endangering stability. radiotherapy does not have to be performed.

Therapy of liver metastases

Metastases of the liver occur in about 40 % of patients with visceral metastasis (own data, Central Registry Melanoma). Uveal melanoma most commonly metastasizes to the liver. Nearly all therapy studies on treatment of predominantly liver metastasis include patients with uveal melanomas. These studies were considered in the search and evaluation. The statements do not differentiate for liver metastasis of cutaneous or uveal melanomas.

Resection of liver metastases

No.	Recommendation	EG	LoE	Sources
3.5.9.1.	In patients with limited liver metastasis, the option of excision should be examined, when it can be performed as a Ro-resection.	B	4	Systematic search of the literature *de-novo*: [202–209]

Local therapeutic measures

No.	Recommendation	EG	LoE	Sources
3.5.9.2.	Ablation, infusion/ perfusion and/or embolization strategies have demonstrated clinical response, but no fundamental improvement or prognosis in studies with a low level of evidence; they may be employed depending on number of metastases and their location.	0	4	Systematic search of the literature *de-novo*: [210–228]

Therapy of brain metastases

Surgery and radiotherapy of brain metastases

No.	Recommendation	EG	LoE	Sources
3.5.10.1.a	Palliative radiotherapy of the brain should be offered for multiple symptomatic brain metastases, if expected survival is longer than three months.	B	1b	Systematic search of the literature *de-novo*: [229]
3.5.10.1.b	Surgery or stereotactic one-step radiotherapy should be employed for limited brain metastases. They improve local tumor control and can improve survival in patients with single metastases.	B	3b	Systematic search of the literature *de-novo*: [230–233]
3.5.10.1.c	With acute signs and symptoms due to brain metastases, the possibility of surgery should be considered.	GCP		
3.5.10.1.d	The role of adjuvant whole-brain radiotherapy after local therapy has not yet been clarified.	GCP		

Brain metastases are the most frequent cause of death in patient with metastatic melanoma and are a great therapeutic problem. They can present with nausea, headache, unilateral neurological symptoms, acute bleeding, organic brain syndrome, seizures and cranial nerve paresis.

Medical therapy in brain metastases

Fundamentally, the same protocols are employed as in the treatment of other organ metastases. The blood-brain barrier is probably not intact in brain metastases (accumulation of gadolinium); therefore, there is no clear advantage for mediations that can penetrate into cerebrospinal fluid.

No.	Recommendation	EG	LoE	Sources
3.5.10.2.	Patients with brain metastases may be offered systemic therapy analogous to the recommendations for metastasis to other visceral organs.	0	4	Systematic search of the literature *de-novo*: [150, 153, 159, 234–242]

3.6. Follow-up

Duration of follow-up

No.	Recommendation	EG	LoE	Sources
3.6.1.	Risk-adapted follow-up of melanoma patients should extend over a time period of 10 years. After this time period, measures should be limited to regular self-examination as well as annual whole-body examination for new melanomas.	B	1b-	Systematic search of the literature *de-novo*: [38, 243–247]

Self-examination

No.	Recommendation	EG	LoE	Sources
3.6.2.	Self-examinations by the patient are viewed as an essential component of follow-up and can lead to early recognition of recurrences or new melanomas. The patients should receive instructions on self-examination to detect a new melanoma or recognize a recurrence themselves.	B	3b	Guidelines adaptation: [4]

Follow-up scheme

No.	Recommendation	EG	LoE	Sources
3.6.3.	Follow-up of melanoma patients should be performed in risk-adapted intervals according to the following scheme.	GCP		

	Year 1–3	Year 4–5	Year 6–10
IA	Every 6 months	Annually	Annually
IB – IIB	Every 3 months	Every 6 months	Every 6–12 months
IIC – IV*	Every 3 months	Every 3 months	Every 6 months

*for Ro-resections

Physical examination

No.	Recommendation	EG	LoE	Sources
3.6.4.1.	Physical examination shall be performed in all melanoma patients during follow-up.	A	2b	Systematic search of the literature *de-novo*: [38, 248–250]

Physical examination encompasses a targeted history, inspection of the entire skin as well as palpation of the primary scar, in-transit and lymphatic drainage basins and lymph nodes.

Lymph node sonography

No.	Recommendation	EG	LoE	Sources
3.6.4.2.	Locoregional lymph node sonography shall be performed during follow-up in melanoma patients with stage IB and above.	A	1a	Systematic search of the literature *de-novo*: [29, 37, 249, 251]

Sonography encompasses sonography of the excision scar of the primary tumor, the in-transit pathway as well as of the locoregional lymph node basin and, if indicated, other stations.

Measurement of S100B

No.	Recommendation	EG	LoE	Sources
3.6.4.3.	The tumor marker S100B should regularly be measured in asymptomatic patients in stage IB or higher during regular follow-up.	B	1a	Systematic search of the literature *de-novo*: [41, 43, 248, 249, 252]

As false-positive values may be due to delayed processing and warm storage of the blood samples, it is recommended first to repeat an elevated measurement. In the event of continued elevation, clarification by use of imaging procedures is recommended.

Chest x-ray

No.	Recommendation	EG	LoE	Sources
3.6.4.4.	Chest x-ray should not be performed routinely during follow-up.	B	2b	Systematic search of the literature *de-novo*: [249, 253, 254]

Abdominal ultrasound

No.	Recommendation	EG	LoE	Sources
3.6.4.5.	Abdominal ultrasound should not be performed routinely in asymptomatic patients in the follow-up of melanoma.	B	2b	Systematic search of the literature *de-novo*: [38, 250, 255, 256]

Cross-sectional imaging

No.	Recommendation	EG	LoE	Sources
3.6.4.6.	Cross-sectional imaging should be performed routinely in the follow-up of melanoma patients in stage IIC or higher.	B	1a	Systematic search of the literature *de-novo*: [29, 255, 257–260]

Cross-sectional imaging may include cranial MRI and PET/CT, whole-body MRI or whole-body CT

Skeletal scintigraphy

No.	Recommendation	EG	LoE	Sources
3.6.4.7.	Skeletal scintigraphy should not be performed routinely in the follow-up of melanoma.	B	3b	Systematic search of the literature *de-novo*: [34, 49]

Follow-up scheme with recommended examinations

No.	Recommendation	EG	LoE	Sources
3.6.4.8.	Follow-up should be performed according to the following scheme and with the following examination methods.	GCP		

Stage	Physical examination			Lymph node sonography			Laboratory S100B			Imaging studies		
Year	1–3	4+5	6–10	1–3	4+5	6–10	1–3	4+5	6–10	1–3	4+5	6–10
IA	Every 6 months	Every 12 months	Every 12 months	-	-	-	-	-	-	-	-	-
IB-IIB	Every 3 months	Every 6 months	Every 6–12 months	Every 6** months	-	-	Every 3 months	-	-	-	-	-
IIC-IV*	Every 3 months	Every 3 months	Every 6 months	Every 3 months	Every 6 months	-	Every 3 months	Every 6 months	-	Every 6 months	-	-

*for R0 resected stages, **only with proper pathologic staging by SLNB, otherwise like IIC

Rehabilitation

No.	Recommendation	EG	LoE	Sources
3.6.5.	Patients with melanoma shall be informed of their entitlement to rehabilitation measures. The application process should be initiated within the context of primary care in patients who have difficulty coping with their disease or participating in the therapy plan. Further prerequisites are the ability to undergo rehabilitation and a positive rehabilitation prognosis.	GCP		

3.7. Concomitant therapy

Employment of complementary medicine

No.	Recommendation	EG	LoE	Sources
3.7.1.	After comprehensive weighing of possible risks (side effects and interactions), complementary measures may be employed in individual cases if the patient desires.	GCP		

Information on complementary and alternative therapies

No.	Recommendation	EG	LoE	Sources
3.7.2.	Patients should be asked about their use of complementary and "alternative" therapies. Patients who employ complementary procedures should be informed about possible risks and interactions. Patients should actively be advised against the use of "alternative" therapies.*	GCP		

*These include, among others, ukrain, vitamin B 17 (apricot stones, bitter almonds), insulin-potentiated therapy, ketogenic diet, vitamins according to D. Rath, Germanic New Medicine®, own blood cytokines, zapper, redifferentiation therapy.

Psycho-oncology

No.	Recommendation	EG	LoE	Sources
3.7.3.	Psychosocial screening of melanoma patients should be implemented routinely in clinical practice. Referral of patients at risk to specialized psychosocial services reduces the probability of developing significant distress.	GCP		

Psycho-oncology encompasses all clinical and scientific efforts to clarify the significance of psychological and social factors in the development and course of malignant diseases as well as the systematic use of this knowledge in the prevention, early detection, diagnostics, treatment, follow-up and rehabilitation [261]. The utmost aim is to recognize burdens of patients and relatives early and supply adequate treatment.

Quality of life

The impact of quality of life on compliance, consistent performance of therapy and possible association with an improved disease course (recurrence-free survival) underscores the importance of recording quality of life. Fundamentally, a targeted, specific assessment is needed, as only this allows for adapted therapy and thus improvement of symptoms.

Palliative medicine

No.	Recommendation	EG	LoE	Sources
3.7.9.	In melanoma patients in stage IV, specialized palliative medicine out- or inpatient services should be integrated at an early time point. In case these are not available appropriate consultation should take place or contact addresses be provided.	GCP		

For optimal care it is important to inform patients and relatives early about possibilities for comprehensive, multi-professional palliative medicine care [262].

Ideally, the initial patient contact to palliative medicine should take place in a familiar environment. The aim should be integration of supportive therapeutic, palliative therapeutic and palliative medicine measures.

3.8. Structure of care and quality management

Skin cancer centers

The heart of the skin cancer center is the interdisciplinary skin cancer conference with the main participants from dermatology, oncology, surgery, radiology and radiation therapy. As many therapeutic decisions as possible should be made here.

A further important point is tumor documentation. All skin cancers must be recorded electronically and be documented. Patient pathways and SOPs (standard operational procedures) for treatment (sentinel lymph nodes, chemotherapy, etc.) are presented. A good cooperation with referring physicians, with psycho-oncology and with social services must be ensured.

The goal is coordination of management and interdisciplinary care of skin cancer patients according to the current status of medical knowledge. The implementation of the present S3-guideline plays an important role here.

Clinical studies

No.	Recommendation	EG	LoE	Sources
3.8.2.	Patients with metastatic melanoma (in stage III or above) shall be presented to an interdisciplinary tumor board to determine further diagnostics and therapy. The possibility of inclusion in clinical studies should be examined in each case.	GCP		

Quality indicators

Quality indicators that have been derived from the strong (A) recommendations of this guideline using standardized methodology can be found in the long version of this guideline.

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