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Malignant Melanoma S3-Guideline "Diagnosis, Therapy and Follow-up of Melanoma"

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Abstract

This first German evidence-based guideline for cutaneous melanoma was developed under the auspices of the German Dermatological Society (DDG) and the Dermatologic Cooperative Oncology Group (DeCOG) and funded by the German Guideline Program in Oncology. The recommendations are based on a systematic literature search, and on the consensus of 32 medical societies, working groups and patient representatives. This guideline contains recommendations concerning diagnosis, therapy and follow-up of melanoma. The diagnosis of primary melanoma based on clinical features and dermoscopic criteria. It is confirmed by histopathologic examination after complete excision with a small margin. For the staging of melanoma, the AJCC classification of 2009 is used. The definitive excision margins are 0.5 cm for in situ melanomas, 1 cm for melanomas with up to 2 mm tumor thickness and 2 cm for thicker melanomas, they are reached in a secondary excision. From 1 mm tumor thickness, sentinel lymph node biopsy is recommended. For stages II and III, adjuvant therapy with interferon-alpha should be considered after careful analysis of the benefits and possible risks. In the stage of locoregional metastasis surgical treatment with complete lymphadenectomy is the treatment of choice. In the presence of distant metastasis mutational screening should be performed for BRAF mutation, and eventually for CKIT and NRAS mutations. In the presence of mutations in case of inoperable metastases targeted therapies should be applied. Furthermore, in addition to standard chemotherapies, new immunotherapies such as the CTLA-4 antibody ipilimumab are available. Regular follow-up examinations are recommended for a period of 10 years, with an intensified schedule for the first three years.

1 Information about this guideline

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1.1.2 Societies in charge

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Dermatologic Cooperative Oncology Group (DeCOG)

1.2 Disclaimer

Medicine is subject to a continuous development process. This entails that all statements, especially with regard to diagnostic and therapeutic procedures, can only reflect scientific knowledge current at the time of printing of this guideline. Utmost care was applied with respect to stated therapeutic recommendations and the selection as well as dosage of drugs. Nevertheless, users are prompted to use package inserts and expert information by the manufacturers as backup and, in case of doubt, consult a specialist. Pursuant to public interest, questionable discrepancies shall be communicated to the OL editors.

The user himself/herself remains responsible for all diagnostic and therapeutic applications, medications, and doses.

Registered trademarks (protected product names) are not specifically marked in this guideline. From the absence of respective indications, it may thus not be inferred that product names are unprotected.

1.2.1 Further guideline documents

Besides the present long version, there are the following supplementary documents:

- Guideline report
- Short version
- Patient guideline (completion planned for 2013)
- Evidence report

These can be accessed via the following web sites:
www.awmf.org/leitlinien/aktuelle-leitlinien.html
www.leitlinienprogramm-onkologie.de/OL/leitlinien.html
www.krebsgesellschaft.de/wub_llevidenzbasiert,120884.html
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1.4 Objectives of the Guideline Program in Oncology

With the Guideline Program in Oncology (OL), the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (Association of the Scientific Medical Societies), the Deutsche Krebsgesellschaft e.V. (German Cancer Society) (DKG), and the Deutsche Krebshilfe e.V. (German Cancer Aid) have set their sights on promoting and supporting the joint development, update, and application of scientifically founded and practicable guidelines in oncology.

This program is based on medical scientific knowledge of the scientific societies and the DKG, on the consensus between medical experts, users, and patients as well as on the set of rules of the AWMF guideline preparation, and the professional support and financing of the Deutsche Krebshilfe.

In order to reflect current medical knowledge and consider medical progress, guidelines have to be regularly reviewed and updated. In doing so, the application of AWMF rules shall be the foundation for the development of high-quality, oncologic guidelines.

As guidelines constitute an important tool for quality assurance and quality management in oncology, they should be introduced into everyday clinical care in a targeted and sustainable fashion. Thus, active measures for implementation and evaluation programs are an important component in the promotion of the Guideline Program in Oncology.

It is the objective of this program to create professional and financially secured (medium-term) conditions in Germany for the development and provision of high-quality guidelines. For these high-quality guidelines not only serve the structured transfer of knowledge, but they may also contribute to structuring the health care system. In this context, it is important to mention evidence-based guidelines as basis for the establishment or updating of disease management programs and the use of quality indicators obtained from guidelines in the certification process of cancer centers.

2 Introduction

2.1 Scope and purpose

2.1.1 Target population

The present guideline contains recommendations with regard to the diagnosis, therapy, and follow-up of cutaneous melanoma at the primary stage as well as at the locoregionally limited and metastatic stage. Mucosal and uveal melanomas were not considered. Issues regarding early detection have been discussed in the S3-guideline "Prevention of Skin Cancer".

2.1.2 Objectives and formulation of questions

The S3-guideline Melanoma aims to provide oncologically-skilled physicians in private office settings and at hospitals with an accepted, evidence-based decision tool for the selection and execution of appropriate measures in the diagnosis, therapy, and follow-up of cutaneous melanoma. The systematic description of clinical trial results with respect to risks and benefits is supposed to aid physicians as well as patients in the decision making process.

Recommendations are based on processing available evidence according to criteria of evidence-based medicine, on the adaptation of existing evidence-based international guidelines, as well as on good clinical practice in cases of lacking evidence. All recommendations were assessed and voted on by interdisciplinary representatives.

The guideline is supposed to set quality standards and thus improve the care of melanoma patients in the long run.

2.1.3 Audience and period of validity

The S3-guideline Melanoma is directed at dermatologists, general practitioners, gynecologists, surgeons, oncologists, radiologists, and radiation oncologists at hospitals and in private office settings as well as other medical specialties involved in the diagnosis and therapy of patients with cutaneous melanoma. The guideline is also aimed at affected patients and their relatives. Moreover, it is supposed to serve as an orientation guide for insurance companies and policymakers.

The maximum period of validity of this guideline as determined by the AWMF is 5 years. A modular update is planned at annual intervals.

An update of the entire guideline and reappointment of participating representatives is scheduled for the year 2015.

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2.2 Principles of methodology

Note: A detailed description of the applied methodology can be found in a separate document (S3 LL Melanom_Leitlinienreport.pdf).

2.2.1 Evidence base

The recommendations were developed on the basis of key questions the representatives agreed upon during a kick-off meeting.

Evidence-based recommendations: Stating level of evidence (quality level of evidence) as well as grade of recommendation (including clinical assessment) and strength of consensus.

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

Non-evidence-based recommendations: A lesser part of the recommendations was answered consensually and not on the basis of evidence: stating GCP (good clinical practice) and strength of consensus, no level of evidence, no grade of recommendation.

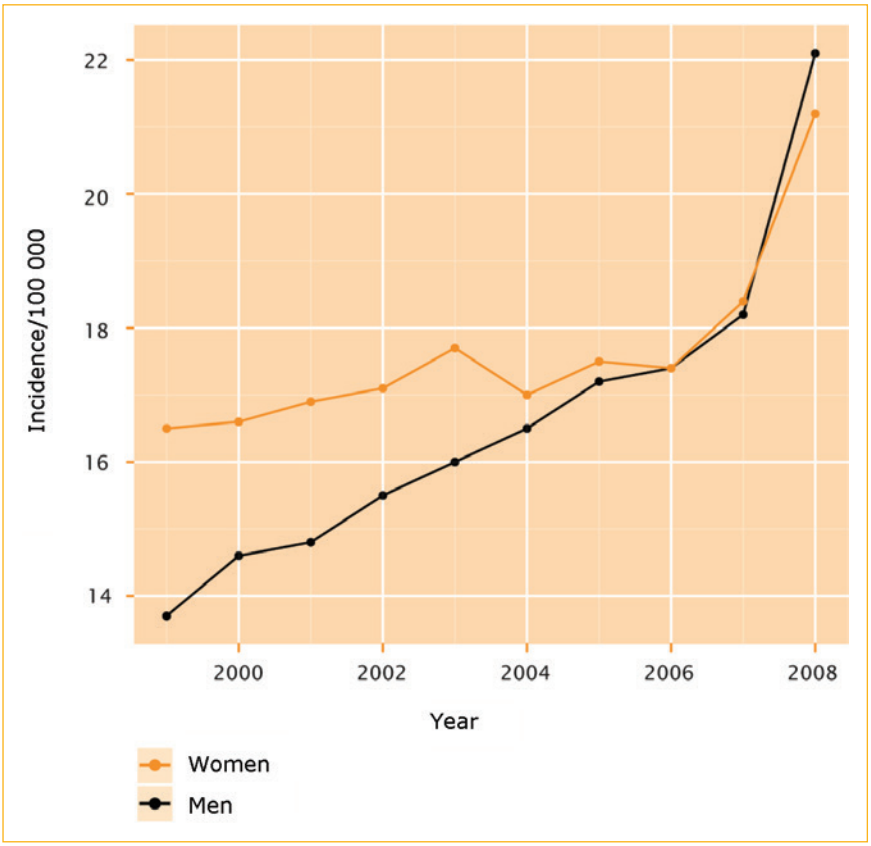

Figure 1 Incidence rates for melanoma in Germany based on non-age-standardized "raw" incidence rates from the Robert Koch-Institute.

2.2.2 Oxford levels of evidence

Level	Therapy/prevention, etiology/harm
1a	Systematic review (SR) (with homogeneity) of randomized controlled trials (RCTs)
1b	Individual RCT (with narrow confidence interval)
1c	All or none
2a	SR (with homogeneity) of cohort studies
2b	Individual cohort study (including low-quality RCT; e.g. < 80 % follow-up)
2c	Outcomes research, ecologic 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, bench research or "first principles"

2.2.3 Grades of recommendation

Grade of recommendation	Description	Syntax
A	Strong recommendation	shall
B	Recommendation	should
0	Recommendation pending	may/can

AWMF regulations provide for the assignment of grades of recommendation by the GL-authors within a formal consensus procedure. Accordingly, multipart nominal group technique proceedings were conducted with the AWMF acting as moderator.

3 Malignant Melanoma

3.1 Epidemiology

C. Garbe, T. Eigentler, U. Leiter

Cutaneous malignant melanoma shows the highest metastatic rate among all skin tumors and accounts for more than

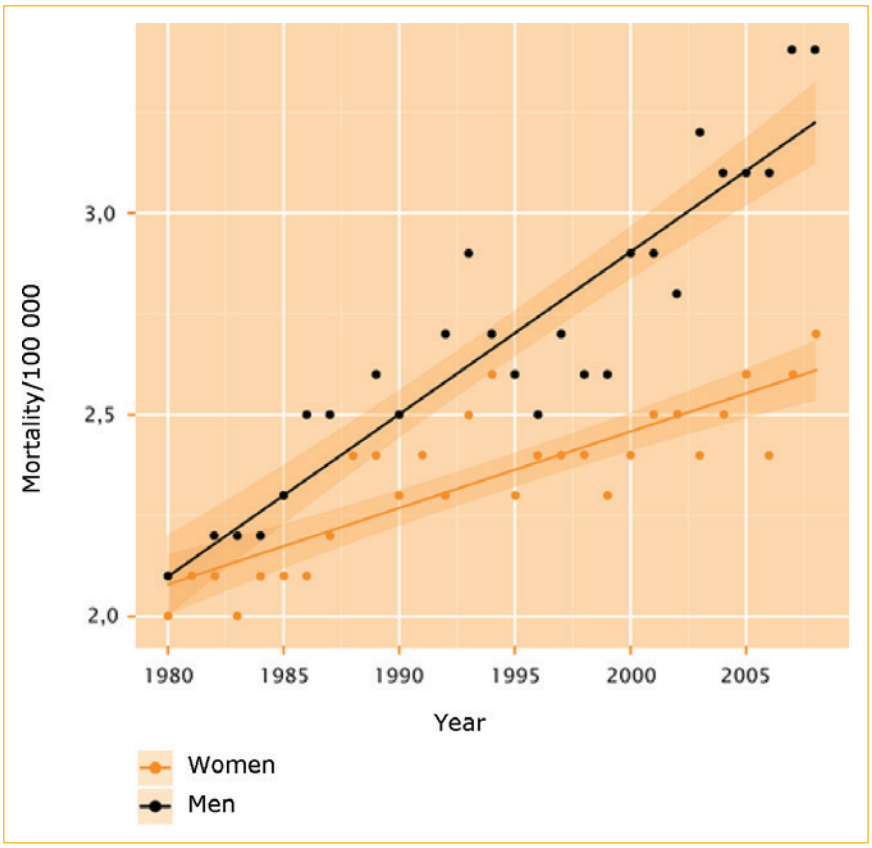

Figure 2 Mortality rates for melanoma in Germany based on non-age-standardized "raw" rates from the Robert Koch-Institute.

90 % of skin cancer-related deaths. Early detection and optimal therapeutic management are therefore pivotal.

Just a few decades ago malignant melanoma was considered rare. However, in 2008 it ranked number five in women and number eight in men among the most common solid tumors in Germany [1]. The most important reason for this rise in incidence over the past 5–6 decades has been a change in leisure and travel habits, resulting in increased UV exposure. While there are generally exact figures with regard to mortality, German incidence rates for melanoma can still only be estimated by taking into account data from cancer registries (still incomplete) in various federal states. Comprehensive nationwide cancer registration has not yet been achieved in Germany [2].

On the basis of these estimations, the Robert Koch-Institute in Berlin calculates estimated values for raw and age-standardized incidence rates of melanoma per 100 000 people and year [2]. Raw rates are best suited for detecting the rise in incidence and mortality over time, as they reflect the actual rise even with an increase in life expectancy among the population. Age-standardized data is preferred when comparing the incidence between different populations (European standard population). However, age-standardized data underestimates the frequency of older age groups (as of the 1960s) and thus leads to lower incidence and mortality rates.

According to most recent data from the Robert Koch-Institute, there were 2 500 deaths in 2008, the number of newly diagnosed melanomas is estimated at 17 800 for the same year [2].

From 1999–2008, there is a rise in incidence rates in men from 13.7 to 22.1 cases per 100 000 people and year and in women from 16.5 to 21.2 cases per 100 000 people and year, i. e. over the past decade, there has been an annual increase in incidence of 6.1 % for men and of 2.8 % for women. In 2008, incidence rates in men were higher than in women for the first time (Figure 1). No other solid tumor (except for epithelial skin tumors) shows a similarly high rise in incidence rates as melanoma.

The state of Saarland with its 1 million inhabitants was the only state within former West Germany where long-term cancer registration had been performed. From 1970–2009, the age-standardized incidence rates grew from 3 to 22 cases in men and from 3 to 20 cases in women per 100 000 people and year. Thus, the annual increase for men and women over the course of these four decades was roughly 17 % [3].

With respect to melanoma, the cancer registry of the

former GDR covers the years from 1970–1989. During this period, a rise in age-standardized incidence rates from 3 to 7 cases per 100 000 people and year was observed in men as well as in women. This amounted to an annual increase of 13 % [4], and thus shows a similar trend as the cancer registry in Saarland.

The available data on the incidence of malignant melanoma in Germany can be summed up as follows: from 1970–2008, there is a noticeable rise in age-standardized incidence rates for melanoma from 3 to 21 cases per 100 000 people and year. Melanoma incidence thus showed a sevenfold (700 %) increase over the course of almost four decades. A leveling off or reversal of this trend of rising incidence rates has not been discernible so far. One can therefore expect a doubling of incidence rates in men over the next 20 years and in women over the next 30 years. Within the first year of introduction of a skin cancer screening program by statutory health insurance companies, the rates of newly diagnosed cases showed an uptick of 15–20 % [1].

In Europe, the highest increases in incidence rates have been reported in Scandinavia, but a considerable rise in incidence has also been seen in central and southern Europe. The highest incidence rates in Europe are in Sweden, Norway, and Denmark, the lowest in the Mediterranean countries. This north-south gradient is likely explained by darker pigmentation of Mediterranean populations, resulting in decreased susceptibility to the dangers of sunlight, as well as by different leisure habits among Mediterranean populations leading to decreased sun exposure.

The highest incidence rates worldwide have been reported in Australia and New Zealand with rates of 50–60 cases/100 000 people and year, rendering malignant melanoma one of the most common tumors in these populations. The highest incidence rates have been observed in areas close to the equator like Queensland/Australia, where incidence rates up to 60 cases/100 000 people and year have been noted. These figures show the extent to which the incidence of melanoma can increase among Caucasians.

Mortality rates have also undergone a marked increase in the past 4 decades (Figure 2). The cancer registry of Saarland showed a rise in mortality rates from 1970–2009 from approximately 1.5 to 4.2 cases/100 000 people and year among men (increase of 280 %) and from approximately 1.5 to 3.8 cases/100 000 people and year among women (increase of 250 %). For the period from 1999 to 2008, figures from unified Germany are available. There was a rise in mortality rates from 2.6 to 3.4 cases/100 000 people and year in men (increase of 31 %) and from 2.3 to 2.7 cases/100 000 people and year in women (increase of 17 %) [1]. This rise in raw mortality rates reflects the increase in melanoma deaths from 2021 in the year 1999 to 2500 in the year 2008 [1].

It is important to realize that the increase in mortality rates has been markedly lower than the rise in incidence rates. One might therefore infer a relative stabilization of mortality rates. The most significant reason for this relative stabilization, in view of still notably rising incidence rates, is most likely enhanced early detection of prognostically more favorable tumors. Future evaluations will have to show whether the statutory skin cancer screening program introduced in 2008 is able to lower mortality rates. At any rate, results gathered from the SCREEN Program in Schleswig-Holstein (2003) point to such an effect [5].

The development of malignant melanoma as well as epithelial skin cancers is based on mutations of oncogenes and tumor suppressor genes predominantly induced by UV radiation. Skin cancer virtually does not occur in people with UV protective pigmentation (Africans, Asians), with the exception of mucosal melanomas as well as melanomas on the palms and soles, showing less or no pigmentation.

The etiological significance of UV radiation in melanoma was initially called into question [6]. In the meantime, there is solid evidence for the significance of UV radiation as etiological factor in the development of melanoma. Especially the following correlations have been worked out:

1. The incidence of malignant melanoma is markedly increased in fair-skinned, UV sensitive persons (skin type I and II) as compared to skin types III–IV.
2. Melanoma incidences in Caucasians rise with increasing proximity of the place of residence to the equator (higher UV radiation). This has been described in particular for persons of European descent living in the USA and Australia.
3. The highest increase in melanoma incidence has been observed in areas of the body that have been increasingly exposed to the sun over the past decades due to changing leisure habits.

Moreover, intermittent high-dose UV exposure, as typically experienced during summer vacations, has been shown to significantly raise the risk for melanoma.

There is a correlation between sun exposure, especially during childhood and adolescence, and increased risk for melanoma. On the one hand, this has been supported by epidemiological studies of adult immigrants who emigrated to a country with high UV exposure, but had spent their childhood in countries with moderate UV exposure. This population displays a lower melanoma risk than Caucasians who spent their childhood in countries with high UV exposure. On the other hand, UV exposure induces development of melanocytic nevi in childhood and adolescence, which are themselves indicators for melanoma risk.

Larger epidemiological studies have consistently identified the total number of melanocytic nevi on the entire integument as the most important risk factor for the development

of cutaneous melanoma [7–9]. Melanocytic nevi, however, are not just risk factors, but, at least to a small extent, also have to be regarded as direct precursors of melanoma [10, 11]. This is evidenced by the fact that remnants of melanocytic nevi are found in some melanomas [12]. The risk for malignant transformation of an individual melanocytic nevus is, however, very low [13, 14].

Epidemiological studies on the correlation between the number of melanocytic nevi and melanoma risk usually distinguish common from clinically atypical nevi. These two terms have been defined on the basis of clinical morphology of melanocytic nevi.

The following groups at markedly increased risk for melanoma have been defined:

Persons with

1. multiple melanocytic nevi (≥ 100 common melanocytic nevi);
2. atypical nevus syndrome (≥ 5 atypical melanocytic nevi and ≥ 50 common melanocytic nevi);
3. ≥ 5 atypical melanocytic nevi with a family history of melanoma (at least two first degree relatives);
4. a history of melanoma.

Regularly conducted screening exams result in earlier melanoma detection in this risk population [5], and are thus able to significantly contribute to reducing health care costs [15]. However, it still has to be proven whether regular screenings of the entire population are able to decrease melanoma mortality [5, 16].

3.2 Diagnosis and therapy in primary care

3.2.1 Classification

3.2.1	Consensus-based recommendation
GCP	The AJCC classification of 2009 should be the standard for reporting the histopathology of melanoma.
	Strength of consensus: 100 %

C. A. Sander

The AJCC classification delineates the extent of anatomic spread in melanoma.

Tumor classifications serve as crucial basis for categorizing tumors. Treatment guidelines are based on TNM staging systems and, in the case of melanoma, this is the 2009 AJCC TNM classification [17]. Here, 30 946 patients with stage I, II, and III melanoma and 7 972 patients with stage IV melanoma were examined on the basis of multivariate analysis.

Tumor thickness (Breslow thickness) is the most important prognostic factor at the primary stages of melanoma. Tumor thickness cutoff points were newly defined in the 2001 AJCC staging system (≤ 1.0 mm, 1,01–2,0 mm, 2,01–4,0 mm, > 4 mm). Unlike previous classifications, the current 2009 classification, apart from tumor thickness and ulceration, also includes mitotic rate in primary melanomas of ≤ 1 mm tumor thickness.

Based on current data, most notably the publication by Azzola et al. from the Sydney Melanoma Unit, measurement of mitotic rate is generally recommended. It has been shown that mitotic rate is of particularly strong diagnostic value in thin melanomas up to 1 mm tumor thickness. These findings were obtained from 3 600 patients between 1960 and 2000. Multivariate regression analysis revealed a significant correlation between mitotic rate and 10-year survival [18]. (Table 1–4).

3.2.2 Clinical diagnosis

3.2.2.a	Consensus-based statement
GCP	Examination of the patient without aids is suitable for making a clinical working diagnosis.
	Strength of consensus: 95 %

3.2.2.b	Evidence-based recommendation
Grade of recommendation A	For the diagnosis of pigmented skin lesions, dermatologists shall offer dermatoscopy and be trained in the field of dermatoscopy.
Level of Evidence 1b	Guideline adaptation: [19]
	Strength of consensus: 91 %

A. Blum, M. Capellaro, C. Czeschik

Whole-body examination comprises complete inspection of the integument including adjacent and visible mucous membranes as well as palpation of lymph nodes and lymphatic drainage areas (Reference: S3-Guideline Early detection and Prevention of Skin Cancer). Clinical examinations shall also be repeated at regular intervals as part of follow-up, refer to chapter 3.6.4.

Dermoscopy (dermatoscopy, epiluminescence microscopy) is a technique allowing for enhanced visualization of skin lesions using a magnifier. In order to reduce light reflections, one may either apply a liquid between lens and skin or use polarized light. "This technique allows the visualisation of diagnostic features of pigmented skin lesions that are not seen with the naked eye [20–23].

Meta-analyses performed on studies in a variety of clinical and experimental settings have shown that using dermoscopy improves diagnostic accuracy for melanoma [24, 25].

Table 1 T classification of the primary tumor in melanoma.

T classification	Tumor thickness	Further prognostic parameters
Tis		Melanoma in situ, no tumor invasion
Tx	Not specified	Stage cannot be assessed*
T1	≤ 1.0 mm	a: without ulceration, mitoses < 1/mm² b: with ulceration or mitotic 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

*Missing determination of tumor thickness and/or ulceration or unknown primary tumor; #Determination of mitotic rate is per-formed on H&E sections.

Table 2 N classification of regional lymph nodes in melanoma.

N classification	Number of metastatic lymph nodes (LN)	Extent of lymph node metastasis
N1	1 LN	a: only microscopic metastasis(es) (clinically occult)+ b: only macroscopic metastasis(es) (clinically detectable)
N2	2–3 LN	a: only microscopic nodal metastasis(es)+ b: only macroscopic nodal metastasis(es) c: satellite(s) or in-transit metastases without regional lymph node metastases
N3	≥ 4 LN, or matted lymph nodes or satellites or in transit metastases *with* affected regional lymph nodes	

+According to the new AJCC classification, the detection of one single immunohistochemically positive cell now counts as micrometastasis. These cases should be marked separately.

Table 3 M classification of distant metastases in melanoma.

M classification	Type of distant metastasis	LDH
M1a	Metastases of the skin, subcutis or lymph nodes beyond regional lymph nodes	Normal
M1b	Lung metastasis(es)	Normal
M1c	Distant metastasis(es) at other location or	Normal
	Distant metastasis(es) at any location with elevated serum levels of lactate dehydrogenase (LDH)	Elevated

*Classification M1a also includes iliacal lymph nodes.

From a meta-analysis of nine level II diagnostic studies subject to varying degrees of verification bias performed prospectively in a clinical setting the diagnostic accuracy for melanoma, as expressed by the relative diagnostic odds ratio, was 15.6 (95 % CI 2.9–83.7) times higher for dermoscopy compared with naked eye examination [26–36]." ([19] p. 29).

Table 4 Stage groups in 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 mitotic 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	Microscopic metastases (clinically occult) in up to 3 lymph nodes	None
IIIB	Any tumor thickness, with ulceration	Microscopic metastases (clinically occult) in up to 3 lymph nodes	None
	Any tumor thickness, no ulceration	Up to three macroscopic nodal metastases	None
	Any tumor thickness, no ulceration	None, but satellites and or in-transit metastases	None
IIIC	Any tumor thickness, with ulceration	Up to three macroscopic nodal metastases or satellite(s) or in-transit metastasis without regional lymph node metastases	None
	Any tumor thickness ± ulceration	Four or more macroscopic nodal metastases or matted lymph nodes or satellites and/or in-transit metastases with regional lymph node metastases	None
IV			Distant metastases

All of these studies were subject to varying degrees of verification bias, because only dermoscopically conspicuous lesions usually underwent histologic evaluation, the diagnostic gold standard. The rate of false negative findings cannot be extracted from diagnostic studies that are subjected this kind of bias.

"Importantly the meta-analysis was restricted to studies that directly compared the two methods within each study. Sensitivity of dermoscopy was 18 % (95 % CI 9 %–27 %; p = 0.002) higher than for eye examination, but there was no evidence of an effect on specificity [36]." ([19] p. 29). The use of dermoscopy by inexperienced or untrained examiners, however, did not result in improved diagnostic accuracy compared to mere clinical examination.

"Specificity can also be examined by its effect on excision rates of benign lesions, which was not addressed in the meta-analysis.

Two such studies suggest reduced rates of excision of benign lesions using dermoscopy (reduced benign to malignant ratio of excised lesions and reduction of patients referred to biopsy) and provide indirect evidence for improved specificity in a specialist setting [31, 32]." ([19], p. 29).

These meta-analyses did not address the issue of positive and negative predictive values.

The use of dermoscopy generally rather appears to enhance the negative than the positive predictive value compared to mere clinical examination [26, 27].

"While there are fewer studies on dermoscopy in general practice, all three that were undertaken in this context (one study with both general practitioners and inexperienced specialists or trainees) show a consistently improved sensitivity for the diagnosis of melanoma or the identification of suspicious lesions requiring biopsy [26, 37, 38]. It should be

noted that all the studies cited were undertaken by clinicians with some training in dermoscopy (restricted to lectures or reading material in some studies).

For this reason, and based on other evidence [39], some formal training in dermoscopy is required to achieve improvement in diagnostic accuracy." ([19], p. 29–30).

The grade of recommendation for dermoscopy is A, the level of evidence 1b. Use of dermoscopy, however, is not a standard benefit offered by Germany's statutory health insurance companies (GKV). Dermoscopy was neither a component of the first extensive skin cancer screening in Schleswig-Holstein in 2003/2004, nor has it been part of the biannual skin cancer screening exams (2008–2013) offered by Germany's statutory health insurance companies for patients at the age of 35 and above [5].

Employment of dermoscopy facilitates differentiation between benign and malignant tumors when examining non-pigmented or scarcely pigmented lesions [40], or nail lesions [41], and dermoscopically accessible mucous membranes [42].

3.2.2.1 Sequential digital dermoscopy

3.2.2.1.a	Evidence-based recommendation
Grade of recommendation B	During the course of observation, sequential digital dermatoscopy can improve early recognition of melanomas that lack specific dermatoscopic criteria of malignancy.
Level of Evidence 2b	Guideline adaptation: [19]
	Strength of consensus: 100 %

3.2.2.1.b	Evidence-based statement
Level of Evidence 3b	Whole-body photography represents one possibility for early recognition of melanoma in collectives at risk.
	Guideline adaptation: [19]
	Strength of consensus: 92 %

M. Kaatz, A. Blum

Sequential digital dermoscopy (SDD) is based on the concept of dermoscopy, but allows additional assessment of pigmented lesions through digital storage and analysis. On the one hand, it facilitates detection of short-term changes in suspicious lesions (1–3 months), on the other hand it enables mid- and long-term screening. The advantage over regular dermoscopy lies in the potential detection of lesions that lack typical dermoscopic criteria for malignancy, but display morphologic and chromatic changes.

With regard to sequential digital dermoscopy, four studies of various clinical settings were discussed in the Australian guideline.

Haenssle et al. [43] demonstrated an improvement in early melanoma detection of 17 %, compared to routine dermoscopy during a median follow-up of 32 months. The incidence of melanoma among all excised tumors was 8.3 %.

Kittler et al. [44] histopathologically examined 499 pigmented lesions after various follow-up intervals (1.5–4.5 months, 4.6–8.0 months and > 8 months). Upon excision, 92 lesions proved to be melanomas. 61.8 % respectively 45 % and 35.1 % of these melanomas had not displayed any typical dermoscopic signs of melanoma over the course of follow-up, but had changed in SDD over time.

According to this study, the short-term follow-up interval for individual lesions should be 1.5–4.5 months, the regular check-up interval 6–12 months.

Using additional SDD, Robinson [45] and Menzies [46] were also able to demonstrate detection of early invasive melanomas that had remained inconspicuous in terms of mere dermosopic criteria. The ratio between excised nevus and melanoma critically depended on applied criteria. In particular, a moderate change in size (< 5 %) was only associated with a low risk for melanoma.

In a recent study by Menzies et al. [47], the validity of dermoscopy and SDD was investigated after proper training of 63 general practitioners in Australia and New Zealand. Use of dermoscopy alone lowered excision rates by 19.3 %, additional use of SDD lowered it by 70.6 % (a total of 374 pigmented lesions were included). However, this study was also subject to identification bias, as not all lesions were histologically examined.

Total body photography

"Total body photography (TBP) is widely used in the follow-up of high-risk patients, particularly those with large numbers of melanocytic nevi or dysplastic nevi" ([19], p. 30). (e.g. FAMMM syndrome).

Most studies on total body photography do not provide separate comparisons to other methods (SDD). Simultaneously employing, but not separately considering dermoscopy and clinical examination, studies by Tiersten [48], Wang [49], Mackie [50], Feit [51], and Kelly [52] have shown an advantage in early detection of melanoma with lower biopsy rates.

Goodson et al. [53] used historic data for comparing similar patient populations. Performing total body photography, he was able to show lower excision rates and improvement in the melanoma-to-nevus ratio.

3.2.2.2 Confocal laser scanning microscopy and other methods

M. Kaatz, A. Blum

Confocal laser scanning microscopy (CLSM) is a light microscopic procedure that uses a laser beam, instead of a conventional light source, to scan objects point-by-point. Imaging of the laser scanning microscope is based on reflectance which is composed of reflection and scattering of light within the examined tissue sections. The procedure facilitates evaluation of the epidermis and upper dermis down to a depth of approximately 250 µm with a lateral resolution of 1–2 µm and an axial resolution of 3–5 µm.

So far, there has been no meta-analysis on the validity of confocal laser scanning microscopy in the diagnosis of pigmented skin lesions. Three studies have revealed a high degree of sensitivity and specificity. However, these were crucially dependent on the examiner's skills and thus showed marked variations. Moreover, these studies exhibited differences in the experimental and clinical setting.

Gerger et al. [54] examined 117 melanocytic lesions, among them 27 melanomas. The five independent "blinded" examiners with varying skills achieved a sensitivity between 59.3 and 96.3 % and a specificity between 94 and 100 % (average sensitivity 88.15 %, average specificity 97.6 %).

Langley et al. [55] studied 125 patients with suspicious melanocytic lesions and compared the results obtained from CLSM with dermoscopy and clinical examination. Of the 125 lesions, 37 were histologically diagnosed as melanoma. Use of dermoscopy resulted in a specificity of 84.1 %, a sensitivity of 89.2 %, a positive predictive value of 70.2 %, and a negative predictive value of 94.6 %. CLSM, on the other hand, showed a specificity of 83 %, a sensitivity of 97.3 %, a positive predictive value of 70.6 %, and a negative predictive value of 98.6 %.

These studies were subject to varying degrees of verification bias, as not all lesions were histologically evaluated. Moreover, six of the seven investigations were performed by the same study group and looked at partly overlapping patient populations [54, 56]. At the same time, most studies did not draw any comparison to dermoscopy respectively mere clinical inspection.

Multiphoton laser tomography

Multiphoton laser tomography (MPT) is a non-invasive procedure that allows for evaluation of cellular and extracellular structures at subcellular resolution. MPT is based on the excitation of biogenic fluorophores by two or more long wave, low-energy photons and the induction of second harmonic generation (SHG). The resolution is less than a micrometer.

At present, one prospective study of 83 melanocytic lesions has been conducted using MPT. Analysis was performed in vivo as well as ex vivo, but not all lesions were examined in parallel. In a blinded setting, four independent examiners achieved a sensitivity between 71 and 95 % and a specificity between 69 and 97 %.

Optical coherence tomography

White-light interferometry constitutes the basis for optical coherence tomography (OCT). The travel time of a signal within the tissue is compared to a reference signal of known optical path length. This technique provides tissue penetration of up to one millimeter and a resolution of 15 µm.

So far, there has been one study on OCT. Apart from melanocytic lesions, this study also looked at other skin tumors. Specificity and sensitivity were not reported and consequently, an assessment is not possible.

3.2.3 Primary excision

3.2.3	Consensus-based recommendation
GCP	When melanoma is suspected clinically, primary complete excision with small safety margins shall be performed.
	Strength of consensus: 100 %

C. Rose

Evaluation of the entire tumor is necessary to make a conclusive histologic diagnosis of melanoma, thus rendering complete excision mandatory. Assessment of tumor symmetry and lateral margins are important histologic criteria [57]. At initial excision, lateral surgical margins of roughly 2 mm and deep margins in the subcutis have been recommended. Larger surgical margins will destroy lymphatic drainage pathways and interfere with potential future detection of the sentinel lymph node [58].

Shave biopsies are not recommended when suspecting melanoma, because they often lead to incomplete removal, making it impossible to assess all lateral margins as well as the tumor base.

Under special circumstances, particularly when dealing with large extensive tumors on the face and on acral skin, where complete diagnostic excision is difficult, a partial or incisional biopsy may be performed. Several studies have shown no negative effect on the prognosis of patients thus treated [59–61].

Tissue sampling may be performed by punch biopsy, shave biopsy, or elliptical excision. The various techniques all have advantages and disadvantages. A shave biopsy is generally broader und allows for better evaluation of the epithelium, whereas a punch biopsy provides deeper sections of the corium [58, 60, 62].

When taking a biopsy, special emphasis should be put on proper communication between clinicians and histopathologists. In order to prevent misdiagnoses and delays in diagnosis, the histopathologist has to be informed, if a partial biopsy out of a larger tumor was performed and where exactly the sample

was taken (e.g. lateral margin, nodular part, zone of regression). Consignment of a clinical picture may be helpful [60].

If the there is strong clinical certitude as to the diagnosis of melanoma, the initial excision may be performed applying definitive surgical margins and possibly further required surgical procedures.

3.2.3.1 Safety margin in primary excision

3.2.3.1.a	Evidence-based recommendation
Grade of recommendation 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.
Level of Evidence 1a	Systematic search of the literature *de-novo:* [63]
	Strength of consensus: 100 %

Stage	Tumor thickness (Breslow)	Surgical margins
pT1, pT2	≤ 1–2 mm	1 cm
pT3, pT4	2.01–> 4.0 mm	2 cm
Strength of consensus: 100 %		

3.2.3.1.b	Consensus-based recommendation
GCP	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.
	Strength of consensus: 100 %

3.2.3.1.c	Evidence-based recommendation
Grade of recommendation B	At the base, the excision should be performed down to the fascia.
Level of Evidence 2b	Systematic search of the literature *de-novo:* [64]
	Strength of consensus: 96 %

E. Dippel, D. Dill

Surgical excision is the only curative treatment for melanoma. As micrometastases and tumor cell clusters affect the prognosis dependent on tumor thickness, the primary tumor should be completely removed during surgery. The excision should be performed with deep margins extending to the fascia. Special locations such as the face and neck that do not show a continuous muscle fascia or excessive adipose tissue require adaptation of the vertical surgical margins to anatomic conditions, e.g. down to the perichondrium on the auricle. Measuring and marking of excision margins (clinical) is done by the surgeon and noted on the operative report.

Surgical margins according to the tumor thickness (Breslow) have been examined and systematically assessed in 5 randomized trials comprising 3 296 patients. There was no significant difference between narrow (1–2 cm) and wide (3–5 cm) surgical margins with regard to overall survival, but a tendency towards lower mortality for wide surgical margins (data consistent with a 15 % reduction in mortality for wide vs. 5 % for narrow surgical margins) [63].

Currently available randomized trials have not been able to solve the issue of optimal surgical margins. Evidence suggests that lateral surgical margins have no decisive effect on the occurrence of distant metastases and thus on overall survival. However, according to Veronesi et al. [65], the risk for locoregional recurrence rises with increasing tumor thickness and narrower lateral margins. Present data shows surgical margins of 1 cm to be sufficient for melanoma up to 1 mm in thickness (Breslow). For tumors of 1–2 mm in thickness, only 4 of 5 randomized trials come into consideration. As there is no direct comparability of these trials, surgical margins of 1–2 cm have been recommended. Patients with melanomas above 2 mm experienced no significant difference in overall survival with surgical margins of 1 cm vs. 3 cm and 2 cm vs. 4 cm respectively. However, margins of 1 cm barely missed a significant reduction in melanoma-specific survival. Wide margins above 2 cm did not reveal any benefit as to overall survival. There has not been a study comparing 2 cm vs. 3 cm surgical margins. Only limited data is available on the excision of melanomas > 4 mm in thickness. Surgical margins > 3 cm are not beneficial. A recent meta-analysis of available controlled, randomized trials on melanoma resection concluded that data regarding disease-specific survival is not sufficient to make a definitive statement about optimal surgical margins.

3.2.3.2 Safety margin for melanoma in situ

3.2.3.2	Consensus-based recommendation
GCP	For in situ melanomas complete excision with a lateral safety margin of 5 mm shall be performed.
	Strength of consensus: 100 %

E. Dippel, D. Dill

Complete excision shall be performed for histologically ascertained in-situ melanomas or lentigo maligna. At present, randomized, controlled trials do not exist. 5 mm surgical margins have shown low recurrence rates. Micrographically controlled surgery is helpful in ensuring complete excision [66–68].

3.2.3.3 Excision using 3D histology

3.2.3.3	Consensus-based recommendation
GCP	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.
	Strength of consensus: 92 %

M. Möhrle

Retrospective studies on melanomas of the face, nose, ears, acra, lentigo maligna melanomas, and acral lentiginous melanomas have shown no increase in local recurrence or decrease in overall survival when using narrower surgical margins aided by 3D histology compared to "conventional" surgical margins.

Removal of subungual melanomas with 3D histology and tumor-free margins including the nail matrix may be regarded as another strategy to prevent amputations without affecting prognosis. Amputations in subungual melanomas should be reserved for advanced disease with bone and joint involvement. [67, 69–72].

3.2.3.4 Procedure in the event of R1- or R2-resection

3.2.3.4	Consensus-based recommendation
GCP	In the R1- and R2 situation (microscopically or macroscopically detected residual tumor) the primary tumor region shall always undergo re-excision if an Ro-situation can be achieved. When surgery cannot achieve an Ro-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.
	Strength of consensus: 88 %

D. Dill

R0 resection shall be sought, if there is intent to cure.

The presence of residual tumor after (surgical) treatment is defined by the R classification with regard to the primary tumor and its locoregional dissemination: *R1 – microscopic residual tumor; R2 – macroscopic residual tumor.* Due to its prognostic significance, it is also used for distant metastases after surgical or combination therapy. This classification is not similarly applied to lymph node dissections.

Primary tumor region

R1 and R2 residual tumors comprise locally persistent melanoma after incomplete excision or local recurrence by satellite and/or nearby in-transit metastases. Surgical resection is the treatment of choice in the absence of evidence for further metastases.

Surgical margins during re-excision depend on tumor thickness of the primary tumor. If tumor dimensions are ill-defined (lentigo maligna, lentigo maligna melanoma, local recurrence), mapping biopsies may aid in determining resection margins [73].

If surgery leads to an unacceptable increase in morbidity, departure from the above-mentioned recommendations is feasible on a case-by-case basis. Micrographically controlled surgery should be the treatment of choice in this situation [70, 74–76].

Locoregional lymphatic drainage area

Lymphogenic metastasis correlates with poorer prognosis. The therapeutic goal is complete removal of local tumor tissue. Here, one has to differentiate between metastatic pathways of the lymphatic drainage area (satellite metastases, in-transit metastases, subcutaneous metastases) and lymph node metastases as a result of lymph vessel invasion. Solitary cutaneous or subcutaneous metastases should be completely (clear surgical margins) resected, if tumor clearance is thus attainable [77]. This applies to R1 as well as R2 situations. If repeatedly recurring metastases cannot be managed surgically any longer, other treatment modalities should be taken into consideration, such as radiation therapy, hyperthermic isolated limb perfusion, cryosurgery, electrochemotherapy, or topical agents. The decision also depends on concomitant diseases and the general condition of the patient.

Striving for R0 resection, complete removal of regional lymph nodes (lymph node dissection) shall be performed in case of regional lymph node metastasis. If residual tumor is present (R1/R2), re-dissection should be undertaken. Additional radiation therapy should be considered (reference: Work Group Adjuvant Therapy) for an R1 resection following adequately performed lymph node dissection. In case of local inoperability, further treatment should be individually tailored upon deliberation at an interdisciplinary tumor conference and in agreement with the patient.

Distant metastases

R0 resection should be sought in a potentially curable situation.

Depending on overall extent of the disease as well as systemic and other treatment options, an individual approach is to be chosen for R1 and R2 residual tumors after surgical resection of distant metastases (stage IV) [78–83]. In a palliative situation, a decision should be made upon deliberation at an interdisciplinary tumor conference and in agreement with the patient.

3.2.4 Radiation therapy of the primary tumor

3.2.4.a	Evidence-based recommendation
Grade of recommendation B	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.
Level of Evidence 4	Systematic search of the literature de-novo: [84–86]
	Strength of consensus: 96 %

3.2.4.b	Evidence-based recommendation
Grade of recommendation 0	In inoperable primary tumors with R1- or R2-resection, radiotherapy with the goal of local control may be employed.
Level of Evidence 4	Systematic search of the literature *de-novo:* [87–89]
	Strength of consensus: 100 %

3.2.4.c	Evidence-based recommendation
Grade of recommendation B	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.
Level of Evidence 3b	Systematic search of the literature *de-novo:* [90–92]
	Strength of consensus: 92 %

D. Vordermark

Available data on definitive radiation therapy for primary tumors predominantly refers to lentigo maligna melanomas and comprises case series from qualified centers over a long time period [84–86]. For lentigo maligna melanomas, various hypofractionated regimens (typical doses of 7 × 6 Gy, 10 × 4.5 Gy to 10 × 10 Gy) with very low energy from the grenz ray, soft ray, and orthovolt range (15–175 kV) have been employed. The highest reported doses come from regimens with the lowest energy (ergo the lowest penetration). Target area was the clinically visible extent plus a lateral margin of roughly 1 cm. In some cases, nodular parts were removed prior to irradiation. Long-term resolution of lentigo maligna melanoma after radiation therapy without recurrence was achieved in 85 % to 95 %. There are no larger studies with regard to primary radiation therapy of inoperable melanomas of other types. It is safe to assume that respective results are comparable to studies on palliative radiation therapy for metastases and that an objective response can be achieved in the majority of cases, in some cases even complete resolution [93]. Data on postoperative radiation therapy of primary tumors is available for desmoplastic melanoma in particular, as the risk for local recurrence is especially high in this type. Following primary resection or re-resection of desmoplastic melanomas, postoperative radiation therapy with median 48 to 50 Gy was performed in smaller case series [90, 91]. Irradiated patients predominantly showed narrow excision margins (< 1 cm) or an R1/R2 situation. Long-term local tumor control was accomplished in 91 % to 100 %. In a cohort study comparing two subgroups of patients with desmoplastic melanomas without and with postoperative radiation therapy (primarily 48–50 Gy), the irradiated group displayed significantly poorer prognostic factors (positive margins or ≤ 1 mm in 5 % vs. 49 %, Breslow > 4 mm in 82 % vs. 41 %, Clark-Level V in 89 % vs. 52 %) [94]. Local recurrence rates were 6 % in the surgery-only group and 7 % in the negatively selected group receiving surgery followed by adjuvant radiation therapy. One group with desmoplastic melanoma, exclusively treated with wide excision (margins > 1 cm) without radiation therapy, showed local recurrence rates of only 4 % [95].

In summary, present data indicates that postoperative radiation therapy for desmoplastic melanoma, a tumor with frequent local recurrence, is not required in cases with sufficiently wide surgical margins (> 1 cm). However, it very likely ensures local tumor control in cases with narrower margins or even R1 or R2 resection.

There is hardly any data on the role of postoperative radiation therapy of primary tumors of other melanoma types. Some studies deal with postoperative radiation therapy of cutaneous melanomas, primarily of the head/neck region, but are not conclusive due to lacking information about patient characteristics and local tumor control [88, 89]. Locoregional control rates after 5 years were 87 % in a case series of 79 patients with cutaneous melanoma in the head/neck region. Because of tumor thickness (> 1.5 mm or Clark level ≥ IV), these patients were treated with hypofractionated radiation therapy (30 Gy in fractions of 6 Gy each), following wide excision (margins 2–4 cm) [87]. However, due to the dominance of distant metastasis, radiation therapy is not believed to have a potential impact on survival rates.

If there is an indication for primary or postoperative radiation therapy of non-lentigo maligna melanomas with intent to cure, it should be conducted using 50–70 Gy in conventional fractionation (5 × 1.8–2.5 Gy/week) with an overlapping margin of approximately 2 cm. In a palliative setting, primary tumor regions may be irradiated using shorter regimens with higher single doses.

3.2.5 Histopathologic examination of the primary tumor

3.2.5	Consensus-based recommendation
GCP	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.
	Strength of consensus: 100 %

C. Rose

The correct diagnosis of melanoma including clinicopathologic correlation is the most important feature of a histopathology report. The most prominent and crucial histopathologic criteria leading to the diagnosis shall be described. In special situations, e.g. marked discrepancy between suspected clinical diagnosis and the histologic diagnosis of melanoma, unusual patient age, or development within a scar, feedback shall be given to the clinician and noted in the pathology report.

The WHO classification clinically and histologically differentiates four types of melanoma (lentigo maligna melanoma, superficial spreading melanoma, nodular melanoma, and acral lentiginous melanoma). The location of melanoma on the integument is relevant with regard to determining tumor type and localizing regional lymph nodes. Rare histologic variants include Spitzoid melanoma (melanoma resembling Spitz nevus), nevoid melanoma, desmoplastic as well as neurotropic melanoma. Perineural invasion is documented by means of the Pn classification. Melanomas may arise in association with congenital or acquired melanocytic nevi. Melanomas developing within a blue nevus are a rarity [96]. Clinical melanoma types have been increasingly associated with molecular changes.

Classification of the primary tumor according to TMN is of paramount significance with respect to further diagnostic and therapeutic approach. The 2009 AJCC melanoma classification comprises determination of Breslow tumor thickness (measured from underneath the stratum corneum to the deepest tumor cell), ulceration of the primary tumor (interruption of the epidermis by melanoma growth), and mitotic rate [17]. Unlike the previous version, Clark level determination is no longer relevant for classification.

Detection of mitoses in thin melanomas (tumor thickness below 1 mm) results in distinction between pT1a and pT1b. Retrospective analyses have revealed a less favorable prognosis for thin melanomas up to 1 mm, if mitoses were detected. A German study group has proposed detailed recommendations regarding determination of the mitotic rate [97]. Determination of the mitotic rate is accomplished on H&E sections with an area of 1 mm², or less in thin melanomas, being sufficient for evaluation. Only mitoses unequivocally located within the corium are considered and given in whole numbers [98].

Both lateral and deep margins shall be examined for the absence respectively presence of melanoma clusters (residual tumor (R) classification).

When determining tumor thickness (Breslow), associated parts of a melanocytic nevus are not taken into account, however, in some cases it may be difficult to clearly distinguish between nevus and melanoma parts. The pathology report should explicitly state how tumor thickness in a nevus-associated melanoma was established.

Melanoma may be associated with clinical and histologic regression, which should be delineated in the pathology report. Areas of regression are morphologically characterized by lymphocytic inflammation with melanophages, marked fibrosis and loss of normal rete ridge pattern [99]. Single cell proliferation of atypical melanocytes along the dermoepidermal junction may still be discernible. Although the prognostic relevance has not been reliably resolved, extensive areas of regression appear to entail a deterioration in prognosis [100].

Venous (V classification) or lymphatic (lymphangiosis melanomatosa) (L classification) invasion is rarely seen in primary tumors. Vascular invasion is associated with poorer prognosis and should be mentioned in the pathology report [101]. Micrometastases and in-transit metastases found at primary excision are taken into account in the TMN classification (N status).

If immunohistologic studies are employed in the melanocytic differentiation of a malignant tumor (e.g. S100B protein, HMB45, Melan A), the respective findings shall be relayed.

3.2.6 Initial staging workup up to stage IIB

Apart from whole-body examination comprising the complete inspection of the integument including adjacent and visible mucous membranes as well as the palpation of lymphatic drainage areas and lymph node basins, the following procedures are recommended (Table 5).

Table 5 Overview of procedural recommendations in the initial staging workup for melanoma patients up to and including stage IIB.

Procedure	Recommendations on staging workup in asymptomatic patients at 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 sonography	No	B	2b
Lymph node sonography	Yes (stage IB and above)	A	1a
Skeletal scintigraphy	No	A	3b
Tumor marker S100B	Yes (stage IB and above)	0	1a
Tumor marker LDH	No	B	2b
Strength of consensus: 95 %			
*PET/CT, CT, MRT (respectively whole body)			

3.2.6.1 Initial staging workup – whole-body CT

3.2.6.1	Evidence-based recommendation
Grade of recommendation A	Whole-body CT shall not be performed as standard in asymptomatic patients with the primary diagnosis of melanoma.
Level of Evidence 1a	Systematic search of the literature *de-novo:* [102–105]
	Strength of consensus: 83 %

H.-P. Schlemmer

Staging workup recommendations apply to melanoma patients up to and including stage IIB. Based on current data, a general recommendation for imaging procedures cannot be issued at these tumor stages. Published data, primarily based on studies with inhomogenous patient groups [102, 105], has shown that additional CT imaging is not indicated in the absence of symptoms. A particular problem is the not clearly quantifiable rate of false negative and false positive findings. Sawyer et al. [102] have pointed to negative ramifications caused by the large number of false positive findings in additional imaging procedures. A meta-analysis by Xing et al. has revealed that the sensitivity for CT in the detection of lymph node metastases as well as distant metastases is only roughly 60 %. The positive predictive value is thus too low to render a clinical indication for CT imaging useful [104].

A particular problem is the not clearly quantifiable rate of false negative and false positive findings. Of particular significance is the notably limited validity as to the detection of small lymph node metastases (< 1 cm) as well as the characterization of small, unspecific lung lesions (< 1 cm). The sensitivity for CT is furthermore dependent on the type of machine and the examination technique used. Whole-body CT may aid in early detection of distant metastases and may therefore be useful for at-risk patients and depending on the clinical situation. Independence from patients and examiners as well as the feasibility to do a whole-body scan in one session (CT of head, neck, thorax, abdomen, pelvis) represent advantages over sonography. However, it is important to note that MRI is distinctly superior to CT when examining the neural axis. One of the downsides to CT is radiation exposure, which dependent on examination protocol amounts to approximately 10–20 mSv. Thus, frequent follow-up exams result in significantly high exposure.

3.2.6.2 Initial staging workup – cranial MRI

3.2.6.2	Evidence-based recommendation
Grade of recommendation A	Cranial MRI shall not be performed as standard in asymptomatic patients with the primary diagnosis of melanoma.
Level of Evidence 3b–	Systematic search of the literature *de-novo:* [106, 107]
	Strength of consensus: 96 %

H.-P. Schlemmer

With respect to detection of cerebral metastases, MRI is more sensitive than CT and FDG-PET/CT. Nevertheless, a general recommendation cannot be issued based on published trials, as there is no valid data concerning detection rate and therapeutic relevance in asymptomatic patients at primary diagnosis of melanoma up to stage IIB. Currently published data refers to studies with inhomogenous patient groups and low evidence levels (3b–). These studies show no benefit for cranial imaging in patients at low risk for metastasis. A particular problem is the not clearly quantifiable rate of false negative findings. The sensitivity for MRI furthermore depends on the employed type of machine and field strength as well as on he applied examination technique. The absence of radiation is an advantage. Overall, its routine use cannot be recommended.

3.2.6.3 Initial staging workup – chest X-ray

3.2.6.3	Evidence-based recommendation
Grade of recommendation A	Chest X-ray shall not be performed as standard in asymptomatic patients with the primary diagnosis of melanoma.
Level of Evidence 2b	Systematic search of the literature *de-novo:* [105, 108–112]
	Strength of consensus: 92 %

H.-P. Schlemmer

Chest X-ray is markedly inferior to CT in the detection of pulmonary metastases. Based on present data, a general recommendation for its use cannot be issued. Published data refers to studies with inhomogenous patient groups and low evidence levels (2b at most). A particular problem is the not clearly quantifiable rate of false negative and false positive findings. While false negative findings give rise to a false sense of safety and thus may even delay timely diagnosis, false positive findings entail upsetting follow-up procedures subjecting patients to further unnecessary stress.

3.2.6.4 Initial staging workup – lymph node sonography

3.2.6.4	Evidence-based recommendation
Grade of recommendation A	Locoregional lymph node sonography shall be performed in patients with the primary diagnosis of melanoma of tumor stage IB or higher.
Level of Evidence 1a	Systematic search of the literature *de-novo:* [113]
	Strength of consensus: 96 %

H.-P. Schlemmer, M. Kaatz

Sonographic imaging is based on tissue-specific differences in impedance. The sound waves applied lie beyond the human hearing threshold. Frequencies between 7.5–18 MHz are adequate for evaluation of peripheral lymph nodes. Higher frequencies offer better resolution, but also decreased penetration.

Numerous studies have been conducted evaluating sonography in melanoma patients. The following criteria suggest malignancy: 1: ballooned shape; 2: loss of central echoes; 3: detectable peripheral perfusion [114]. A total of 6 642 patient were included in a meta-analysis by Bafounta et al. [113] comprising 12 trials that assessed the validity of sonography, compared to mere palpation, in the evaluation of lymph node invasion in melanoma patients. Use of sonography resulted in a higher differentiation (odds ratio of 1 755 [95 % CI 726–4 238] versus 21 [95 % CI 4–111]; p = 0.0001) not only at initial staging, but also during follow-up. These findings have been confirmed in subsequent studies.

Applying conventional sonographic criteria, a sensitivity and specificity of roughly 80 % may be attained. Sensitivity and specificity of lymph node sonography observed in clinical trials vary immensely and are stage-dependent. In particular, this method exhibits low sensitivity in the detection of small lymph node metastases. Due to risk differences between stage IA and IB, indication for this procedure is therefore only recommended for stage IB and above. Even though quantification of the exact rate of false negative findings in clinical trials is difficult for methodologic reasons, lymph node sonography has proven to be more sensitive than palpation [113]. The practicability of this method with regard to quality, reproducibility, and costs depends on the area of the body examined. Sonography of superficial areas (e.g. cervical, axillary, inguinal) is simpler compared to abdominal lymph nodes. Lymph node sonography is also employed during melanoma follow-up.

3.2.6.5 Initial staging workup – abdominal sonography

3.2.6.5	Evidence-based recommendation
Grade of recommendation B	Abdominal ultrasound should not be performed as standard in patients with the primary diagnosis of melanoma.
Level of Evidence 2b	Systematic search of the literature *de-novo:* [108, 115–117]
	Strength of consensus: 92 %

H.-P. Schlemmer, M. Kaatz

Currently published data predominantly refers to single case-control studies with low evidence levels (2b at most).

Conventional abdominal sonography may be routinely done, however, it is more patient- and examiner-dependent as well as less sensitive than MRI, CT, and PET/CT. Abdominal sonography may aid in detecting parenchymatous distant metastases and abdominal lymph node metastases. Screening for abdominal (peritoneal and retroperitoneal) lymph node metastases is especially time-consuming. A particular problem is the not clearly quantifiable rate of false negative findings. While false negative findings give rise to a false sense of safety and thus may even delay timely diagnosis, false positive findings entail upsetting follow-up procedures subjecting patients to further unnecessary stress.

3.2.6.6 Initial staging workup – S100B, MIA, LDH

3.2.6.6.a	Evidence-based recommendation
Grade of recommendation 0	S100B may be measured in asymptomatic patients with the primary diagnosis of melanoma.
Level of Evidence 1a	Systematic search of the literature *de-novo:* [118]
	Strength of consensus: 92 %

3.2.6.6.b	Evidence-based recommendation
Level of Evidence 2b–	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.
	Systematic search of the literature *de-novo:* [119–122]
	Strength of consensus: 100 %

3.2.6.6.c	Evidence-based recommendation
Grade of recommendation B	Serum LDH should not be determined in patients with the primary diagnosis of melanoma.
Level of Evidence 2b	Systematic search of the literature *de-novo:* [112]
	Strength of consensus: 86 %

C. Czeschik

The TNM staging system by the AJCC [17] stratifies melanoma patients according to prognostic aspects. Prognostic patient data still varies immensely within the various stages making a more subtle classification, by means of further prognostic factors, desirable. Numerous studies have shown that levels of certain serum markers correlate with disease-free or overall patient survival. A majority of serum markers has been assessed in small retrospective and cross-sectional studies.

S100B

Concerning the prognostic value of serum S100B levels, a meta-analysis of 22 smaller studies with a total of 3 393 patients exists [118]. A majority of included studies show that S100B levels are significantly correlated with patient survival and constitute an independent prognostic factor in multivariate analysis. For patients with stage I to III disease, neither relevant heterogeneity of the studies nor publication bias were demonstrated. However, stage I and II patients were separately evaluated in only two of the included studies. One of these studies with 596 patients revealed no significant correlation between S100B levels and survival. The other study with only 67 patients did show such a correlation. Current trial results are therefore insufficient to recommend routine measurement of S100B as standard in asymptomatic patients at primary diagnosis of melanoma. As this is a scarcely invasive procedure, whose benefit has been unambiguously shown for higher tumor stages, measurement of S100B may be performed optionally.

MIA

Measurement of the melanoma inhibitory activity (MIA) protein is currently not a standard diagnostic procedure in melanoma patients. In a study of 112 melanoma patients [119], 350 clinically tumor-free patients after surgical removal of melanoma as well as 72 healthy control subjects and 316 control subjects with other diseases, MIA levels were elevated in all 50 stage III and IV melanoma patients (> 95. percentile of healthy controls = 6.5 ng/ml), but only in 13 % at stage I and 23 % at stage II. MIA levels, however, did not correlate with tumor thickness. Of the 350 patients status post melanoma resection, 32 exhibited elevated MIA levels. In 15 of those patients, metastases were simultaneously detected during clinical examination, in one patient 6 months after the lab test.

A study of 296 clinically tumor-free stage II and III patients [120] demonstrated that elevated MIA levels (> 95. percentile of 120 healthy control subjects = 10.49 ng/ml) showed a sensitivity of 0.22 with respect to recurrence (worse than S100B, but better than AP and LDH). However, at 0.97 it had the highest specificity of all parameters examined. In this study, the recurrence-free interval for patients with normal levels of S100B as well as MIA was significantly longer than the recurrence-free interval for patients with respectively pathologic levels.

A larger study of 1 079 stage I and II patients [121] evaluated different cutoff values for MIA. A value of 12.0 ng/ml yielded a sensitivity and specificity of 67.6 % respectively 76.9 % at stage I and of 65.6 % respectively 66.7 % at stage II. There was an increased rate of false positive findings in older women as well as men with large tumor thickness. The authors attributed this to the secretion of MIA by activated

chondrocytes, e.g. in various forms of arthritis, or to the secretion by circulating tumor cells in thicker tumors.

Smaller studies on MIA show a sensitivity and specificity similar to S100B [122, 123] (a distinctly poorer specificity for MIA [124]). Moreover, a drop in MIA levels has been observed following successful tumor resection or response to chemotherapy [125, 126]. With regard to the issue, whether MIA levels are negatively correlated with survival time, available studies yield inconsistent results (no correlation in Garbe et al. [120]; Tas et al. [127]; correlation in Juergensen et al. [128], Garnier et al. [129], Meral et al. [126]).

LDH

The current version of the AJCC classification [17] acknowledges the role of elevated serum lactate dehydrogenase (LDH) levels as independent prognostic factor for poorer survival rates in stage IV disease (1- and 2-year survival rates with normal LDH 65 % and 40 % as opposed to 32 % and 18 % with elevated LDH, $p < 0.0001$). However, in asymptomatic patients, serum LDH has no prognostic validity at primary diagnosis of melanoma [112].

3.2.6.7 Initial staging workup – PET/CT

3.2.6.7	Evidence-based recommendation
Grade of recommendation A	PET and PET/CT shall not be performed routinely as initial staging procedures up to stage IIA/IIB.
Level of Evidence 1a	Systematic search of the literature *de-novo:* [104, 105, 130]
	Strength of consensus: 100 %

S. Reske

Functional imaging using PET and PET/CT is able to sensitively detect melanoma lesions due to a distinctly increased uptake of the glucose analog 2-F-18-fluorodeoxyglucose (FDG) as a result of upregulated glucose consumption. Fusion of PET and CT images facilitates morphologic detection of lesions picked up by PET, thus giving rise to markedly enhanced diagnostic validity [104]. At present, numerous other melanoma-sensitive tracers are under – mostly preclinical – evaluation and will herein not be dealt with [131]. PET and PET/CT have undergone rapid technological developments. Compared with PET alone, PET/CT enables exact anatomic localization of lesions and thus merges the advantages of high-resolution morphologic imaging with sensitive, metabolism-based disease detection. It currently represents the state of the art in PET-based imaging.

High-quality studies have shown that the diagnostic significance of PET and PET/CT in melanoma differs depending on tumor stage [104, 132, 133].

In the course of initial staging up to stage IIB, the sensitivity of PET and PET/CT for the detection of clinically occult locoregional lymph node metastases is low and clearly inferior to sentinel lymph node scintigraphy with subsequent lymph node dissection [104, 105, 130, 132, 134–139]. PET or PET/CT with fluorodeoxyglucose (FDG) should not be performed for the detection and/or localization of locoregional lymph node metastasis.

The prevalence of distant metastasis up to stage IIB is very low. In a current meta-analysis, Xing et al. suggest a 5-year recurrence rate of 5 % in low-risk patients [104]. Recurrence of lymph node or distant metastases has been observed in 5–11 % of patients with stage IIA or IIB disease within approximately 0.5 to 1 year after primary diagnosis [105, 130]. PET/CT findings in these patients were almost always negative during initial staging [105, 130]. The authors cited inability to detect micrometastases and/or circulating tumor cells as explanation for negative findings in PET/CT and conventional imaging [105, 130]. Moreover, there was a relatively high rate of ambiguous or false positive findings in all imaging modalities under scrutiny, including PET and PET/CT [104, 105, 130]. PET and PET/CT shall not be routinely performed as initial staging procedures up to stage IIB. On the other hand, patients with stage IIC disease exhibit considerably higher recurrence rates compared with stage IIA or IIB patients and shall therefore undergo the same diagnostic procedures as patients with stage III disease (ref. chapter 3.4.1).

3.2.6.8 Initial staging workup – skeletal scintigraphy

3.2.6.8	Evidence-based recommendation
Grade of recommendation A	Skeletal scintigraphy shall not be performed as standard in the initial staging workup in patients up to stage IIA/IIB.
Level of Evidence 3b	Systematic search of the literature *de-novo:* [109, 115, 140–142]
	Strength of consensus: 100 %

S. Reske

The diagnostic value of skeletal scintigraphy in the evaluation of skeletal metastasis in melanoma has only been investigated in older, methodologically insufficient studies. More recent developments in scintigraphic skeletal workup such as SPECT/CT or PET and PET/CT using the bone-sensitive tracer F-18-fluoride have not been systematically examined and can therefore not be assessed at present.

Considering the high validity of PET/CT even for the detection of skeletal metastasis, skeletal scintigraphy should only be employed in special cases when clinically indicated.

SPECT/CT

When compared to planar scintigraphy, SPECT/CT imaging for sentinel lymph node (SLN) detection provides the advantage of exact CT-based localization of lesions. One study has also demonstrated an increase in sensitivity of roughly 10 % compared to planar sentinel lymph node scintigraphy [143]. Due to limited data, a recommendation can presently not be issued.

3.2.7 Sentinel lymph node biopsy

3.2.7.1 Indications for sentinel lymph node biopsy

3.2.7.1.a	Evidence-based recommendation
Grade of recommendation 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.
Level of Evidence 1a	Systematic search of the literature *de-novo:* [144–150]
	Strength of consensus: 86 %

3.2.7.1.b	Evidence-based recommendation
Grade of recommendation 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 mitotic rate and/or younger age (<40 years).
Level of Evidence 1a	Systematic search of the literature *de-novo:* [144–150]
	Strength of consensus: 100 %

R. Gutzmer

The indication for sentinel lymph node biopsy (SLNB) is determined by parameters of the primary tumor and patient characteristics. Unequivocal indication parameters based on studies do not exist.

When considering the indication, it has to be noted that, according to current scientific knowledge, SLNB is primarily a diagnostic means for the determination of stage, prognosis, and adjuvant therapy. SLNB potentially followed by subsequent completion lymph node dissection results in reduced recurrence rates in regional lymph nodes [147, 149]. A large multicenter, prospective trial (Multicenter Selective Lymphadenectomy Trial MSLT-1) compared patients with a primary tumor thickness of 1.2–3.5 mm who had either undergone SLNB at the time of diagnosis or just clinical follow-up [147]. The third interim analysis of this trial has revealed that patients with SLNB experienced significantly fewer recurrences in regional lymph nodes, but showed no benefit with regard to overall survival. Conclusive analysis of this study with longer follow-up intervals is still pending. Retrospective analyses have not only shown fewer metastases in regional lymph nodes, but also overall survival benefits in patients treated with SLNB [151, 152].

When considering the indication for SLNB, the potential gain in information with respect to staging, prognosis, and potential adjuvant therapy as well as improved tumor control in regional lymph nodes has to be weighed against the risk of an invasive procedure.

SLNB is a surgical procedure frequently performed under local anesthesia. Complications arise in about 10 % of patients and include seromas, hematomas, wound infections, and, in rare cases, functional deficits and nerve lesions [153–155].

The most important parameter for the indication for SLNB is tumor thickness. In this context, a limit of ≥ 1 mm for the indication for SLNB is often cited. However, the risk for a positive sentinel lymph node rises continuously with increasing thickness of the primary tumor [146, 148, 156, 157]. In a meta-analysis of 34 studies, a tumor thickness of < 1 mm was associated with a positive sentinel lymph node in 5.6 % of patients, with values ranging from 0–14.3 % [150]. This large spread may likely be explained by the diversity of patient groups involved. In particular, younger patients < 40 years with a tumor thickness of 0.75–1 mm frequently (19.5 %) showed a positive sentinel lymph node [158]. 159/632 patients (25.2 %) with a tumor thickness between 1 and 4 mm displayed a positive sentinel lymph node [144], and even within subgroups of this 1–4 mm range, the rate in positive sentinel lymph nodes increased with rising tumor thickness. Between 1–1.59 mm, 66/762 patients were positive (8.7 %) and between 1.6–2 mm 67/348 patients (19.3 %) [145].

Tumor thickness > 4 mm resulted in a positive SLN in 43/75 patients (57.3 %, [144]), respectively 74/152 (48.5 %) [159] and 100/240 (41.7 %) [160].

In any primary tumor thickness, sentinel lymph node positivity is always associated with poorer prognosis, especially in tumors > 4 mm [159, 160].

Besides tumor thickness, ulceration of the primary tumor plays a crucial role. In the presence of primary tumor ulceration, the sentinel lymph node was significantly more often positive than in the absence of ulceration [144, 146, 148, 157].

A higher mitotic rate correlates with sentinel lymph node positivity and the risk for nodal recurrence.

Detection of tumor cells in peritumoral lymph vessels (lymphangiosis melanoblastomatosa) around the primary melanoma also correlates with an increased rate of positive sentinel lymph nodes [161–164].

Regression of the primary tumor either has not been correlated with sentinel lymph node positivity [144, 165, 166] or it has been correlated with lower sentinel lymph node positivity [148, 167]. Primary tumor location plays no role in the indication for SLNB. In cutaneous melanoma, SLNB is usually performed in the head/neck region as well as on the trunk and the extremities [144].

Previous removal of the primary tumor with surgical margins does not constitute a contraindication for SLNB, as similar detection rates have been reported [168]. However, the rate of false negative sentinel lymph nodes following wider excisions and wound closure with a flap may be elevated [168, 169].

Age significantly correlates with sentinel lymph node positivity. Younger patients more frequently show a positive sentinel lymph node, especially those with thin tumors < 1 mm [146, 158, 164].

3.2.7.2 Methods for detection of the sentinel lymph node

3.2.7.2	Consensus-based recommendation
GCP	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.
	Strength of consensus: 100 %

C. Löser, R. Gutzmer

Nowadays, there is a well-documented consensus on preoperative localization and intraoperative detection of sentinel lymph nodes in melanoma [170–174]. The corresponding procedure is delineated below, complementary procedures are mentioned.

The first step in localizing sentinel lymph nodes is mapping of the lymphatic drainage pathways through lymphoscintigraphy using mutually complementary dynamic and static procedures. By definition, a sentinel lymph node is the first lymph node within the lymphatic drainage area with an afferent (detectable) lymphatic pathway. During the initial dynamic stage of lymphoscintigraphy, the course of the efferent lymphatic pathways is therefore traced with a gamma camera following injection of a radioactive tracer substance around the excision site or in proximity to the scar. The injection is performed strictly intracutaneously. In Europe, the tracer substance used is technetium-labeled nanocolloid (99mTc) with a particle size of 0.05–0.8 µm. As soon as the contrast medium has accumulated within the sentinel lymph node, its position can be determined by static imaging in two planes and marked on the skin using a pen. The imaginary intersection of the sagittal and transversal projection originating from the skin marking determines the position of the sentinel lymph node inside the patient's body. It facilitates the surgeon's assessment of the depth of the sentinel lymph node and its localization with respect to other structures that possibly need to be spared.

More than 98 % of sentinel lymph nodes may be identified by lymphoscintigraphy [175]. Detection may be hampered, if the sentinel lymph node is located in immediate proximity to the tumor. Usually, sentinel lymph node detection and extirpation is implemented first. Only then, re-excision to warrant sufficient surgical margins is performed, in order to be able to repeat tracer application in case of technical problems. In cases of pronounced proximity between sentinel lymph node and tumor, deviation from the aforementioned sequence is possible to enhance detection by gamma probe.

Identification of the sentinel lymph node by gamma probe is frequently complicated, if there is a close proximity of primary tumor and sentinel lymph node (as is commonly the case in the head/neck region). Static single-photon-emission-computed tomography/ computed tomography (SPECT/CT) combines high-resolution CT-images with functional gamma camera imaging and thus facilitates exact anatomic localization of sentinel lymph nodes [176, 177]. Intraoperative use of a gamma camera instead of a gamma probe may also be helpful in such cases [178, 179]. If available, these procedures may be used complementarily.

In lymphoscintigraphy, one-day and two-day protocols are applied [171]. Superiority of either option has not been shown so far. Depending on protocol, extirpation of sentinel lymph nodes is conducted a few hours or a day after localization by lymphoscintigraphy. Preoperatively, the sentinel lymph node location is percutaneously verified by acoustic and optical gamma probe signals. Intraoperative use of the gamma probe in combination with careful manual palpation leads to detection of the sentinel lymph node. The tracer substance frequently accumulates in more than one lymph node. Every labeled lymph node counts as sentinel lymph node, is removed, and histologically examined.

3-D navigation devices that display the location of the sentinel lymph node three-dimensionally on a screen are currently being tested [180]. The traceability of the sentinel lymph node may be enhanced by immediately preoperative injection of a lymph vessel permeating dye (Patent Blue V) at the tumor site, thus exposing lymphatic pathways and dyeing the sentinel lymph node blue [181, 182]. The use of blue dye has been viewed critically by some centers because of the risk for anaphylactic reactions, a permanent tattoo, and the painfulness of the injection [183].

The aforementioned procedure for preoperative localization and intraoperative detection of sentinel lymph nodes by lymphoscintigraphy and gamma probe may also be

conducted in pregnancy [171]. However, the complementary use of a lymph vessel permeating dye is contraindicated in pregnancy. For nursing mothers, a 24-hour nursing interval shall be observed, as the radioactive tracer is excreted into breast milk [184].

Prior to sentinel lymph node extirpation, lymph node sonography should be performed. On the one hand, this helps determine whether changes are benign or malignant, on the other hand the tracer may possibly not accumulate in malignant sentinel lymph nodes, which may then only be localized sonographically.

3.2.7.3 Evaluation and technical processing of sentinel lymph nodes

3.2.7.3	Consensus-based recommendation
GCP	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.
	Strength of consensus: 100 %

R. Gutzmer

Various protocols have been proposed allowing for extensive processing of the sentinel lymph node, in order to detect small metastases [172, 185–188].

With regard to sections and blocks, these protocols provide for the following:

The sentinel lymph node was laminated into slices roughly 2 mm thick, each of which was embedded into a block, of which 4–12 sections were respectively examined [189–191].

Alternatively, the sentinel lymph node was halved through the hilus in the longitudinal axis, embedded with the cut surface facing downward, and then sectioned in various ways (GL France). In the first method, the entire block was used up by taking sectional planes 50–150 µm apart from each other, cutting them in 3 sectional planes respectively and applying H&E staining and immunohistochemistry. In a second method, 10 sections each 4 µm thick were alternately stained with H&E or immunohistochemistry [172]. In a third method, now adopted by the EORTC [186, 192], 20 sections spread over 6 sectional planes of 50, 100, 150, 200 and 250 µm were alternately stained with H&E and immunohistochemistry.

Consensus recommendations provide for examination of at least 4 sections per lymph node half as minimum requirement. This number may be lower in very small sentinel LN [97].

Staining should be done by means of hematoxylin and eosin (H&E) as well as immunohistochemical staining, the most common markers being HMB45, S100B and MelanA/MART-1. A combination of these markers may also be used. In a comparative study, two protocols (lamination and halving according to EORTC recommendations) were equivalent in detecting melanoma metastases in the sentinel lymph node [189]. Using these protocols, various studies have shown 25–30 % of melanoma patients with a primary tumor > 1 mm to be positive [189–196].

Due to low sensitivity, intraoperative quick sectioning by cryostat has not become established (French guidelines, [197]). Molecular detection of melanoma cells within the sentinel lymph node by polymerase chain reaction (PCR) has been evaluated in various studies using different markers [198–202]. Especially due to its low specificity and lack of distinction between melanoma cells and melanocytic nevus cells in the sentinel lymph node [203], this method has not become established outside clinical trials.

3.2.7.4 Histological report of the sentinel lymph node

3.2.7.4	Consensus-based recommendation
GCP	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
	Strength of consensus: 100 %

R. Gutzmer

In the course of the histopathologic evaluation, melanoma cells have to be differentiated from melanocytic nevus cells. The latter are defined as cytologically inconspicuous melanocytic cells in the capsule or trabeculae of the lymph node [19, 203].

If melanoma cells are detected in the sentinel lymph node, there is so far no clear definition about which parameters of tumor load or tumor cell distribution within the lymph node have to be specified in the histology report. However, some parameters are looming, which have prognostic relevance or may be able to predict involvement of further, non-sentinel lymph nodes in the affected basin. In particular, they include length of the largest melanoma cell cluster [193, 196, 204, 205], maximum depth of melanoma cell penetration from the lymph node capsule into the lymph node parenchyma [191, 193, 195], infiltration of the lymph node capsule [190, 193], lymphangiosis, i.e. accumulation of tumor cells within lymph vessels outside the sentinel lymph node [204–206], and location of melanoma cells inside the lymph node, e.g. subcapsular versus parenchymal [207]. In one study, the specification of quantitative parameters (diameter largest

tumor cell cluster, depth of penetration) by various histopathologists corresponded very well, whereas matching of qualitative parameters was insufficient [208].

At present, it is unclear which parameters inside the sentinel LN best predict prognosis and positivity of further, non-sentinel lymph nodes. Further comparative studies with sufficiently long follow-up intervals are necessary [19, 193]. Based on current data, specification of the following parameters in the report are recommended:

1. largest diameter of the largest tumor cell cluster in tenths of millimeters,
2. maximum depth of melanoma cell penetration from the inner side of the lymph node capsule into the lymph node parenchyma,
3. invasion of melanoma cells into the lymph node capsule or capsular rupture,
4. location of melanoma cells in perinodal lymph vessels (lymphangiosis), as this increases the likelihood for further lymph node involvement.

3.2.7.5 Tumor burden in the sentinel lymph node

3.2.7.5	Evidence-based statement
Level of Evidence 2b	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.
	Systematic search of the literature *de-novo:* [17, 193, 209, 210]
	Strength of consensus: 100 %

R. Gutzmer

Sentinel lymph node status (determined as positive or negative) is a significant and statistically independent parameter for the prognosis of melanoma patients [17, 209]. Various studies have been able to demonstrate a correlation between tumor load or tumor cell location in the lymph node parenchyma and prognosis. Different parameters have been described. Among them are:

1. number of involved sentinel lymph nodes [17, 209],
2. maximum diameter of the metastasis [190, 193, 196, 204, 211–213],
3. "area" occupied by the metastasis in the histologic section (absolute or relative to the cross-sectional area of the lymph node) [190, 205, 212, 214],
4. presence of isolated melanoma cells versus cell clusters [215],
5. maximum depth of melanoma cell penetration from the lymph node capsule into the lymph node parenchyma [191, 193, 195, 210],
6. infiltration of the lymph node capsule [190, 193] or capsular rupture with tumor cells present outside the lymph node capsule [211],
7. relative location of tumor cells within anatomic structures of the lymph node parenchyma [207],
8. lymphangiosis, i.e. the accumulation of tumor cells in lymph vessels outside the sentinel lymph node [204–206].

Current data suggests that a combination of various parameters of tumor load and location of the micrometastasis provides the best prognostic prediction. It is becoming increasingly evident that several statistically independent prognostic parameters may be ascertained within the sentinel lymph node.

One study demonstrated the independent significance of the following three parameters: length of the largest tumor cell cluster (limit value 0.1 mm); depth of penetration of melanoma cells into the lymph node parenchyma (limit value 2 mm); infiltration of the sentinel lymph node capsule (present/not present) [193]. Besides the length of the largest tumor cluster (limit value 0.1 mm), another study revealed the anatomic location according to Dewar as prognostic factor [213].

Available data is problematic due to the retrospective nature of the studies and the relatively short follow-up of 2–4 years. Further comparative studies with a prospective design and longer follow-up intervals are required to make a conclusive assessment.

3.3 Information and communication

3.3.1 The physician's patient briefing

3.3.1	Consensus-based recommendation
GCP	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.
	Strength of consensus: 96%

A. Werner

The patient briefing is one of the physician's pivotal tasks and a critical component of physician-patient communication. It facilitates trust building and active cooperation between physician and patient [216]. Experience has shown that there is a strong desire for information on the part of patients [217]. Informing patients is generally not done in a single conversation, but rather spans the entire scope of the treatment process. Successful conveyance of information has beneficial effects on e.g. compliance, tolerance of adverse events, and overall therapeutic satisfaction [218, 219].

Surveys among cancer patients have consistently revealed deficits with respect to their need for information. It is among the most important and most common unmet needs of cancer patients of all tumor types and stages [220–222].

Studies have demonstrated favorable effects of an adequate information sharing process on coping, improved psychological condition, and higher quality of life [223–227].

Professional communication skills of physicians ensure adequate and comprehensible conveyance of information oriented towards the patient's respective needs [225, 228, 229].

It is crucial that the information given is oriented towards the patient's current desire for information. Patients shall be encouraged to communicate to the physician their current need for information, which information is presently important to them, how comprehensive and how detailed it shall be. Furthermore, the patients' individual preference concerning shared decision making has to be clarified (e.g. regarding tumor treatment) and taken into account [230, 231].

Therapeutic options including possible alternatives should be conveyed in a clear and understandable fashion. This should include realistic information about efficacy and potentially unfavorable effects on various aspects of life. Adequate preparation for the consequences of surgery with regard to functional deficits is of particular significance in this context [232–234]. Further counseling by specialized nursing or psychosocially skilled personnel contribute to better understanding and enhanced memorization of received information.

Personal conversations are to be complemented by other means of information (brochures etc.).

Over the entire course of disease and treatment, patients shall have access – oriented towards respective needs – to information. Repeated conversations with physicians/counselors facilitate coping and integration and should therefore be included. Whenever possible, relatives and other attachment figures should be involved in the information process.

3.3.2 Contents of the patient briefing

3.3.2	Consensus-based recommendation
GCP	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.
	Strength of consensus: 100 %

M. Weichenthal

In patients with different tumor types, studies have shown that providing patients with comprehensive information about their disease may result in improved coping and reduced psychological stress [235, 236].

Patients have the legally binding and constitutionally documented right to comprehensive and adequate information. This is reflected in the medical code of ethics and in various legal norms, e.g. the Medicinal Products Act.

Access to pertinent medical facts is helpful and necessary for comprehension and acceptance of therapeutic and follow-up measures. The quality of communication with the patient constitutes the basis for long-term trustful and active cooperation between physician and patient [237, 238].

Information given to the patient about the diagnosis "malignant melanoma" should therefore facilitate understanding of the problematic nature of potentially metastasizing cancerous diseases and associated ramifications. Intensity and scope of the information should take disease stage and individual prognosis into account [239–241].

In most cases, it is beneficial to involve persons close to the patient, e.g. spouse, in important informative discussions. Studies have shown that patient age has a significant impact on manner and scope of requested and perceived information. This has to be appropriately taken into consideration during informative discussions [241–249].

Using current literature, the "European Organization for Research and Treatment of Cancer (EORTC)" study group on quality of life in cancer patients has put together a catalog of possible contents of information for tumor patients. This catalog serves as a guideline for recommendations on contents of information for melanoma patients [250–252].

List of possible relevant contents of information [250]:

- diagnosis (in general terms)
- diagnosis (exact/detailed description)
- cause of the disease
- extent of the disease

- all available as well as relevant therapeutic options
- prognosis (in general terms)
- prognosis (related to time)
- treatment and nursing facilities
- social facilities, social benefits
- financial support
- paramedical treatment (physical therapy, nursing service, medical cosmetic care etc.)
- alternative treatment methods
- written means of information
- other means of information (DVD, MP3, …)
- information on medical examinations:
  - goal and purpose of examinations
  - procedural information
  - information on findings
- information on treatment:
  - information on therapeutic regimen (number of cycles of radiation therapy or other procedures)
  - information on therapeutic benefit
  - information on adverse events
  - therapeutic effects on disease symptoms
  - therapeutic effects on social and sexual activity
- information, if the cancer is under control or in remission
- management of symptoms (including adverse events)
- things the patient himself/herself may contribute to recovery or well-being
- rehabilitation
- supportive services in the community
- management of disease and adverse events at home
- psychosocial support

General Information

Patients generally have a strong desire to learn about possible causes of their disease. Here, currently accepted concepts regarding the development of cancer in general should be outlined in an understandable fashion [235]. With respect to melanoma, essential endogenous (disposition for melanocytic neoplasms) and exogenous (UV exposure) risk factors should be explained. The patient should moreover be appropriately informed, e.g. also through pertinent brochures, about primary preventive measures, especially sufficient sun protection to prevent secondary tumors [253, 254].

An increased melanoma risk due to a potentially inherited predisposition should be discussed, in order to possibly encourage relatives to undergo primary and/or secondary preventive measures [255].

Stage and prognosis

Patients should receive information that allows for realistic and adequate assessment of the consequences of their disease. This implies explaining individual, prognostic factors [256, 257], which, in the case of melanoma, include depth of penetration and other prognostic parameters of the primary tumor as well as possible lymph node involvement or presence of metastatic disease [17].

Manner and scope of information have to account for the patient's expressed need for information as well as his/her individual educational background and intellectual capacity [258, 259].

For patients wishing to have children, counseling should be given about possible implications in high-risk melanomas or lack thereof in low-risk melanomas [260–262].

Adjuvant therapeutic measures

Depending on disease stage, information should be offered about potential adjuvant therapeutic measures respectively the lack of their necessity or usefulness. As needed, this may include information about alternative or complementary methods [263].

Follow-up exams

Information about manner and scope of follow-up exams requires an understanding on the part of the patient with respect to possibilities and limitations of melanoma follow-up.

Such information therefore includes explanation of diagnostic measures that have sufficient quality to be considered effective in the detection of recurrence, progression, or secondary tumors during follow-up. Potential limitations and disadvantages of recommended methods regarding sensitivity, specificity, or other potential harmful effects should be mentioned. If required, the patient should be informed about methods whose use is currently not recommended due to lack of efficacy. The information given may differ depending on disease stage.

According to present recommendations, self-examination is regarded as crucial a component of follow-up. It is therefore vital to give patients detailed instructions about whole-body inspection as well as palpation of the scar area, in-transit route, and regional lymph nodes. As melanoma patients are at significantly increased risk for secondary cutaneous tumors, they should have access to all relevant information about the detection of early and telltale signs of melanomas and epithelial skin cancers.

Here, brochures and audiovisual media may also be used. If applicable, relatives should be involved in the instruction process [248, 264, 265].

Psychosocial questions

Melanoma patients should be informed about the option to receive psycho-oncologic counseling and care. Manner and scope of this offer should be oriented towards disease stage and individual patient needs. The question, whether there is a general benefit of psychologic care in melanoma patients, cannot be conclusively answered based on current data.

Smaller studies point to a potential benefit of structured short-term intervention [264, 266–268].

Socio-medically, tumor patients are entitled to rehabilitation benefits as well as consideration of their disease within the context of social security and disability laws. Patients should be comprehensively informed about opportunities and ways to claim these socio-medical benefits [269].

3.3.3 Communication with melanoma patients and relatives

3.3.3	Consensus-based recommendation
GCP	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.
	Strength of consensus: 100 %

G. Strittmatter

Communication as interactive process between patient, relatives, and physicians constitutes the foundation for preventive, therapeutic, and coping aspects in the care of patients and their attachment figures.

Good communication between patient and physician respectively treatment team is the basis for a trustful relation, successful information sharing, good compliance, and a vital prerequisite for any therapeutic success [270, 271].

Participatory decision-making as pivotal element of strong patient orientation requires specific communication skills. Studies have shown the positive effect with respect to participation in and quality of decisions, patient satisfaction, and compliance [272].

According to recent data, one third of physicians involved in the care of oncologic patients feel overwhelmed as to their communicative competence. This negatively affects their job satisfaction and psychologic well-being [273, 274]. Formal communication training yields improved communication skills (more open questions, more empathy, more intense exploration of the patient's psychologic state) and greater satisfaction of cancer patients [234, 270, 273–278]. Regardless of the content of a conversation, poor communication entails far-reaching consequences such as permanent stress and insecurity on the part of the patient, whereas good communication by the physician is perceived as helpful in coping and accepting bad news as well as the malignancy in general. Various studies have consistently demonstrated that good communication results in greater satisfaction, less psychosocial stress, enhanced coping, and improved quality of life on the part of patients. [224, 227, 270, 271, 278].

Suboptimal communication has clinically relevant effects for patients: psychologic stress, anxiety, depression, physical discomfort, pain, and adverse events of tumor treatment are insufficiently diagnosed and thus often go untreated [279–282]. Good communication connotes that physician and patient adjust their respective goals, in order to avoid conflicting ideas or bring them to conformity. Therefore, knowledge of the patient's communicative preferences and needs is crucial [270].

A communication rule ("best practice") preferred by patients and recommended in the literature calls for face-to-face, and not over the phone, disclosure of the diagnosis by a familiar physician in a quiet room [283–285].

A physician trusted by patient and relatives should comprehensively convey all vital information. This information should not be given in passing, in the presence of other patients, or on daily rounds. Disclosure of menacing findings should always be done in conjunction with a perspective on how to move forward (clear therapeutic option). When concluding a discussion burdensome to the patient, the opportunity for further conversations should be offered. Every informative conversation should always leave hope. Statements with regard to survival time should not be made. It would be a grave mistake to say: "There is nothing more I can do for you!" [286].

In metastatic disease, communication shall include in particular: explaining innovative treatment strategies, e.g. clinical trials; commenting on information gathered from the internet and other media; discussing the request for "second and further opinions" or unconventional treatments; realistically conveying hopeful options on newly available palliative second- or third-line therapies; comprehensibly delineating the transition from disease-specific to symptom-specific, palliative treatment and, in the terminal phase, constantly evincing empathy and understanding also towards relatives [216].

Melanoma patients are more satisfied with the communication and show less psychologic morbidity (anxiety and depression) despite disclosure of unfavorable findings, if: 1) they are prepared for the potential diagnosis of cancer, 2) the diagnosis is communicated in the presence of desired attachment figures, 3) they receive as much information as requested, 4) the information comes in written form, 5) the information is conveyed comprehensibly, 6) their questions are answered on the same day, 7) their feelings are addressed, and 8) they are encouraged [227, 285].

Melanoma patients exhibit fewer signs of depression, if the word "cancer" is used, the seriousness of the situation, life expectancy, and potential encroachment on life style are addressed and they are encouraged to participate in therapeutic decision-making. The use of clear and unequivocal language in disclosing bad news (recurrence, metastases, treatment failure) may trigger increased anxiety in the short term, but has

a favorable impact on long-term coping. Here, cultural differences have to be taken into account, though [227, 270, 287].

Even at an incurable disease stage, empathic and open communication conveys hope, as it shows realistic ways forward, displays empathy, and respects autonomy. During disease progression, key elements of relationships become more and more significant. Addressing death does not preclude hope for moribund oncologic patients and their relatives. It only puts it into context [216, 288].

In a palliative situation, families with scarce communication, low emotional coherence, and high potential for conflict have been shown to be at high risk and unable to cope with stress. Supportive family therapy is recommended, during which the vulnerable situation of the dying is addressed, the distress of everyone involved is discussed, existential and spiritual questions are taken up, and familial coping resources are strengthened. The ability for open and direct communication also potentially facilitates better coping on the part of the family, after their family member has passed [289–291].

Open communication between patient and relatives can only work, if there is also open communication between patient, family, and physicians. A prerequisite is a functional team of physicians with resolved areas of competence and good communication between physicians and other staff members. If tensions arise between patient, family, and physicians, a discussion should be sought with all involved, in order to protect the patient, relieve the entire family, or "clear the air" between family and physicians. Conflicts have to be addressed directly and openly. Subliminal problems have to be brought to light [291].

Various studies have demonstrated that more than a third of all surveyed patients indicate unfulfilled information and support needs. Patients should be repeatedly informed about support offers and possibly referred to respective services [270, 282, 292].

Internet use for communication purposes has been gaining more and more significance. In Germany and Anglo-Saxon countries, target groups that hardly use other means of information (phone services, support groups) may be reached by internet-based cancer information and online communication (internet platforms, "virtual" support groups, and patient forums) [293].

3.4 Diagnostics and therapy in the event of locoregional metastasis

3.4	Consensus-based recommendation
GCP	Therapy recommendations for patients in stage III or above should be made within the context of interdisciplinary tumor conferences.
	Strength of consensus: 86 %

A. Pflugfelder

Melanoma at the stage of locoregional metastasis (AJCC 2009 stage IIIA, IIIB and IIIC) comprises clinically and prognostically very heterogeneous patient groups. 5-year survival rates range between 23 % and 87 % [209]. Following successful primary excision, the majority of stage III patients develop lymph node or in-transit metastases only over the further course of their disease. Retrospective data points to a better prognosis of these patients vis-à-vis patients with initial stage III disease [294, 295].

In case of regional metastases, the best therapeutic option available should be individually deliberated within the context of an interdisciplinary tumor conference following thorough staging workup. There is generally intent to cure in stage III disease. Successful immunotherapies in particular yield long-term remissions [296].

Since a large part of tumor-free stage III patients is cured and since there has been no evidence for a clear benefit of adjuvant surgical or medical procedures with respect to survival, risks and benefits of adjuvant treatments have to be carefully considered.

3.4.1 Staging diagnostics

3.4.1	Consensus-based recommendation
GCP	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.
	Strength of consensus: 100 %

C. Kochs

According to the 1997 AJCC classification, melanoma patients with a tumor thickness of > 4 mm were grouped in stage III, even without evidence for lymph node metastases.

After the AJCC validation study had revealed ulceration of the primary tumor to be the second most important prognostic factor besides tumor thickness [297], it was introduced into the 2002 AJCC classification. This resulted in further division of tumor stages into sub-stages [297, 298]. According to the current 2009 AJCC classification, stage IIC is defined as tumor thickness > 4 mm and ulceration of the primary tumor (pT4b).

Recurrence rates for patients with stage IIC disease have been reported to be 44.3 % [299], for stage III patients 51 % [300]. Overall, patients with ulcerated melanomas show lower survival rates than those with non-ulcerated melanomas [17]. 5-year survival rates for stage IIC patients was 53 % in a study by Balch et al., whereas survival rates for those with stage III disease were 78 %, 59 % and 40 % at stage IIIA, IIIB and IIIC respectively [17].

Table 6 Overview of recommendations on staging procedures at stage IIC and III.

Procedure	Recommendations on staging workup for patients with suspected locoregional metastasis or evidence thereof**	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 sonography	No	B	2b
Lymph node sonography	Yes	A	1a
Tumor marker S100B	Yes	A	1a
Tumor marker LDH	Yes	0	1b
Strength of consensus: 95 %			
*PET/CT, CT, MRT (whole-body respectively), **Patients at stage IIC and III.			

Apart from whole-body examination comprising inspection of the entire integument including adjacent and visible mucous membranes as well as palpation of lymphatic drainage areas and lymph node basins, the following procedures are recommended (Table 6).

3.4.1.1 Abdominal ultrasound in locoregional metastasis

3.4.1.1	Evidence-based recommendation
Grade of recommendation B	Abdominal ultrasound should not be performed as standard in patients with suspected or proven locoregional metastasis of a melanoma.
Level of Evidence 2b	Systematic search of the literature *de-novo:* [108, 109]
	Strength of consensus: 91 %

H.-P. Schlemmer

Abdominal sonography is a frequently performed procedure in clinical practice. Its practicability with regard to quality, reproducibility, and cost depends on the examiner and the area of the body examined. Technical limitations result from the low depth of sound wave penetration as well as the sound shadow due to abdominal air and osseous structures. Thus, especially intestinal and osseous metastases cannot be detected early. Diagnostic validity studies have been frequently limited by low case numbers, variation of diagnostic standards over time, inconsistent determination of the gold standard, missing histopathologic correlation, and difficult quantifiability of false negative findings. In general, sonography has a low sensitivity for the detection of small metastases.

3.4.1.2 Chest x-ray in locoregional metastasis

3.4.1.2	Evidence-based recommendation
Grade of recommendation B	A chest x-ray should not be performed as standard in patients with suspected or proven locoregional metastasis of a melanoma.
Level of Evidence 2b	Systematic search of the literature *de-novo:* [108, 109, 111]
	Strength of consensus: 96 %

H.-P. Schlemmer

Currently published data refers to studies with inhomogeneous patient groups and low evidence levels (2b–3b). A particular problem is the high rate of false positive findings as well as the not clearly quantifiable rate of false negative findings. Moreover, conventional chest X-ray has been proven to be clearly inferior to CT for the detection of pulmonary metastases. In a retrospective study with 994 patients and 1938 analyzed conventional chest X-ray films of asymptomatic patients, there was no survival benefit in the event of a positive X-ray finding [111].

3.4.1.3 Lymph node sonography in locoregional metastasis

3.4.1.3	Evidence-based recommendation
Grade of recommendation A	Locoregional lymph node sonography shall be performed in patients with suspected or proven locoregional metastasis of a melanoma.
Level of Evidence 1a	Systematic search of the literature *de-novo:* [104, 108, 113]
	Strength of consensus: 100 %

H.-P. Schlemmer

A meta-analysis [113] of 12 studies with a total of 6 642 patients at AJCC stage I–II (5 studies), III (6 studies), and IV (1 study) revealed that lymph node sonography is superior to palpation for the detection of lymph node metastases. A diagnostic study with 100 consecutive patients [108] found a sensitivity of regional lymph node metastases of only 8 %, with a specificity of 88 %. Another study with a small case number (52 patients) reported an accuracy of 89 % for the detection of metastases in newly appearing and palpable lymph nodes [301]. Just like Jimenez-Requena [132], Xing et al. confirmed that lymph node sonography had the highest accuracy and highest diagnostic validity in the initial and follow-up staging of regional lymph nodes [104].

The accuracy of lymph node sonography depends on the location of affected lymph nodes. For example, retroperitoneally or intrathoracically located lymph node metastases cannot be detected by sonography. Here, the use of CT, MRT or PET/CT would be necessary. Lymph node sonography shall be performed in stage III patients, if there is a potential intent to cure.

3.4.1.4 Cross-sectional imaging in locoregional metastasis

3.4.1.4	Evidence-based statement
Level of Evidence 1a	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.
	Systematic search of the literature *de-novo:* [104]
	Strength of consensus: 100 %

H.-P. Schlemmer

In a meta-analysis, Xing et al. showed that PET/CT is the most sensitive and most specific procedure for the detection of extracerebral distant metastases [104]. According to comparative studies on the detection of extracerebral metastases in melanoma patients between PET/CT versus whole-body MRI [302] and whole-body MRI versus whole-body CT [303], PET/CT is superior to whole-body MRI und whole-body MRI is superior to whole-body CT. Regarding the practical implementation of cross-sectional imaging, the practical and economic availability of the respective imaging method has to be taken into account. Thus, whole-body MRI or whole-body CT may also be used as alternatives to PET/CT.

3.4.1.5 Cranial MRI in locoregional metastasis

3.4.1.5	Consensus-based statement
GCP	MRI possesses the highest diagnostic accuracy for the detection of brain metastases of melanoma.
	Strength of consensus: 100 %

H.-Schlemmer, M.-K. Ganten

As mentioned before, cranial MRI is generally more sensitive for the detection of cerebral metastases than CT and FDG-PET/CT. However, currently published studies of melanoma patients only feature low evidence levels and inhomogeneous patient groups. These studies suggest the use of cranial MRI only in patients with stage III–IV disease as well as in patients whose adjuvant therapeutic regimen would change, if cerebral metastases were detected [106, 107].

3.4.1.6 S100B, LDH, MIA in locoregional metastasis

3.4.1.6.a	Evidence-based recommendation
Grade of recommendation A	S100B shall be determined in patients with suspected or proven locoregional metastasis.
Level of Evidence 1a	Systematic search of the literature *de-novo:* [118, 304]
	Strength of consensus: 83 %

3.4.1.6.b	Evidence-based recommendation
Grade of recommendation 0	LDH may also be employed as an additional prognostic marker in patients with suspected or proven locoregional metastasis.
Level of Evidence 1b	Systematic search of the literature *de-novo:* [305]
	Strength of consensus: 100 %

3.4.1.6.c	Evidence-based recommendation
Level of Evidence 2b–	The significance of MIA especially in patients with suspected or proven locoregional metastasis is unclear.
	Systematic search of the literature *de-novo:* [119, 122, 127]
	Strength of consensus: 100 %

C. Kochs, D. Schadendorf

Numerous studies have been conducted in melanoma patients evaluating the significance of serum proteins as tumor markers. Three markers in particular have turned out to be potentially useful: S100B, MIA, LDH.

S100B

A host of studies have demonstrated that elevated levels of S100B are associated with poorer prognosis. A meta-analysis by Mocellin took a look at the prognostic value of S100B in a total of 3 393 stage I–IV melanoma patients included in 22 studies. Positive S100B values were linked to lower survival rates (HR = 2.23, p > 0.0001; in a subgroup of patients at stage I–III: HR = 2.28, p < 0.0001). Unlike stage IV patients, this subgroup (stage I–III) exhibited no relevant heterogeneity. Technical parameters, e.g. an appropriate cut-off value, could not be identified in meta-analysis [118].

Separate evaluation of S100B at stage III was not conducted in this meta-analysis, in-stead combined assessment of stage I–III and I–IV. Only few studies, like the one by Kruijff et al., exclusively included stage III patients. Here, the prognostic value of S100B was examined in patients with clinically and histologically proven regional lymph node metastases before and after therapeutic lymph node dissection. Multivariate analysis revealed that preoperatively elevated S100B levels were associated with lower recurrence-free survival rates (HR 2.6; p = 0.03) [304]. The sensitivity of S100B in stage III melanoma varies in the literature: Using a cut-off of 0.3 µg/l, Schultz et al. reported it to be 31 % (stage II 0 %, stage IV 69 %); in a prospective study by Brouard et al., sensitivity was 46 % (86 % at stage IV) [306, 307]. Other studies performed combined evaluation of stage III and IV patients. A study by Kaskel et al. with a total of 570 stage I–IV melanoma patients set out to find an appropriate S100B threshold value that would allow for the differentiation of patients with new lymph node, organ, and brain metastases from those without metastases. Depending on cut-off, the trial yielded a sensitivity for S100B of 94 % (cut-off 0.114 µg/l) and 92 % (cut-off 0.2 µg/l) [308]. A study by Krahn et al. compared various tumor markers in 373 melanoma patients (284 stage I/II, 89 stage III/IV). In patients with new metastases, S100B turned out to be a more reliable tumor marker in peripheral blood than MIA, albumin or LDH. The sensitivity for new metastases (excluding cutaneous metastases) was 86 % (80 % for MIA, 48 % for LDH and 15 % for albumin) [122].

Considering that elevated S100B levels are associated with prognostic deterioration, it is recommendable to measure S100B in patients with locoregional metastasis.

LDH

LDH is a nonspecific serum marker frequently used besides S100B as tumor marker in melanoma.

In a retrospective study of 255 patients, Nowecki et al. assessed the prognostic value of LDH in stage III melanoma patients before lymph node dissection. Using univariate analysis, preoperatively elevated LDH levels in patients with macrometastases were linked to poorer overall survival. This, however, was not the case in patients with micrometastases. Multivariate analysis confirmed that, in patients with macrometastases, elevated serum LDH levels represent an independent factor for poorer overall survival (p = 0.01, HR = 1.6) [305].

The sensitivity of LDH is below that of S100B. Patients with stage III/IV melanoma exhibited higher LDH levels than patients at stage I/II [122, 129].

Due to the inconsistency of available data, LDH is not suitable as sensitive tumor marker for the detection of new metastases of melanoma. LDH may be used as additional prognostic parameter in patients with suspected locoregional metastasis or evidence thereof.

MIA

As with LDH, there is presently no consistent data regarding melanoma inhibitory activity (MIA). Measurement of MIA is not performed routinely.

Bosserhoff et al. examined whether MIA is suited to be a significant parameter in melanoma. All 50 patients with metastatic melanoma showed elevated MIA levels, albeit only six patients had stage III melanoma. Elevated levels were also observed in other neoplastic diseases such as ovarian, pancreatic, and mammary carcinoma [119].

In the aforementioned study by Krahn et al., elevated MIA levels were detected in 6 of 19 tumor-free stage III and IV patients and in 16 of 20 patients with new metastases. MIA's sensitivity for new lymph node, organ, and cerebral metastases (excluding cutaneous metastases) is 80 % (S100B 86 %) and for existing metastases 62 % [122].

Tas et al. reported a statistically significant correlation between MIA levels and clinical tumor stage in 48 patients, yet the Cox model revealed no statistical significance with regard to outcome [127]. Stahlecker and Guba et al. also detected higher MIA concentrations in stage III and IV patients than in stage I and II patients [309]: 326 melanoma patients; [310]: 70 patients. It has to be mentioned, though, that the percentage of stage III and IV melanoma patients in the study by Stahlecker et al. was only very small (5 patients at stage III, 19 at stage IV). The second study by Guba et al. showed no significance with respect to shorter survival rates in stage III and IV patients with elevated MIA levels. With a cut-off of > 8.8 ng/l, specificity was 95 %. A similar correlation between the two markers S100B and MIA was described by Juergensen in a study with 378 blood samples of 50 stage III and IV patients, specificity: 81.7 % for MIA and 80.3 % for S100B. The survival curves showed a correlation between serum levels and survival (for MIA p < 0.0001 and for S100B p = 0.0015) [128]. The Cox regression model with data from a prospective diagnostic trial with 170 melanoma patients identified S100B and MIA as two survival predictors and also demonstrated a strong correlation between S100B and MIA [129].

Currently published studies on the biomarker MIA for the most part include small patient groups and exhibit low evidence levels. The significance of MIA in patients with suspected locoregional metastases or evidence thereof is unclear. Therefore, a general recommendation cannot be issued.

3.4.2 Lymphadenectomy

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

3.4.2.1 Elective lymphadenectomy

3.4.2.1	Evidence-based recommendation
Grade of recommendation A	Elective (prophylactic) lymphadenectomy is not recommended for melanoma, independent of the Breslow depth of the primary tumor.
Level of Evidence 1a	Guideline adaptation: [19]
	Strength of consensus: 84 %

C. Czeschik, E. Dippel

All patients with invasive melanoma are at risk for lymphogenic metastasis. Lymph node examinations are therefore essential during initial staging and follow-up.

The risk for lymph node metastases correlates with primary melanoma thickness (Breslow) [311].

The question remains whether there is an indication for lymph node dissection (LND) of clinically inconspicuous lymph nodes at the time of primary diagnosis. Randomized, controlled trials have shown that elective LND does not result in statistically significant survival benefit compared to therapeutic LND [311].

Elective LND in patients with invasive melanoma therefore cannot be recommended.

This recommendation applies to patients with negative sentinel lymph node or patients in whom no sentinel node biopsy was performed and who exhibit no clinical signs of lymph node involvement.

3.4.2.2 Therapeutic lymphadenectomy

3.4.2.2.a	Consensus-based recommendation
GCP	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).
	Strength of consensus: 100 %

3.4.2.2.b	Consensus-based recommendation
GCP	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.
	Strength of consensus: 100 %

P. Hohenberger

Therapeutic lymph node dissection is indicated in case of cytologic or histologic evidence for metastasis by e.g. fine-needle biopsy or following surgical lymph node extirpation. Patients with unequivocal clinical signs of lymph node metastases shall undergo lymph node dissection of the respective drainage basin (stage IIIB and IIIC). Clinically unequivocal signs are:

- clinical examination by an experienced physician revealing hard, enlarged or enlarging LNs and
- sonography of lymph node basins by a physician experienced in sonography yielding justified suspicion for metastasis on the basis of sono-morphologic criteria and/or
- detection of lymph node metastases by CT, MRI or PET.

There is currently no data answering the question whether therapeutic LND results in prolongation of long-term survival, albeit there have been numerous publications on disease-free or overall survival after LND. These studies usually compared early versus delayed lymph node dissection.

Radical LND is a relatively difficult surgical procedure that should only be performed by properly trained surgeons. There is substantial risk for tumor recurrence in patients with clinically positive lymph nodes that may only be controlled by thorough formal dissection of the drainage basin. Yet, if performed adequately, complete tumor removal may be achieved. Thus, it is a potentially curative procedure.

Particularly melanomas of the head/neck region show markedly variable patterns of lymphatic drainage that may lead to varying dissection areas. Recurrence rates in these areas (neck dissection) are generally distinctly higher than in the axillary or inguinal region [312].

No therapeutic benefit exists for prophylactic lymph node dissection, i.e. surgery without tumor evidence by clinical, imaging, and/or cytologic/histologic procedures, compared to dissection upon detection of LN metastases (meta-analysis of 3 studies with 1 533 patients, [311]).

There is consensus in the literature and in published guidelines about the indication for LND in the presence of lymph node metastases [313], in order to prevent regional recurrence and pursue a curative approach. If the indication has to be determined by findings other than SLNB, regional sonography by an experienced examiner is superior to mere clinical examination by palpation in the detection of suspicious lymph nodes. Both methods, however, are inferior to sentinel lymph

node biopsy in sensitivity and specificity. Prior to LND, distant metastases shall be ruled out [108, 109, 113, 314, 315].

The LND specimen should allow for orientation along anatomic structures and dissected lymph node levels. The histopathology report shall state the total number of dissected lymph nodes and the number of positive lymph nodes within the LND specimen. It shall also indicate extracapsular dissemination of lymph node metastases.

The indication for LND in case of lymph node recurrence in a lymph node basin previously operated on should be considered, if it constitutes the only tumor manifestation. Following previous simple lymph node resection, radical LND according to quality criteria may offer a curative approach.

In case of isolated lymph node recurrence within a previously adequately dissected drainage basin, an extended procedure involving vascular reconstruction and/or plastic surgical wound closure may be taken into consideration, if anatomically feasible.

3.4.2.3 Lymphadenectomy in the event of micrometastases in the sentinel lymph node

3.4.2.3.a	Evidence-based recommendation
Grade of recommendation B	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.
Level of Evidence 2b	Systematic search of the literature *de-novo:* [17, 193, 209, 210, 213]
	Strength of consensus: 100 %

3.4.2.3.b	Evidence-based recommendation
Grade of recommendation o	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.
Level of Evidence 2b	Systematic search of the literature *de-novo:* [191, 193, 213]
	Strength of consensus: 100 %

B. Frerich

All melanoma metastases detected by sentinel lymph node biopsy (SLNB) or elective lymph node dissection are labeled micrometastases. Unlike clinically or radiologically obvious macrometastases, micrometastases to the sentinel lymph node (SLN) occur significantly more often as the only manifestation of lymph node involvement and carry a markedly better survival prognosis [209]. In patients with micrometastasis to the SLN, the overall risk for metastasis to additional non-sentinel lymph nodes (N-SLN) is roughly 20 % (16 %–21 %, [205, 209, 213]. Within this prognostically inhomogeneous patient group [17, 209], it is therefore necessary to identify those patients at low risk for positive N-SLN who do not require completing lymph node dissection (CLND) following SLNB. So far, there has been no consensus on appropriate cut-off values or scores (like e.g. mammary carcinoma < 0.2 mm = submicrometastases) that would aid in proper assessment of tumor load and reliably facilitate the decision as to the need for subsequent CLND [210]. The number of additionally positive N-SLN and the survival prognosis have been shown to depend on 1) the maximum diameter of metastasis and the location within the sentinel node [190, 193, 205, 211], 2) the "area" of metastasis in the histologic section (absolute or relative to the cross-sectional area of the lymph node) [190, 205, 212], 3) the depth of invasion measured from the capsular margin (Starz classification) [190, 193, 205], 4) the number of positive SLN [193], 5) the microanatomic location with respect to the lymph node capsule ("Dewar criterion"), and 6) capsular infiltration [190, 193, 205] (reviews in [210, 213]). According to published data, a combination of various parameters of tumor load and location of the micrometastasis provides the best potential for gauging involvement of N-SLN.

When considering both size criteria and Dewar classification, a group of subcapsular metastases < 0.1 mm was identified at very low risk (2 %) for positive N-SLN [213]. In a retrospective analysis of patients with the lowest scores, the "Hannover system" [193], developed from [190]), which is based on the combination of maximum diameter of metastases (cut-off 0.1 mm), TPD (tumor penetrative depth, cut-off 2 mm) and capsular infiltration (present/not present), yielded overall and recurrence-free survival rates similar to SLN-negative patients. The Starz classification [191] is also in principle based on a combination of size criteria and microanatomic location. In a prospective monocentric study by van der Ploeg et al. [210], no additional lymph node manifestations occurred in patients with S-I/S-II classified positive SLN who did not undergo CLND. Overall and recurrence-free survival was 100 % (follow-up 2.5 years).

The aforementioned results and scoring systems are for the most part based on retrospective studies, in which all patients received CLND. As previous prospective studies (interventional waiver of CLND) feature only small patient

numbers, presently conducted prospective multicenter trials dealing with the issue of post-SLNB observation have to be awaited (i.e. Multicenter Selective Lymphadenectomy Trial II (MSTL-II), (EORTC MINITUB) [213] and ADO trial (controlled and prospective randomized therapeutic trial on the comparison of elective radical lymph node dissection versus observation). Only then can a general recommendation be issued for the waiver of CLND based on such scores.

Retrospective research of the AJCC data base [17, 209] shows prognostic inhomogeneity of patients with micrometastases. In multivariate analysis, the variables age, tumor thickness, mitotic rate of the primary tumor (second most significant variable besides positive SLN), ulceration, anatomic location of the primary tumor, and number of positive lymph nodes were independent prognostic factors in stage IIIA patients. Risk stratification using these variables yielded greater prognostic variability for micrometastases than for patients with macrometastases [209]. Thus, it is necessary to also include these factors for risk assessment when determining the indication for CLND. Various other studies, with lower case numbers, however, indicated age, tumor thickness, tumor regression, ulceration, number of positive SLN, vascular and lymphatic invasion, perinodal dissemination, and location in the head/neck region as predictive for the risk of additional positive N-SLN [204, 211, 213, 214]). Prior to conclusion of the aforementioned multicenter trial, patients with these risk factors therefore remain candidates for CLND [213]. Mitotic rate was not always evaluated and, where available, not significantly predictive of N-SLN status. However, in view of the above-mentioned prognostic data, it should be taken into account.

With this in mind and based on retrospective data, weighted scores have been developed for risk stratification of the rate of additional positive N-SLN, e.g. "N-SNORE" [204]. In addition to the maximum diameter of the largest tumor cluster, this score draws on clinical parameters (gender, proportion of positive among all removed sentinel lymph nodes) and other histopathologic parameters (regression, perinodal lymphatic invasion). As there is presently no prospective data on these parameters, the same recommendations apply as for histomorphometry-based scores.

Isolated immunohistochemically positive tumor cells (IPC) (defined as isolated pigmented cells, a maximum of 2 contiguous cells) in the SLN should be viewed separately. Satzger et al. [215] demonstrated in a retrospective analysis that patients in this group had the same survival prognosis as sentinel-negative patients. It is therefore questionable, whether IPCs have any prognostic significance. Under these circumstances, the indication for CLND has to be discussed with the patient.

The results of PCR-based "SLN ultra-staging" have been inconsistent, so that this diagnostic tool can only be recommended in the context of clinical trials.

3.4.2.4 Extent of lymph node dissection

3.4.2.4	Consensus-based recommendation
GCP	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.
	Strength of consensus: 100 %

B. Frerich, A. Krause-Bergmann, T. Dettenborn

The removal of lymph nodes within a lymph node basin (lymph node dissection LND) is implemented for metastasis to regional lymph nodes, irrespective of micro or macrometastasis. The question, whether lymph node dissection (LND) following a positive sentinel node improves survival, is currently being evaluated in clinical trials. Concomitant diseases on the part of patients also influence the extent of the procedure.

Data on morbidity and therapeutic results varies due to differing procedural techniques and differing extent of surgical measures [316–318].

Because of the substantially increased risk for recurrence after dissection, regional radical lymph node dissection should only be performed by properly trained surgeons, as they are able to improve the prognosis by reliably removing the largest number of lymph nodes [319].

This radicality may entail a greater risk for postoperative complications requiring further treatment.

Complications of dissection are above all lymphedema or seroma and in the head/neck region formation of a chylous fistula [320]. Due to high recurrence rates for metastasis within the mentioned lymph node regions (lymph node and/or soft tissue metastases), such complications and the higher morbidity of this procedure are generally accepted. Since LND in stage III melanoma shall be performed radically, the following is a description and consensus-based determination of this procedure.

Area	Extent	Extension
Head/neck region	Modified radical neck dissection (MRND)	Superficial (lateral, nerve-conserving) parotidectomy Posterolateral neck dissection (retro-auricular, suboccipital LN groups, lateral neck triangle, parts of level II–IV dorsal of internal jugular vein)
Axillary (upper extremities, trunk)	Level I -III, depending on the site of the primary tumor	
Inguinal (lower extremities, trunk)	Femoral triangular lymph nodes	Iliacal and obturator lymph nodes

Head/neck region

The most common site of lymph node metastasis in head/neck melanomas are lymph nodes in the parotid gland region and cervical lymph node groups. The extent of neck dissection and the potential necessity for lateral parotidectomy are determined by the anatomic location of the metastasis as well as by the primary tumor site [312, 321–323]. Melanomas of the parietal/frontal, temporal, latero-frontal, buccal or auricular region, located anterior of a virtual plane through the external auditory canal, drain via parotid lymph nodes and/or lymph nodes along the facial nerve (at the mandibular edge) into cervical lymph node basins. On the other hand, melanomas located dorsal of this plane, rather drain into retroauricular and occipital lymph nodes [321, 324].

Mandatory basis for dissection margins and the definition of dissection methods is the classification of cervical dissection levels ("Academy's Committee for Head and Neck Surgery and Oncology") [325, 326]. Basic procedure for therapeutic cervical lymph node dissection is the modified radical neck dissection (MRND) as complete dissection of levels I–V between mandibular edge and clavicle while saving important non-lymphatic structures (sternocleidomastoid muscle, internal jugular vein, accessory nerve) [318], or, if applicable, as so-called ERND ("extended") adding lateral parotidectomy (see below). Resection of the jugular vein, accessory nerve, and/or sternocleidomastoid muscle in terms of a classic radical neck dissection (RND) should nowadays only be performed, if these structures are directly infiltrated, in the presence of large, otherwise irremovable metastases, or after prior surgery, e.g. re-dissections [318, 321, 324]. The question regarding the use of selective forms of neck dissection for therapeutic indications has not been conclusively answered, e.g. selective neck dissection (SND) I–IV sparing level V in anterior melanomas. In a N1 situation, SND appears to be equivalent to MRND [327]. In N2 and N3 situations, however, SND appears to be inferior to MRND. Based on current data, therapeutic neck dissection should involve dissection of lymph node basins along the internal jugular vein (level II–IV). It remains to be seen, whether, depending on primary tumor site and status of dissemination, dissection of level V may be relinquished in favor of lower morbidity [328, 329].

Standard procedure for dissection of the parotid region is conservative (facial nerve-conserving) lateral (= superficial) parotidectomy. The deeper (medial to the facial nerve plane) located part of the gland generally does not contain any lymph nodes serving as drainage basin for face and scalp. Repeated procedures involving the parotid gland are associated with a markedly increased risk for facial nerve damage. The first procedure on the parotid gland should therefore preferably be definitive.

Procedure depending on location

The standard for therapeutic dissection in primary melanomas of the frontal/parietal, temporal, fronto-lateral, buccal, and auricular region (anterior of the above-mentioned plane) is lateral parotidectomy in combination with a MRND (= ERND). Dissection of level V (lateral cervical triangle) is debatable in this situation (alternatively as SND I–IV).

For melanomas located in the chin and neck region, parotidectomy is usually not required and MRND or SND I–IV thus become the method of choice.

Occipital and parietal melanomas dorsal of the above-mentioned plane require postero-lateral neck dissection [321, 324]. This comprises retroauricular and suboccipital lymph nodes as well as the lateral cervical triangle up to the jugular vein (Robbins-level V and partially II–IV).

The extent of therapeutic dissection for midline melanomas has to be determined according to metastatic manifestation. In these cases, but also in all other head/neck melanomas, lymphoscintigraphy may help indicate drainage patterns. There is currently no trial-based data.

Extent of axillary LND

Primary tumors of the upper extremities/trunk are subject to axillary dissection.

Axillary metastases arise from tumors in the following areas:

- arm and shoulder region
- trunk

The extent of axillary dissection is designated by levels I to III according to Berg [318]. The minor pectoral muscle is the anatomic structure that defines various levels (level I lateral of the minor pectoral muscle, level II behind this muscle, and

level III medial and cranial of the axillary vein). Level III dissection is associated with higher complication rates. It still remains to be seen whether this level classification will persist for tumors of the shoulder and upper extremities. Studies evaluating modification of radical axillary LND are pending. This classification is based on insight of lymphatic drainage pathways in mammary carcinomas und may in some cases not be applied without modification. If several lymph node basins are involved in primary tumors on the trunk or in the shoulder/arm region, a combined procedure may have to be chosen, such as e.g. axillary lymph node dissection with selective neck dissection or extended radical neck dissection. As to the procedure applied, no distinction is currently made between tumors of unknown primary site and so-called midline tumors and tumors of the trunk or shoulder/arm region.

Positive lymph nodes above the axillary vein should be extirpated and the vein freed from any tumor mass [330]. Other lymph nodes such as e.g. epitrochlear or antecubital lymph nodes are only removed on a case-by case basis [331, 332].

The fascia of all surrounding muscles can generally be spared during axillary lymph node dissection [333].

Extent of inguinal/femoral LND

Primary tumors of the lower extremities/trunk are subject to inguinal lymph node dissection.

Inguinal/femoral metastases arise from tumors in the following areas:

- leg and hip region
- trunk

The depth of extent of inguinal/femoral LND is defined by the fascia lata. Inguinal dissection of superficial lymph nodes, as described in the literature, ends above this fascia. Removal of deep lymph nodes requires dissection underneath the fascia and opening of the inguinal ligament. Whether deep LND is prognostically beneficial, currently remains unclear [334], except for recurrence surgery.

Inguinal lymph node dissection comprises the entire femoral triangle below the inguinal ligament. The superior anterior iliac spine marks the most proximal cutaneous resection point containing subcutaneous adipose tissue. The great saphenous vein is always included from distal thigh to the saphenofemoral junction.

A sartorial muscle flap should be considered in unfavorable circumstances when there is not enough soft tissue to cover the inguinal vessels.

Iliacal lymph node dissection and dissection of the obturator region shall be performed by an experienced surgeon for affected lymph nodes proximal to the inguinal ligament [335].

Lymph nodes in the popliteal fossa are not regularly extirpated. Lymph nodes medial of the pectin pubis are only removed in case of proven involvement.

3.4.3 Adjuvant radiotherapy after lymphadenectomy

3.4.3.a	Evidence-based recommendation
Grade of recommendation B	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
Level of Evidence 1b	Systematic search of the literature *de-novo:* [336–345]
	Strength of consensus: 100%

3.4.3.b	Consensus-based recommendation
GCP	To improve tumor control in the lymph node region, postoperative radiotherapy should be performed after resection of a lymphatic recurrence.
	Strength of consensus: 100%

3.4.3.c	Evidence-based recommendation
Grade of recommendation A	If there is an indication for radio-therapy of the lymphatic drainage basin, radio-therapy shall be performed with 50-60 Gy in conventional fractionated doses (5 x 1.8 -2.5 Gy/week).
Level of Evidence 2b	Systematic search of the literature *de-novo:* [336–345]
	Strength of consensus: 100%

3.4.3.d	Evidence-based statement
Level of Evidence 2b	A positive effect of postoperative radiotherapy of the regional lymphatic drainage basin on survival time has not yet been proven.
	Systematic search of the literature *de-novo:* [338, 339, 341–343, 346]
	Strength of consensus: 100%

O. Kölbl

Two randomized controlled trials [338, 339] confirmed six retrospective cohort studies [336, 337, 340, 341, 343, 345] in showing significantly higher locoregional control rates in patients with lymph node metastases undergoing postoperative adjuvant radiation therapy of the affected lymph node basins. In Burmeister et al., 34 of 127 patients without radiation therapy sustained locoregional lymph node recurrence,

whereas in the patient group subjected to adjuvant radiation therapy, 20 patients suffered recurrence within the lymph node basin. This difference was significant (HR 0.56, CI 0.32–0.98, p = 0.041). Recurrence-free as well as overall survival, however, were not positively affected by adjuvant radiation therapy [338]. Creagean et al. [339] reported prolongation of median recurrence-free survival by postoperative radiation therapy from 9 to 20 months. Although five cohort studies [336, 337, 341, 343, 345] corroborated the efficacy of postoperative radiation therapy, two different cohort studies and a case study revealed conflicting findings [342, 344, 346]. Due to methodological flaws, however, the validity of these studies is diminished. Moncrieff et al. [342] included significantly more patients with macroscopic residual tumors in the postoperatively irradiated group than in the surgery-only group. Shen et al. [344] used disproportionate group sizes, 196 solely underwent surgery and only 21 received additional irradiation.

In five of the studies, patients with cervical, axillary as well as inguinal lymph node metastases [336, 337, 339, 346, 347] were included. Only three of these cohort studies subsequently differentiated between lymph node regions in their evaluation. Agrawal et al. [336] reported local control rates in the cervical lymph node region after 5 years of 43 % without and 93 % with irradiation and in the axillary lymph node region of 48 % without and 91 % with irradiation. Inguinal control rates were 69 % for both treatment arms respectively. In Bibault et al., local control rates with and without postoperative radiation therapy respectively amounted to 85 %/50 % (cervical), 90 %/70 % (axillary), and 80 %/72 % (inguinal) [337]. Three cohort studies exclusively included patients with cervical lymph node metastases. In the presence of risk factors, they also demonstrated substantial reduction in local recurrence rates by postoperative radiation therapy of the cervical lymph node region [341, 343, 345]. Cohort studies in particular exhibited a significant imbalance of risk factors within treatment arms [341–343]. In Hamming-Vrieze et al., 85 % of patients in the postoperatively irradiated group featured at least two positive lymph nodes and 35 % showed capsular penetration. In the surgery-only group, 37 % had more than 2 positive lymph nodes and 8 % capsular penetration [341].

Risk factors for recurrence in regional lymph node basins are capsular penetration, number of positive lymph nodes, and size of lymph node metastases [336, 337, 339–341, 343–345]. Bibault et al. not only reported a significant impact of capsular penetration on regional recurrence rates, but also on survival. Survival rates of patients with capsular penetration were 55 % after 2 years , without 71 % [337]. In Agrawal et al., locoregional recurrence rates in all lymph node regions (cervical, axillary, inguinal) in patients with 4 or more lymph node metastases were 26 %, in those with 3 or fewer lymph node metastases 15 % [336]. With respect to the cervical region only, Strojan et al. reported recurrence rates of 65 % in patients with 3 or more lymph node metastases and of 17 % in patients with 2 or fewer lymph node metastases [345]. In a prospective controlled trial by von Henderson et al., lymph node metastases of 3 cm (cervical, axillary) respectively 4 cm (inguinal) in size were defined as risk factors [347].

Postoperative radiation therapy of lymph node basins shall be implemented using 50–60 Gy in conventional fractionation (5 × 1.8–2.5 Gy/week). Bibault et al. showed that local control rates in patients treated with a dose of less than 50 Gy were significantly lower than in those treated with 50 Gy or more (35 % vs. 80 %). Strojan et al. also found markedly elevated local recurrence rates of 50 % for doses below 50 Gy. Employing postoperative radiation therapy with conventional fractionation, therapy-induced toxicity was not increased in the cervical and inguinal region and only slightly raised in the axillary region. Severe adverse reactions were not observed [337].

In a prospective randomized trial with only small patient numbers, survival time following surgery and radiation therapy of a lymph node region was 33 months versus 22 months for surgery alone [339]. In a cohort study by Agrawal et al., disease-specific survival 5 years after surgery and irradiation was 48 % and 40 % after surgery alone [336]. Other cohort studies were not able to confirm a benefit for postoperative radiation therapy following surgery of lymph node metastases [341–343]. As no risk stratification was performed in these studies, there were more patients with prognostically unfavorable risk factors in treatment arms with irradiation. Overall, current data does not suffice to postulate a positive impact of postoperative adjuvant radiation therapy of regional lymphatic drainage areas on survival time.

In conclusion, postoperative radiation therapy of lymph node basins may enhance regional tumor control. It should therefore be implemented in the presence of risk factors, in order to improve symptoms and thus quality of life. Prolongation of life through postoperative radiation therapy has not been shown.

3.4.4 Adjuvant medical therapy

3.4.4.1 Adjuvant chemotherapy

3.4.4.1	Evidence-based recommendation
Grade of recommendation A	Dacarbazine shall not be administered in the adjuvant therapy of melanoma.
Level of Evidence 1a	Guideline adaptation: [194, 348]
	Strength of consensus: 90 %

P. Mohr

"A total of 8 randomized trials on adjuvant chemotherapy were evaluated. Two trials compared dacarbazine versus observation [349, 350], one trial compared dacarbazine to placebo [351], and one trial investigated dacarbazine in combination with BCG versus observation [352]. Only one study examined methyl-CCNU [353].

None of the three studies on dacarbazine monotherapy was able to show a significant difference in overall survival [349–351]." ([194], p. 39). One of the most comprehensive studies of the Central Oncology Group (COG) (USA) even revealed poorer survival rates for patients receiving chemotherapy compared to untreated controls [349].

"A meta-analysis, conducted by CCOPGI, of 7 randomized trials on adjuvant chemotherapy found no significant difference with respect to mortality rates after 3 years (risk ratio 0.94; 95 % CI 0.84–1.06; p = 0.3) [350–356]. The study by Fisher et al. comparing methyl-CCNU versus observation showed no significant difference between both comparative arms [353]." ([194], p. 39).

In summary, unlike previous studies with historic control groups, a number of prospective randomized trials have yielded no significant benefit for patients treated with systemic adjuvant dacarbazine compared to untreated individuals. Adjuvant chemotherapy with dacarbazine should therefore not be administered.

Another randomized study investigated the efficacy of vindesine versus observation in the adjuvant therapy of melanoma [357]. Unlike a prior retrospective trial [358], this analysis demonstrated no significant differences neither in recurrence-free nor in overall survival. Thus, no adjuvant chemotherapy has until now been proven to be beneficial.

3.4.4.2 Adjuvant vaccination therapy

3.4.4.2	Evidence-based recommendation
Grade of recommendation A	Vaccination therapy shall not be administered in the adjuvant therapy of melanoma outside of clinical studies.
Level of Evidence 1b	Guideline adaptation: [194]
	Strength of consensus: 95 %

A. Mackensen

A total of 8 randomized trials were analyzed. One study evaluated BCG versus observation versus BCG + allogenic melanoma vaccine versus CCNU [353]. Four trials examined various melanoma cell vaccines consisting of allogenic melanoma cell lysates or irradiated melanoma cell lines. Two of these studies investigated vaccine versus observation [359–361]. One study compared the combination of an allogenic melanoma vaccine plus BCG to BCG alone [365]. Two further trials examined adjuvant vaccination with ganglioside GM2-KLH21. One of these studies compared GM2-KLH21 with high-dose IFN α2b [366], the other versus observation [367].

One trial examining BCG in combination with an allogenic melanoma vaccine did not show a significant difference with regard to disease-free or overall survival [353].

None of the adjuvant melanoma cell vaccinations revealed a significant difference in disease-free or overall survival [353, 359, 362–365]. In one trial, follow-up was insufficient for assessment of overall survival [360]. One prospective subgroup analysis in the SOGT-9035 trial showed significantly prolonged disease-free survival in the vaccine group for those patients expressing ≥ 2 of 5 defined HLA class I molecules. Here, HLA A2 and HLA C3 were the key antigens for this beneficial effect [361]. Two adjuvant studies by Morton et al. in stage III and IV disease respectively indicated that an allogenic melanoma vaccine (Canvaxin) neither improved disease-free nor overall survival compared to BCG. Surprisingly, there was, however, significantly poorer overall survival in patients with stage III disease treated with vaccination [365].

Both vaccination trials examining ganglioside GM2-KLH21 showed no benefit for disease-free or overall survival compared to high-dose IFN-α2b [366] or observation [367].

In summary, a number of prospective randomized trials on adjuvant vaccine therapy yielded no significant benefit for treated versus untreated patients or those receiving CCNU, high-dose IFN-α2b, or IL-2. Adjuvant vaccine therapy should therefore not be administered outside clinical trials.

3.4.4.3 Adjuvant isolated limb perfusion

3.4.4.3	Evidence-based recommendation
Grade of recommendation A	Adjuvant isolated limb perfusion with melphalan shall not be administered in the adjuvant therapy of melanoma.
Level of Evidence 1b	Guideline adaptation: [194]
	Strength of consensus: 95 %

A. Hauschild

Isolated limb perfusion with cytostatic agents, mostly performed with hyperthermia, has been used in two different scenarios: in an adjuvant (prophylactic) setting after excision of medium to high-risk primary melanomas as well as in non-resectable satellite and/or in-transit metastases.

There are two prospective, randomized phase III trials on adjuvant hyperthermic isolated limb perfusion with melphalan. A relatively small German study compared patients receiving regional lymph node dissection in combination

with hyperthermic (performed at 42 °C) isolated limb perfusion to patients exclusively undergoing wide excision of the primary tumor followed by regional lymph node dissection. After recruitment of 107 patients and median follow-up of 5 years and 11 months, the trial was aborted, as there were 26 recurrences in the control arm, but only 6 in the perfusion arm ($p < 0.001$). Retrospective subgroup analysis revealed significant differences in recurrence-free survival, particularly in primary tumors of more than 3 mm in thickness (4/28 recurrences (14.3 %) in the perfusion group versus 16/29 (55.2 %) in the control group). 11 patients in the control group ($p < 0.01$) versus 3 patients in the perfusion group had died at the time of final publication in 1990. The authors interpreted the results of this study, just like they had done in a previous publication (Annals of Surgery 1984), as clear evidence for the benefit of adjuvant hyperthermic isolated limb perfusion with melphalan compared to standard surgical procedures [368, 369].

In 1998, a large prospective randomized trial of the EORTC-MG (trial 18832), the WHO melanoma group (trial 15), and the North American Perfusion Group Southwest Oncology Group (trial 8 593) was published. This study included patients with primary cutaneous melanomas of at least 1.5 mm in thickness. A total of 832 evaluable patients were recruited in 16 centers worldwide. One patient group underwent wide excision of the primary tumor, the other received wide excision of the primary tumor in combination with adjuvant hyperthermic isolated limb perfusion with melphalan. Median patient age was 50 years, 68 % of patients were female, and 79 % of melanomas were located on the lower extremities. 47 % of patients exhibited a tumor thickness of ≥ 3 mm. Median follow-up at the time of publication was 6.4 years.

Analysis indicated a trend (but no statistical significance) towards prolonged disease-free survival with slightly fewer in-transit metastases (3.3 versus 6.6 %) as well as regional lymph node metastases (12.6 versus 16.7 %). There was, however, no difference in the interval until distant metastasis or in overall survival. Adverse events were more pronounced in patients receiving adjuvant limb perfusion than in surgery-only patients. There were two treatment-induced amputations of the respective extremity after hyperthermic limb perfusion.

The authors of this cooperative study group concluded that prophylactic isolated limb perfusion with melphalan could not be recommended as standard therapy for high-risk primary melanoma of the extremities [370].

In summary, adjuvant isolated limb perfusion with melphalan cannot be recommended. At best, enhanced local tumor control on the extremity may be expected, but there is no evidence for prolongation of distant metastasis-free or overall survival. Thus, no published guideline recommends this therapeutic procedure for the treatment of melanoma patients.

3.4.4.4 Adjuvant immunostimulation

3.4.4.4.a	Evidence-based recommendation
Grade of recommendation A	Adjuvant therapy with the unspecific immunostimulant levamisole shall not be administered.
Level of Evidence 1a	Guideline adaptation: [194, 348]
	Strength of consensus: 95 %

3.4.4.4.b	Evidence-based recommendation
Grade of recommendation A	Adjuvant therapy with the unspecific immunostimulant BCG shall not be administered.
Level of Evidence 1b	Guideline adaptation: [194, 348]
	Strength of consensus: 95 %

A. Pflugfelder

Levamisole

Due to its immunostimulatory properties, the antihelminthic agent levamisole has been evaluated in the adjuvant therapy of melanoma. There are 4 randomized trials, 3 of which had a placebo arm. The first placebo-controlled randomized trial of 203 patients by Spitler et al. showed no effect of levamisole on disease-free and overall survival as well as on the interval until visceral metastasis. Long-term follow-up confirmed these negative findings [371]. Two further placebo-controlled studies with a total of 156 and 325 patients revealed no benefit for levamisole, either [351, 372]. A fourth, non-placebo-controlled, trial by the NCIC (National Cancer Institute of Canada Clinical Trials Group) compared levamisole vs. levamisole + BCG vs. BCG vs. observation. After 5 years, there was a significant benefit for the 135 patients in the levamisole arm with respect to overall survival (74 % vs. 62 %; $p = 0.0268$) [373]. Meta-analysis of 5-year survival data from all 4 trials yielded no significant benefit for levamisole in terms of mortality risk (RR 0.94 [95 % CI 0.75–1.20; $p = 0.6$]) [348].

BCG (Bacillus-Calmette-Guérin)

In the beginning of the 20th century, BCG was developed as live vaccine against tuberculosis. As BCG induces a nonspecific immune response, it has been used in various tumor types. Apart from adjuvant melanoma therapy, BCG has also been examined in the treatment of distant and in-transit metastases.

There are 3 randomized, non-placebo-controlled trials on adjuvant therapy. The first trial, between 1974 and 1980, included a total of 761 patients that were randomized into 4 treatment arms (observation vs. DTIC vs. BCG vs. BCG + DTIC). 3-year survival rates in the BCG arm were not significantly better than in the observation arm (48.7 % versus 41.6 %) [350]. The above mentioned NCIC study did not show any benefit for the 136 patients in the BCG arm compared to observation, either (5-year survival 59 % vs. 62 %) [373]. Another trial with 4 treatment arms (observation vs. BCG; BCG vs. BCG + DTIC) from 1974 to 1978 altogether included 734 patients. There was no significant benefit in 5-year survival rates (67 % versus 62 %) for the 267 patients in the BCG arm [374].

3.4.4.5 Adjuvant mistletoe therapy

In Germany, mistletoe therapy is implemented in very diverse ways. The predominantly anthroposophic preparations contain mistletoe lectins in markedly varying concentrations. A comparative clinical trial of the various preparations has not been conducted.

Mistletoe therapy results in immunologic changes that may individually differ. Various components of mistletoe extracts stimulate, in vitro and in vivo, immunologically relevant cellular (macrophages, dendritic giant cells, T cells) and humoral (interleukin 2, interleukin 6) responses, whose benefit is controversial. The negative survival trend suggested by one-year adjuvant mistletoe therapy [375] could be the consequence of stimulation of macrophages and interleukin in and around tumor tissue, which are known to be unfavorable prognostic parameters [376].

3.4.4.5	Evidence-based recommendation
Grade of recommendation A	Adjuvant therapy with mistletoe preparations shall not be administered.
Level of Evidence 1b	Systematic search of the literature *de-novo:* [375, 377–379]
	Strength of consensus: 95 %

J. Hübner

A systematic literature review [380], meta-analysis [381] as well as Cochrane analysis [382] have come to the conclusion that most of currently published trials on mistletoe therapy in various tumor types lack sufficient quality. Methodologically well-conducted studies have shown minimal or no effects of mistletoe therapy on survival time or quality of life.

4 clinical trials have been found assessing the question whether mistletoe therapy provides a benefit in melanoma.

A large prospective randomized EORTC phase-III trial did not yield a positive result, indicating a tendency, yet without statistical significance, towards increased risk for disease progression and metastasis [375].

A retrospective cohort study compared 273 patients (from a total of 1 288 melanoma patients) treated with mistletoe at the University Hospital Freiburg with 819 melanoma controls from the national registry [377]. Group comparability was limited by unequal distribution of age groups and, in particular, by higher Clark levels in the control group.

A study by Grossarth-Maticek combined 2 trials, one non-randomized and one described as randomized. In the non-randomized comparative study, there were no significant differences in survival between mistletoe therapy and control-arm patients. In the randomized study, no randomization was implemented between mistletoe and control, but rather between a recommendation for mistletoe therapy (to be administered by a general practitioner) and no recommendation. Thus, this study does not constitute a comparative therapeutic study of two therapies actually performed. The effect of mistletoe therapy on survival therefore cannot be assessed [379].

The study by Augustin is described as retrolective cohort study – and corresponds to a retrospective cohort [378]. Here, patients were only recruited from hospitals that used preparations by a particular mistletoe manufacturer (although the authors described a random selection of hospitals).

Due to poor methodological quality, both studies by Stumpf and Schuppli were not included in this evaluation [383, 384].

In summary, due to lack of evidence for positive effects and justified suspicion for negative consequences (among others tumor progression), patient safety has to be given priority.

3.4.4.6 Adjuvant interferon therapy

3.4.4.6.a	Evidence-based recommendation
Grade of recommendation A	Patients in the AJCC 2009 tumor stage IIB/C and IIIA -C shall be offered adjuvant therapy with interferon.
Level of Evidence 1a–	Systematic search of the literature *de-novo:* [385–390]
	Strength of consensus: 82 %

3.4.4.6.b	Evidence-based recommendation
Grade of recommendation 0	Patients in the AJCC 2009 tumor stage IIA may be offered a low-dose adjuvant interferon therapy.
Level of Evidence 1b	Systematic search of the literature *de-novo:* [391, 392]
	Strength of consensus: 95 %

3.4.4.6.c	Consensus-based recommendation
GCP	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.
	Strength of consensus: 82 %

3.4.4.6.d	Evidence-based statement
Level of Evidence 2b	Pegylated interferon prolongs recurrence-free survival in comparison to untreated control patients in stage III.
	Systematic search of the literature *de-novo:* [393]
	Strength of consensus: 90 %

3.4.4.6.e	Consensus-based recommendation
GCP	In patients with high-risk melanomas, the possibility of participation in a clinical study should be assessed.
	Strength of consensus: 95 %

3.4.4.6.f	Evidence-based statement
Level of Evidence 1a–	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.
	Systematic search of the literature *de-novo:* [385–390]
	Strength of consensus: 95 %

C. Sunderkötter, M. Schiller, P. Mohr, A. Hauschild, A. Pflugfelder

Trials on interferon therapy have been conducted for varying doses, tumor stages, and therapeutic durations. Because of changes in the AJCC melanoma classification, the trials are not directly comparable with respect to patient cohorts. Meta-analyses show no significant difference between various interferon doses, regimens, and therapeutic durations. This means that no concrete recommendations on interferon regimens can be issued.

A total of 15 randomized clinical trials have been published comparing interferon alpha versus observation.

Two trials were only published as abstracts and are not part of this evaluation [394, 395]. Placebo-controlled trials do not exist. 2 trials revealed a benefit regarding overall survival [396, 397], 6 trials regarding progression-free survival [391–393, 396–398].

There are a total of 6 systematic reviews that evaluated different trials depending on date of publication and the applied inclusion criteria, respectively. Taking all studies (displaying great heterogeneity regarding patient groups and dose regimens) into account, current meta-analyses consistently yielded a significant, albeit small, benefit for overall survival and a significant benefit for progression-free survival [193, 387]. As to overall survival, Mocellin et al. calculated a benefit for the relative risk of 11 % and a "number needed to treat" of 29 patients (95 % CI 18–81 patients). This corresponds to a reduction in absolute risk of 3.4 % (95 % CI 5.6–1.2 %) [387] (Review Manager 5.1, The Cochrane Collaboration: ARR = 1/NNT).

Neither did meta-analyses show a statistically significant advantage for a particular dose or therapeutic duration nor for the administration at various tumor stages. A three-armed trial investigated high-dose versus low-dose therapy versus observation. Here, high-dose and low-dose regimens revealed nearly identical survival curves with respect to progression-free as well as overall survival, yet with significantly higher toxicity rates for high-dose therapy. Both treatment arms showed no significant difference versus observation [399]. In a meta-analysis by Mocellin et al. 2011, relative risk reduction for recurrence was distinctly higher for high-dose (25 %) vis-à-vis low-dose therapy (15 %). The difference, however, was not significant.

In stage III disease, one of three high-dose therapeutic trials showed a significant improvement of progression-free survival, and another trial demonstrated improved survival in the initial evaluation [397, 399, 400]. Concerning low-dose therapy in stage III disease, only one of 6 trials revealed improvement in progression-free and overall survival [375, 396, 399, 401–403]. Administration of high-dose therapy seems to be justified at stage IIIB and IIIC despite increased toxicity.

Nearly all trials attempted to identify subgroups of patients benefiting from interferon treatment. Due to conflicting results, current data is insufficient for a clear recommendation. In a meta-analysis by Wheatley et al., an analysis of the Sunbelt Trial [395], and a current summary of two EORTC trials [404], a benefit is postulated for patients with ulcerated primary tumors and, in the latter trials, also for patients with micrometastatic lymph node involvement. The EORTC is planning a randomized trial to further verify this correlation.

Pegylation of interferon alpha induces longer half-life with equal biologic activity and thus enables once-weekly drug administration compared to conventional interferon alpha. Pegylated interferon alpha (dose 6 µg/kg) was first evaluated versus observation in the EORTC-18991 trial. After 7 years, significantly more patients were recurrence-free in the treatment arm (39 % versus 35 %). Overall survival was not affected by treatment [393]. In the EADO Trial by Grob et al., 100 µg pegylated interferon alpha was directly compared to conventional low-dose interferon alpha in 898 patients. After 5 years, both treatment arms showed

nearly identical survival rates of 65.9 % versus 64.8 % for progression-free survival and 71.1 % versus 72.6 % for overall survival. In contrast, significantly more adverse events occurred with pegylated interferon alpha (fatigue, weight loss, lab parameters). A superiority of pegylated interferon alpha could not be demonstrated [405].

During interferon treatment, dose-dependent adverse events occur that partly entail substantial limitations on the quality of life. This is reflected by high drop-out rates reported to be as high as 31 % [393], and up to 15 % in low-dose trials [403]. Up to 46 % of patients in the EORTC-18952 trial suffered grade 3 or 4 toxicities [393].

Upon initiation of treatment, patients frequently experience flu-like symptoms and later also fatigue, muscle and joint pain as well as depression. Patients also very often report increased irritability during treatment. Elevation of liver enzymes and neutropenia may occur as well as thyroid dysfunction, which is not always reversible after discontinuation of therapy.

In summary, all trials combined – with a total of more than 8 000 patients – show a small, but significant benefit for overall survival and a significant benefit for recurrence-free survival in patients treated with interferon alpha. Until now, no single interferon regimen has been shown to be significantly superior to any other interferon regimen. Regarding patient response to adjuvant interferon therapy at particular disease stages, there is insufficient data for a recommendation, but interferon treatment below stage IIA is not rational. Impairment of patients' quality of life by adverse events has to be anticipated (during high-dose therapy to a greater extent than during low-dose therapy). This is particularly relevant in an adjuvant situation, since a large percentage of patients remains recurrence-free without treatment or suffers a recurrence despite interferon. For melanoma patients at increased risk for recurrence, adjuvant interferon therapy is presently the only approved and efficacious systemic treatment. The use of interferon shall therefore be considered and discussed with the patient. An Overview of randomized trials on interferon alpha in various doses is shown in Table 7. Occurrence of grade 3 and 4 toxicity in high-dose versus low-dose versus observation in the E1690 trial [399] is shown in Table 8.

3.4.5 Algorithm for locoregional metastases (Figure 3)

3.4.6 Surgical therapy in locoregional metastases

3.4.6	Consensus-based recommendation
GCP	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 (Ro-resection) of the metastases.
	Strength of consensus: 96 %

E. Dippel

Definition: The following recommendations refer to cutaneous and subcutaneous locoregional metastases (in-transit and satellite metastases).

Cutaneous and subcutaneous regional metastases along with regional lymph node metastases constitute the most frequent initial metastases. 21 % of all patients with metastatic disease initially exhibit in-transit or satellite metastases [406]. Overall, the occurrence of in-transit metastases point to an unfavorable prognosis. In primary melanomas with in-transit or satellite metastases, a positive sentinel lymph node is also found in 41 % [407]. Still, depending on primary tumor thickness, 12–60 % of patients survive more than 5 years.

In the event of solitary or only few cutaneous in-transit metastases, the therapeutic goal is curative. Histologically controlled excision should therefore be performed, if an R0 situation can be achieved (macroscopically and microscopically complete removal of metastases). Excisions of multiple cutaneous metastases should be critically weighed, if complete removal is unlikely. In the presence of multiple, inoperable, locoregional cutaneous metastases on an extremity, regional chemotherapy as isolated limb perfusion comes into consideration [408]. In general, this is a palliative measure, albeit it entails long-term (> 1 year) tumor-free survival for a subgroup of patients. Metastases outside of the perfusion area may be treated by local application of immunomodulatory or cytostatic substances. Other procedures such as radiation therapy, electrochemotherapy, cryosurgery, or laser destruction may also be applied for local tumor control. Fundamental superiority of one over the other has not been proven and their use depends on individual factors.

3.4.7 Radiotherapy in locoregional metastases

3.4.7	Evidence-based recommendation
Grade of recommendation o	Local radiotherapy may be employed in satellite and in-transit metastases with the goal of local tumor control.
Level of Evidence 4	Systematic search of the literature *de-novo:* [93, 409–412]
	Strength of consensus: 100 %

P. Feyer

Current trial data reveals a good response of satellite and in-transit metastases to local radiation therapy [409, 411]. In-transit and satellite metastases may represent an indication for palliative radiation therapy. Palliative dose-adapted radiation therapy leads to reduction in tumor size, with smaller lesions manifesting better response rates and longer-lasting remissions [413–415]. Irradiation with fast electrons is preferable in superficial tumors, whereas deeper tumors

Table 7 Overview of randomized trials on interferon alpha in various doses.

Trial	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**
Medium-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	287	Update: not sign., HR = 1.22§	0.18	**Update: sign., HR = 1.38§**	**0.02**
		Initial: sign., HR n.r.	**0.0237**	**Initial: 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**

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).

are irradiated with photons after CT-based 3D planning. Applied doses vary prognosis-dependent between 5 × 4 Gy, 10 × 3 Gy or 20 to 25 × 2 Gy [93]. By additionally applying hyperthermia, complete response rates may be raised up to 62 % [411]. In select cases, HDR brachytherapy is employed [409].

3.4.8 Medical procedures in locoregional metastases

3.4.8.a	Consensus-based recommendation
GCP	Patients with satellite and in-transit metastases should be treated within the context of clinical studies if possible.
	Strength of consensus: 95 %

3.4.8.b	Evidence-based recommendation
Grade of recommendation o	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.
Level of Evidence 4	Systematic search of the literature *de-novo:* [416–425]
	Strength of consensus: 95 %

Table 8 Occurrence of grade 3 and 4 toxicity in high-dose versus low-dose versus observation in the E1690 trial [399].

	HDI (n = 212)				LDI (n = 214)				Obs. (n = 207)			
	Grade 3		Grade 4		Grade 3		Grade 4		Grade 3		Grade 4	
Toxicity	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Granulocytopenia	85	40	9	4	12	6	–	–	–	–	–	–
Liver toxicity	61	29	–	–	8	4	1	0.05	6	3	–	–
Fatigue	49	23	2	1	7	3	–	–	–	–	–	–
Neurology	42	20	–	–	14	6	–	–	2	1	–	–
Myalgia	35	16	2	1	18	8	–	–	–	–	–	–
Leukopenia	30	14	–	–	2	1	–	–	–	–	–	–
Nausea	19	9	–	–	5	2	–	–	2	1	–	–
Neuro-psychiatric symptoms	18	8	2	1	5	2	–	–	–	–	–	–
Neuro-motor symptoms	12	6	1	0.05	2	1	–	–	–	–	–	–
Emesis	11	5	1	0.05	3	1	–	–	2	1	–	–

HDI = high dose Interferon alpha, LDI = low dose Interferon alpha, Obs. = Observation

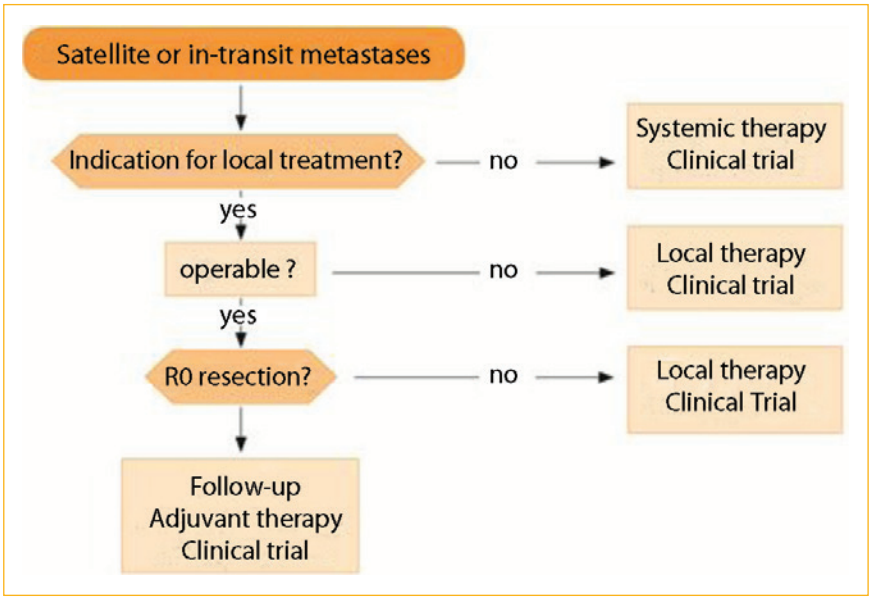

Figure 3 Algorithm for locoregional metastases. Options for local therapy: Intralesional Il-2 therapy, radiation therapy, intratumoral electrochemotherapy, topical immunotherapy with DNCB or DCP, isolated limb perfusion, CO_2 laser ablation.

J. Hassel

Cutaneous/subcutaneous metastases at a distance of up to 2 cm from the primary tumor/excision scar are categorized as satellite metastases, whereas cutaneous/subcutaneous metastases following the course of lymph vessels leading to a regional drainage basin are designated as in-transit metastases. These metastases frequently occur in multiple numbers and pose therapeutic problems. As surgery is the therapy of choice, solitary metastases may be resected.

When the number of satellite and in-transit metastases exceeds 5–10, surgical removal becomes difficult and other procedures are applied for local metastatic control. In this context, local procedures such as cryotherapy and radiation therapy may be considered. There are no studies examining response rates and long-term follow-up regarding these local therapeutic measures. Pharmacotherapeutic procedures may be employed as well. The most extensively studied among them is intratumoral application of interleukin 2, for which

high complete response rates have been reported. Topical treatments with imiquimod and obligate contact allergens like dinitrochlorobenzene (DNCB) or diphencyprone (DCP) are efficacious as well. Electrochemotherapy is another therapeutic alternative.

If tumor control by means of local and topical measures becomes impossible in the presence of multiple and larger in-transit and satellite metastases, hyperthermic isolated limb perfusion comes into consideration. This complex procedure is associated with greater risks for patients potentially resulting in the necessity for amputation of the perfused extremity.

Immunotherapy

Potential systemic effects represent one advantage of local immunotherapy. However, systemic adverse events such as flu-like symptoms may frequently be anticipated.

Intratumoral IL-2 therapy is a very efficacious local immunotherapy with reported response rates of more than 80 % when applied 2 to 3 times a week over the course of 2–57 weeks (3–18 MIU/session). Weide et al. treated 51 patients with a total of 917 in-transit metastases achieving local complete response (CR) rates of 69 %. With regard to injected metastases, a CR was seen in 79 %, and 1 % showed a partial response (PR) [425]. Ensuing evaluation suggested potential systemic effects of intratumoral IL 2, as unexpectedly good response rates to subsequent chemotherapy and unexpectedly long survival rates were demonstrated [296]. In a precursory trial, Radny et al. [421] treated a total of 24 patients with altogether 245 in-transit metastases and obtained a CR in 62 % and a PR in 21 % of patients. Regarding injected metastases, the CR was 85 % and PR 6 %. Smaller case series also showed good response rates to intratumoral IL 2 therapy [418, 420, 426].

Another therapeutic approach is stimulation of an immune response through dinitrochlorobenzene (DNCB) or diphencyprone (DCP)-induced obligate contact dermatitis. Strobbe et al. [424] combined 4-week long topical DNCB (2 % solution) application with subsequent DTIC chemotherapy in 59 patients. This led to local therapeutic response rates in 37 % of patients. In a retrospective analysis of 72 patients treated with a combination of DNCB and DTIC IV, Terheyden et al. [427] found response rates of 62 % in patients with stage III disease, yet only of 9 % in patients with stage IV disease. The latter finding was not superior to DTIC alone.

Electrochemotherapy

Electrochemotherapy (ECT) has proven to be an effective and well-tolerated, yet technically complex, therapeutic option for in-transit metastases. Due to unpleasant muscle contractions induced by electric pulses, ECT should be performed under sedation or general/regional anesthesia. ECT represents a combination of (local) cytostatic therapy with cisplatin or bleomycin and intralesionally applied electric pulses. These pulses render cell membranes more permeable to chemotherapeutic agents resulting in increased uptake of these drugs.

Sersa et al. [423] compared intratumoral application of cisplatin with and without subsequent electroporation. In this study, electroporation yielded an increase of objective remissions from 38 % in the cisplatin group (27 metastases) to 78 % in the combination group (82 metastases). Moreover, local tumor control after 2 years showed significant improvement in the combination group with 77 % compared to 19 % in the cisplatin group ($p < 0.0001$). Response rates between 77 and 87 % were achieved by applying intratumoral bleomycin [416, 419]. Byrne et al. even reported complete remission in 72 % following onetime treatment of 54 metastases in 19 patients.

Intratumoral cytotoxic therapy

Intratumoral injection of rose bengal, a fluorescein derivative, showed response rates of 48 % in 11 patients with large metastases [428]. A clinical phase III trial is currently being planned. As rose bengal is not listed in the European Pharmacopeia and is only available as chemical compound, its use in Germany is currently problematic. Rose bengal is thus not approved for use in humans and its compound purity is not assured.

Historic procedures

As to interferons, intratumoral interferon alpha, beta and also gamma have been used. In 51 patients, intratumoral interferon alpha 3 times/week yielded local response rates of 47 % and systemic response rates of 17,5 % for metastases not injected [429]. Interferon beta, characterized by high tissue permeability compared to interferon alpha, showed response rates of 50 % in 10 patients [430] and markedly fewer adverse events. Khorana et al. [431] conducted intratumoral adeno-interferon gamma (TG1041) therapy in 11 patients. However, this transgenic adenovirus, as vector for local interferon gamma production, did not display any noteworthy clinical events. Studies comparing various interferons are missing.

Intratumoral immunotherapy with Bacille-Calmette-Guerin (BCG) has been examined in several case series. Depending on approach, response rates between 45 % [432] and 74 % [433] were attained. In a meta-analysis with data from 15 small uncontrolled trials on BCG between 1966–1992, Tan and Ho [434] found complete remissions in 19 % and partial remissions in 26 %.

3.4.9 Limb perfusion in locoregional metastases

3.4.9	Consensus-based recommendation
GCP	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).
	Strength of consensus: 100 %

P. Hohenberger

In case of the above-mentioned metastasis, local tumor control marks the therapeutic goal. Individual patterns of metastatic dissemination and rapidity of progression vary greatly. Recurring metastases may be treated with a host of therapeutic methods such as surgery, CO2 laser ablation, cryotherapy, intralesional injections, regional drug therapy, immunomodulating agents, or radiation therapy [419, 435]. There is no evidence for the superiority of one method over the other or for potentially better results than through surgery, if an R0 resection is technically feasible [88]. Management of these patients strongly depends on the anatomic site of metastases.

Isolated limb perfusion is a standard treatment. Performed under general anesthesia, this technically complex surgical procedure aims at vascularly isolating an extremity by establishing a separate circulation. Mild tissue hyperthermia of 39–40 °C is induced within the perfusion circuit and, by means of nuclear medical procedures, it is ensured that no leakage into the systemic circulation exists. 10 mg melphalan/liter of perfused extremity volume is then applied within the perfusion circuit for 90 minutes, if applicable in combination with 3–4 mg rhTNF alpha (recombinant human tumor necrosis factor alpha). Cisplatin or dacarbazine may also be administered. Postoperative complications like erythema, hyperthermia, blistering, or desquamation of the stratum corneum are typical. Rhabdomyolysis potentially resulting in compartment syndrome as well as cardial stress upon application of rhTNF alpha may occur.

Primarily used in Australia, isolated limb infusion (ILI) [428, 436] is less invasive, does not require general anesthesia, and may be performed repeatedly [437], but is limited with respect to drug application (no administration of TNF).

Isolated limb perfusion with rhTNF alpha can only be performed at accredited centers.

Clinical aspects with regard to indication

On principle, there is an indication for isolated limb perfusion (ILP) at stages IIIB, IIIC and IV. At any rate, it should be considered prior to limb amputation (e.g. because of ulceration of recurrent melanoma) [435, 438].

Patients with in-transit metastases display 5-year survival rates of roughly 25 % [17]. Isolated limb perfusion or isolated limb infusion allow for a rate of lasting complete or partial remissions.

In a systematic review of 22, almost exclusively observational, studies with 2 018 patients [438], isolated limb perfusion yielded median complete remission (CR) rates of 58 % and response rates (PR + CR) of 90 %. Response rates for ILP with melphalan alone was lower than for melphalan and rhTNF alpha combined (46 % vs. 69 %). In a randomized trial comparing ILP with melphalan alone to ILP with melphalan and rhTNF alpha [439], no significant benefit was detected for combination therapy. However, the trial was aborted at the behest of the DSMB. The rate of complete remissions in the TNF/melphalan arm was 42 % versus 20 % in the melphalan arm ($p = 0.1$). Predictive parameters for a response, particularly for CR, are tumor stage, number of in-transit metastases (< 10) and maximum tumor diameter < 4 cm [438, 440]. For large-volume melanoma metastases (bulky disease), there is evidence that ILP with TNF may be more efficacious than ILP with melphalan alone [441, 442].

Not all studies evaluated recurrence rates after achieving CR through ILP. The median recurrence-free interval was 10.5 months [438].

Long-term results of isolated limb perfusion are stage-dependent. For stage IIIB disease, Deroose et al. reported 10-year survival rates of 31 %. In stage IIIC patients receiving ILP, relatively rapid systemic progression (median systemic progression-free interval 11 months versus 55 months for ILP at stage IIIB) has to be expected. Patients with a complete response after ILP exhibit disease-specific median survival time of 44 months [440]. For melanoma patients with multiple in-transit metastases, satellitosis, and soft tissue metastases, isolated limb perfusion constitutes an effective, but complex treatment option in the absence of tumor control by other local therapeutic measures.

3.5 Diagnostics and therapy in the stage of distant metastasis

3.5.1 Algorithm initial stage IV (Figure 4)

3.5.2 Staging diagnostics in stage IV

Apart from whole-body examination comprising inspection of the entire integument including adjacent and visible mucous membranes as well as palpation of lymphatic drainage areas and lymph node basins, the following procedures are recommended (Table 9).

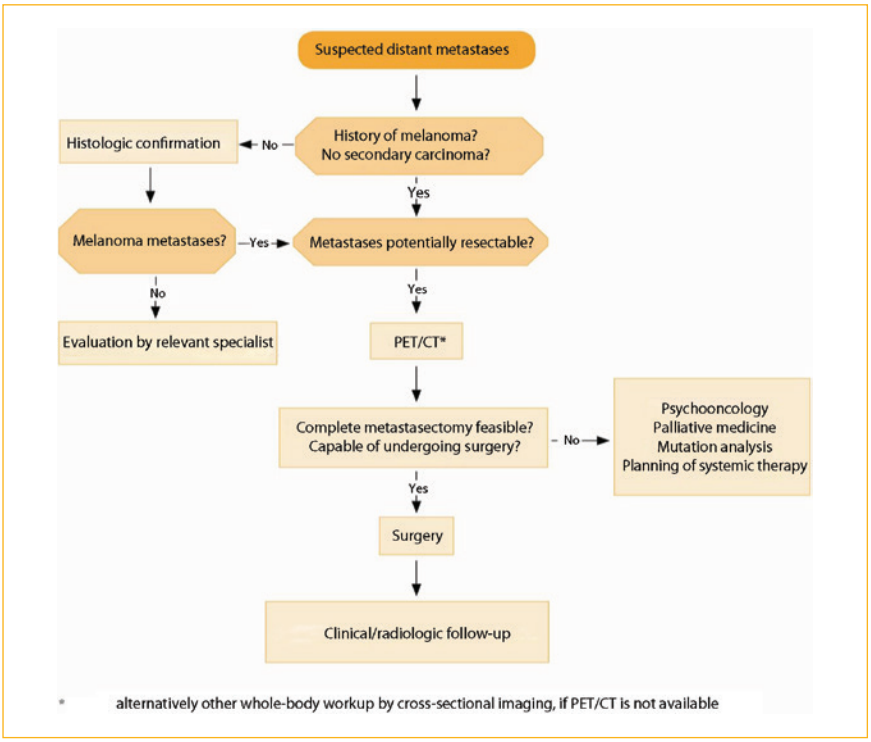

Figure 4 Algorithm for workup and surgery indication for suspected distant metastases.

3.5.2.1 Abdominal ultrasound in distant metastasis

3.5.2.1	Evidence-based recommendation
Grade of recommendation o	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.
Level of Evidence 3b	Systematic search of the literature *de-novo:* [443–445]
	Strength of consensus: 100 %

H.-P. Schlemmer

Abdominal sonography is a frequently performed procedure in clinical practice. Its practicability with regard to quality, reproducibility, and cost depends on the examiner and the area of the body examined. Technical limitations result from the low depth of sound wave penetration as well as the sound shadow due to abdominal air and osseous structures. Thus, especially intestinal and osseous metastases cannot be detected early. Diagnostic validity studies have been frequently limited by low case numbers, variation of diagnostic standards over time, inconsistent determination of the gold standard, missing histopathologic correlation, and difficult quantifiability of false negative findings. In general, sonography has a low sensitivity for the detection of small metastases and is inferior to MRT, CT, and PET or PET/CT.

3.5.2.2 Lymph node sonography in distant metastasis

3.5.2.2	Evidence-based recommendation
Grade of recommendation o	Locoregional lymph node sonography may be performed in patients with suspected or proven distant metastases of a melanoma.
Level of Evidence 1a	Systematic search of the literature *de-novo:* [113, 104]
	Strength of consensus: 92 %

H.-P. Schlemmer

Lymph node sonography is a frequently performed procedure in clinical practice. Superficially located lymph nodes, such as e.g. cervical, axillary, and inguinal, can be more reliably detected and evaluated than abdominal lymph nodes. Technical limitations result from the low depth of sound wave penetration as well as the sound shadow due to abdominal air and osseous structures. Thus, especially intestinal and osseous metastases cannot be detected early. Published studies exhibit low evidence levels. Diagnostic validity studies have been frequently limited by low case numbers, variation of

Table 9 Overview of procedure recommendations at stage IV.

Procedure	Recommendations on staging workup in patients with suspected distant metastases or evidence thereof	Grade of recommendation	Level of Evidence
Cranial MRI	Yes	GCP	–
Cross-sectional imaging (whole-body without head)*	Yes	B	1a
Abdominal sonography	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
Strength of consensus: 95 %			
*PET/CT, CT, MRT (whole-body respectively)			

diagnostic standards over time, inconsistent determination of the gold standard, missing histopathologic correlation, and difficult quantifiability of false negative findings. In general, sonography has a low sensitivity for the detection of small lymph node metastases.

A meta-analysis [113] of 12 studies with a total of 6 642 patients at AJCC stage I–II (5 studies), III (6 studies), and IV (1 study) revealed that lymph node sonography is superior to palpation for the detection of lymph node metastases. A diagnostic study with 100 consecutive patients [108] found a sensitivity of regional lymph node metastases of only 8 %, with a specificity of 88 %. Another study with a small case number (52 patients) reported an accuracy of 89 % for the detection of metastases in newly appearing and palpable lymph nodes [301]. Just like Jimenez-Requena [132], Xing et al. confirmed that lymph node sonography had the highest accuracy and highest diagnostic validity in the initial and follow-up staging of regional lymph nodes [104].

The accuracy of lymph node sonography depends on the location of affected lymph nodes. For example, retroperitoneally or intrathoracically located lymph node metastases cannot be detected by sonography. Here, the use of CT, MRT or PET/CT would be necessary. Lymph node sonography shall be performed in stage III patients, if there is a potential intent to cure. It may be performed in stage IV patients, but its indication is particularly dependent on individual disease progression and potential therapeutic approaches.

For the most part, there is no curative intent in stage IV patients. Therefore, depending on therapeutic consequences, sonography "may" be recommended at stage IV.

3.5.2.3 Cross-sectional imaging for distant metastasis

3.5.2.3	Evidence-based statement
Level of Evidence 1a	Cross-sectional imaging methods are today the standard in the staging diag-nostics of melanoma of stage III and above. Here it has been shown that PET/CT is superior to the other methods in diagnostic accuracy.
	Systematic search of the literature *de-novo:* [104]
	Strength of consensus: 100 %

H.-P. Schlemmer

In a meta-analysis, Xing et al. showed that PET/CT is the most sensitive and most specific procedure for the detection of extracerebral distant metastases [104]. According to comparative studies on the detection of extracerebral metastases in melanoma patients between PET/CT versus whole-body MRI and whole-body MRI versus whole-body CT, PET/CT is superior to whole-body MRI und whole-body MRI is superior to whole-body CT [302]. This holds true for specialized centers. Regarding the practical implementation of cross-sectional imaging, the practical and economic availability of the respective imaging method has to be taken into account. Thus, whole-body MRI or whole-body CT may also be used as alternatives to PET/CT.

In stage IV melanoma patients undergoing treatment, cross-sectional imaging procedures should be repeated at regular intervals, i.e. depending on therapeutic agent every 6–12 weeks.

3.5.2.4 Cranial MRI for distant metastasis

3.5.2.4	Consensus-based statement
GCP	For the detection of brain metastases, MRI possesses the greatest diagnostic accuracy.
	Strength of consensus: 96 %

H. Schlemmer, M. Ganten

As mentioned before, cranial MRI is generally more sensitive for the detection of cerebral metastases than CT and FDG-PET/CT. However, currently published studies of melanoma patients only feature low evidence levels and inhomogeneous patient groups. These studies suggest the use of cranial MRI only in patients with stage III–IV disease as well as in patients whose adjuvant therapeutic regimen would change, if cerebral metastases were detected [106, 107].

3.5.2.5 Skeletal scintigraphy for distant metastasis

3.5.2.5	Consensus-based recommendation
GCP	In patients with advanced disease with bone pain, skeletal scintigraphy may be employed in addition for clarification of skeletal metastasis.
	Strength of consensus: 92 %

S. Reske

With regard to skeletal scintigraphy, available data provides no reliable evidence.

3.5.2.6 S100B and LDH for distant metastasis

3.5.2.6	Evidence-based recommendation
Grade of recommendation A	S100B shall be measured in patients with suspected or proven distant metastases.
Level of Evidence 1a	Systematic search of the literature *de-novo:* [118, 446]
	Strength of consensus: 92 %

3.5.2.7	Evidence-based recommendation
Grade of recommendation A	LDH as part of the current AJCC classification shall be measured in patients with suspected or proven distant metastases.
Level of Evidence 1b	Systematic search of the literature *de-novo:* [17, 447, 448]
	Strength of consensus: 92 %

C. Kochs, D. Schadendorf

S100B

The meta-analysis by Mocellin was able to demonstrate a significantly increased risk for poorer survival rates (HR = 2.23; $p < 0.0001$) in S100B-positive melanoma patients (stage I–IV). Unlike stage I–III, studies in stage IV melanoma patients displayed relevant heterogeneity. The meta-risk, however, was – independent of subgroup – always higher for S100B-positive patients [118], confirming a positive correlation between TNM stage and S100B-positivity. There is a significant rise in the percentage of S100B-positive patients when comparing various trials with patients at stage I–III (13.4 %), stage I–IV (28.3 %), and stage IV (41.8 %) alone ($p < 0.0001$). In a prognostic trial with 208 patients (54 at stage III, 129 at stage IV), Paschen et al. also showed a significant correlation between S100B values and tumor stage ($p < 0.0001$) [446]. Scientific literature provides varying data on the sensitivity of S100B in stage IV disease: it was 94.1 % in a diagnostic and prognostic trial examining blood samples from 90 patients with histologically proven melanoma metastases. In a previous study, it was 89.4 %, specificity being 84.8 % [449]. Schultz et al. reported an S100B sensitivity of 69 % using a cut-off of 0.3 µg/l [307], Brouard et al. of 86 % [306].

Given the proven correlation with disease stage, S100B shall be measured in patients with suspected distant metastases or evidence thereof.

LDH

Various studies have demonstrated the significance of LDH as prognostic parameter in advanced melanoma.

According to the current AJCC classification [17], LDH is always to be measured after progression to stage IV. Based on data from the AJCC Melanoma Staging Database 2008, elevated LDH levels in stage IV patients represent a highly significant and independent prognostic parameter for survival. In stage IV patients with normal LDH serum levels at the time of diagnosis, 1- and 2-year survival rates were 65 % and 40 % respectively, compared to 32 % and 18 % in patients with elevated serum LDH levels ($p < 0.0001$).

Analysis of two large randomized trials in patients with advanced melanoma also showed a correlation between rising serum LDH levels (even when within normal limits) and poorer survival (Oblimersen GM301 [n = 760], EORTC 18951 [n = 325]) [447].

Deichmann et al. [448] investigated serum levels of various tumor markers for their potential to differentiate between progressive and non-progressive melanoma. Evaluation of 71 consecutive patients with stage IV disease yielded a sensitivity for LDH of 79 % (S100B 91 %) and a specificity of 92 % (S100B 76 %) in progressive melanoma. Regression analysis revealed LDH to be the only statistically significant marker for progressive disease [448].

3.5.3 Diagnostics in metastasis of occult melanoma

3.5.3.	Consensus-based recommendation
GCP	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.
	Strength of consensus: 100 %

S. Reske

"Patients with occult primary melanoma usually present with lymph node disease, a soft tissue metastasis, or widespread systemic disease, in the absence of a primary tumour and the diagnosis is made by pathological examination of the lymph node, or metastasis which shows the characteristics of melanoma. Such patients should be examined carefully to exclude the possibility of a hidden primary by examination of the eyes, inner ears […], and possibly colonoscopy [450]. The presenting lymph nodes or metastases should be treated appropriately", according to guidelines, "regardless of the inability to detect the primary tumour." ([19], p. 141). A preceding staging workup also follows applicable standards for stage III and IV melanoma [451–453].

"Melanoma is among a number of cancers in humans where the primary tumour cannot always be found. In some patients the primary may be in an obscure site such as the eye, ear or the intestine, but in the majority it is likely that the primary tumour has been destroyed by the host's immune system via lymphocyte activation. [451, 453]. It is likely that total regression occurs in 10–20% of melanomas, though only those where there have been metastases are diagnosable (about 5 % of melanomas)." ([19], p. 141). Two studies have revealed that patients with an occult primary melanoma show better 5-year [454] and 1-year survival rates [455] than those with known primary melanoma. "This suggests an intrinsically superior host tumour interaction in those with occult primary melanoma." ([19], p. 141). Using FDG-PET/CT, roughly 30 % of patients exhibit additional melanoma metastases during workup for an occult primary tumor. The rate of false positive PET/CT findings is approximately 5 % [456].

3.5.4 Molecular pathology workup

3.5.4	Consensus-based recommendation
GCP	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.
	Strength of consensus: 100 %

C. Rose

New and effective drugs that specifically inhibit mutations in activating oncogenes have been increasingly used in the treatment of metastasized melanoma. Prior to their administration, respective mutations have to be detected by means of molecular biology methods. This may be done on paraffin sections. As these therapeutic agents are currently given in metastatic disease or surgically non-resectable tumors, mutation testing shall only be performed in high-risk patients [385]. Testing is best conducted on tissue of current metastases to ascertain that the tumor actually displays the mutation.

50 % of primary melanomas feature BRAF mutations, making it the most frequently mutated oncogene in melanoma [457]. Treatment with selective BRAF inhibitors shows an objective clinical response in 48 % of patients [458].

Approximately 5 % of acral and mucosal melanomas exhibit activating kit mutations. Upon detection of such a mutation, treatment with c-kit inhibitors may be initiated. Testing for respective mutations shall be confined to the aforementioned melanoma subgroup [459, 460]. Once targeted therapeutic agents become available for N-RAS mutations, testing should be extended respectively. Activating N-RAS mutations may be found in roughly 15 % of melanomas [461].

3.5.5 Surgical therapy for distant metastases

3.5.5	Evidence-based recommendation
Grade of recommendation B	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.
Level of Evidence 2b	Systematic search of the literature *de-novo:* [462–464]
	Strength of consensus: 100 %

P. Hohenberger, L. Swoboda

No randomized trials exist investigating surgical interventions for distant metastases in melanoma. Before deciding on surgery, the extent of tumor dissemination should be ascertained, e.g. by imaging methods over the course of time [463, 465–467].

Prospective data has been obtained from adjuvant therapeutic studies, in which patients had to undergo surgery for new distant metastases [365]. Collective analysis of systemic therapy in metastatic disease reveals that patients with skin and subcutaneous metastases show more favorable survival rates than those with lung or visceral metastases [468]. In addition, there is data from retrospective cases series that evaluated metastasectomy in patients with metastases to the skin, soft tissue, abdomen (small intestine and liver), adrenal glands, and lungs. For lung metastases, long-term data from the "International Registry of Lung Metastases" (5 206 patients, among them 328 with melanoma) may be used [463].

The same requirements should apply concerning surgery indication for other metastatic sites.

Apart from duration of the metastasis-free interval, the number of metastases as well as initial tumor stage have been shown to be prognostically relevant for all analyzed metastatic sites (lung, adrenal glands, small intestine, liver, brain) [462, 464]. These surrogate parameters of tumor biology provide valuable information that is used in the decision process for metastasectomy.

Alternatively, a wait-and-see approach or systemic chemotherapy may initially be chosen, if this course of action facilitates differentiation of an initially solitary metastatic location as the only or merely the first of many other sites.

There is comprehensive data for the following metastatic sites:

Lung metastases
Approximately 13 % to 19 % of melanoma patients develop lung metastases within 5 years of primary diagnosis [467, 469]. 2-year survival rates are 14 %; after 5 years, 6 % of patients are still alive [467]. Retrospective studies show that patients undergoing complete resection (R0) of pulmonary metastases may achieve 5-yaear survival rates of 21 % [467] and up to 33 % [463, 470, 471]. On the other hand, incomplete resection (R1, R2) resulted in 5-year survival rates of only 13 % [467] and 0 % [463]. Repeated surgery may also be useful, if an R0 situation can be achieved [467].

Visceral metastases
The prevalence of visceral metastases in stage IV patients is up to 28 %. In this patient group, the stool guaiac test has proved to be useful in the workup for metastases [472]. In intestinal metastasis, potentially curative resections may be performed with little morbidity in up to 63 % of cases. Median survival time in patients undergoing R0 resection is up to 24 months and median disease-free interval up to 13.1 % [464, 473]. When deciding on surgery, expected procedural complexity as well as potential morbidity are of great significance. Retrospective studies have revealed that patients undergoing resection showed better survival rates than those receiving systemic treatment protocols [474, 475].

Cerebral metastases
In the absence of extracranial disease manifestations, resection of solitary cerebral metastases is advocated for melanoma patients in otherwise good general condition.

Other metastatic sites
Upon resection of liver metastases, median survival intervals of 28 months have been reported for melanoma patients [476]. Long-term survival of more than 5 years has been repeatedly observed. Analysis of patients with solitary metastases to the adrenal glands yielded median survival times of 60 months [477].

In a palliative situation, deviation from the prerequisites stated in the recommendation is acceptable, if the procedure is aimed at markedly enhancing quality of life.

3.5.6 Medical therapy in stage IV

3.5.6.1 Adjuvant medical therapy after excision of metastasis

3.5.6.1	Consensus-based recommendation
GCP	A general recommendation on adjuvant therapy after excision of metastasis cannot be given due to lack of data.
	Strength of consensus: 100 %

F. Meier, C. Garbe

Median survival time in metastatic stage IV melanoma is estimated to be 8 months (+ 2 months) [17], albeit great interindividual variations occur. There is general consensus that surgery is the method of choice for melanoma metastases, if complete removal (R0 resection) is feasible. No data exists on adjuvant therapy following successful R0 resection in stage IV disease. Inclusion into a clinical trial should be considered and close clinical and radiologic follow-up is recommended.

3.5.6.2 Algorithm medical therapy in stage IV (Figure 5)

3.5.6.3 Therapy with signal transduction inhibitors (BRAF inhibitor)

F. Meier, C. Garbe

BRAF mutations are detected in 40–60 % of melanomas [478]. 90 % of these mutations result in a substitution of the amino acid valin (V) for glutamate (E) (BRAFV600E),

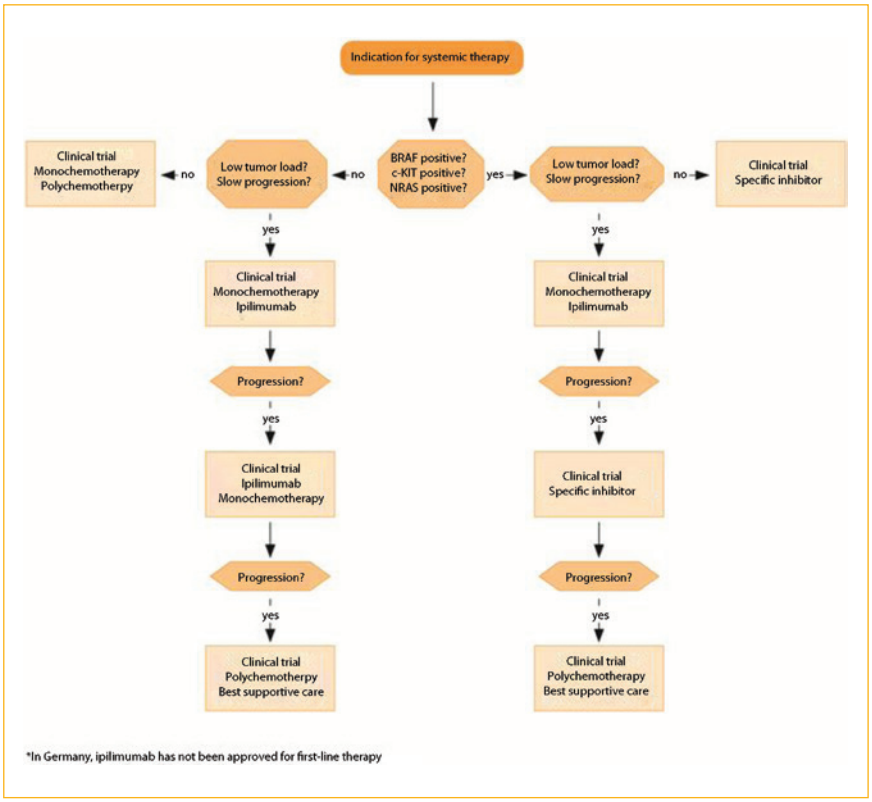

Figure 5 Algorithm for systemic therapy at stage IV as well as non-resectable stage III.

whereas other BRAF inhibitor-sensitive mutations like BRAFV600K occur less frequently. This leads to constitutive activation of the RAF-MEK-ERK signal transduction pathway, which is relevant for tumor development and progression in melanoma.

3.5.6.3	Evidence-based recommendation
Grade of recommendation A	In BRAF inhibitor-sensitive BRAF mutation, therapy with a BRAF inhibitor shall be performed.
Level of Evidence 1b	Systematic search of the literature *de-novo:* [458, 479]
	Strength of consensus: 76 %

By June of 2012, the results of two randomized clinical trials on BRAF inhibition in patients with metastatic melanoma had been published.

In a phase III trial of stage IIIC–IV melanoma with inoperable, previously untreated metastases and BRAFV600E mutation, patients either received the BRAFV600E kinase inhibitor vemurafenib (960 mg PO bid) or dacarbazine (1 000 mg/m2 BSA IV q 3 weeks) [458].

Objective response rates for vemurafenib and dacarbazine were 48 % and 5 % respectively. The duration of the response interval has not yet been ascertained. Furthermore, vemurafenib resulted in significant improvement of survival rates after 6 months compared to dacarbazine (84 % versus 64 %).

The second phase III trial examining the BRAF inhibitor dabrafenib in comparison with dacarbazine in 250 patients with previously untreated metastases and BRAFV600E mutation yielded comparable results [479]. Objective response rates were 50 % versus 6 % respectively. Duration of median response was 5.5 months for dabrafenib, yet has not been determined for dacarbazine.

Remarkably, patients with a high tumor load (M1c) particularly benefited from BRAF inhibitor therapy. Response duration, however, is limited by the development of resistance and amounts to approximately 5–7 months.

In patients with only few pulmonary metastases, chemotherapy has frequently shown very good response rates. Alternatively, ipilimumab may be used. The two latter therapeutic options may be primarily considered in patients with low tumor load, slow progression, and only few clinical symptoms.

BRAF inhibitors are contraindicated for melanoma patients with wild-type BRAF. The recommended dose for vemurafenib (already approved) is 960 mg twice daily. Dose reduction by more than 50 % is not recommended.

Table 10 Overview of randomized trials on BRAF inhibitors.

Trial	Design	Treatment arms	Patient(s)	Overall survival	Median progression-free survival	Response rate*	Median response duration
Chapman et al. 2011	RCT, open label	Vemurafenib DTIC	337 338	Rate after 6 months: 84 % vs. 64 % HR 0.37 (95 % CI 0.26–0.55; p < 0.001) sign.	5.3 months vs. 1.6 months HR 0.26 (95 % CI 0.20–0.33; p < 0.001) sign.	48 % vs. 5 %, p < 0.001, sign.	Not yet ascertainable
Hauschild et al. 2012	RCT, open label	Dabrafenib DTIC	187 63	HR 0.61 (95 % CI 0.25–1.48)	5.1 months vs. 2.7 months HR 0.30 (95 % CI 0.18–0.51; p < 0.0001) sign.	50 % vs. 6 %	5.5 months vs. not yet ascertainable

RCT = randomized clinical trial, HR = hazard ratio, CI = confidence interval, vs. = versus, sign. = significant.
*Response rate: complete remission plus partial remission (= decrease in the sum of longitudinal diameters of all measurable metastases by more than 30 %). (Note: in the trial by Chapman et al., response assessment was performed by the examiners themselves, not blinded).

Most common adverse events of BRAF inhibition (> 30 %) include arthralgia, rash, alopecia, fatigue, photosensitivity, nausea, pruritus, papillomas, and squamous cell carcinomas, frequently of the keratoacanthoma-type.

An overview of randomized trials on BRAF inhibitors is shown in Table 10.

3.5.6.4 Therapy with signal transduction inhibitors (c-KIT inhibitor)

3.5.6.4	Consensus-based recommendation
GCP	In a c-KIT inhibitor-sensitive c-KIT mutation, the option of therapy with a c-KIT kinase inhibitor shall be examined.
	Strength of consensus: 88 %

F. Meier, C. Garbe

So far, observations from phase II studies suggest that patients with c-KIT aberrations may respond to c-KIT kinase inhibitor therapy [459, 460]. Patients with a c-KIT mutation in exon 11 or 13 responded best to imatinib (400 mg/d). Generally rare, c-KIT mutations most likely occur in acral lentiginous and mucosal melanomas. Most common adverse events include edema, fatigue, diarrhea, anorexia, nausea, neutropenia, and elevated liver enzymes. Overall, adverse events are usually mild to moderate.

3.5.6.5 Immunotherapy at stage IV

3.5.6.5	Evidence-based recommendation
Grade of recommendation A	In melanoma patients with non-resectable metastases, the option of immunotherapy with ipilimumab shall be examined.
Level of Evidence 1b	Systematic search of the literature *de-novo:* [480, 481]
	Strength of consensus: 79 %

F. Meier, C. Garbe

Ipilimumab is a human IgG1 monoclonal antibody that blocks the cytotoxic T lymphocyte associated antigen (CTLA-4), which negatively regulates previously activated T cells. By blocking CTLA-4, activation and proliferation of T cells, autoimmunity and antitumor immunity is augmented. In a phase III study, patients with inoperable, previously treated metastatic stage III–IV melanoma received ipilimumab (3 mg/kg body weight), a vaccine (gp100), or ipilimumab + gp100 [480]. The trial revealed significant improvement in median overall survival for ipilimumab and the combination arm (10.1 and 10.0 months respectively) compared to the vaccine arm (6.4 months). Severe (grade 3 or 4) immune-mediated adverse events were observed in 10–15 % of patients treated with ipilimumab and in 3 % of vaccine patients. Another phase III trial examined patients with inoperable, previously untreated metastatic stage III–IV melanoma who received either ipilimumab

Table 11 Overview of randomized trials on ipilimumab.

Trial	Design	Treatment arms	Patient(s)	Overall survival	Response rate*	Median response duration
Hodi et al. 2010	RCT, double blind	Ipi + gp100 Ipi gp100	403 137 136	10.0 months vs. 10.1 months vs. 6.4 months, sign., HR 0.68; p < 0.001	5.7 % (n = 23) vs. 11 % (n = 15) vs. 1.5 % (n = 2), sign., p = 0.04	11.5 (5.4–NR) vs. NR (28.1–NR) vs. NR (2.0–NR) months therapy-related deaths: n = 14
Robert et al. 2011	RCT, double blind	Ipi + DTIC Placebo + DTIC	250 252	11.2 months (95 % CI 9.4–13.6) vs. 9.1 months (95 % CI 7.8–10.5) HR 0.72; p < 0.001	15.2 % vs. 10.3 %, n.s., p = 0.09	19.3 months (95 % CI 12.1–26.1) vs. 8.1 months (95 % CI 5.19–19.8), p = 0.03
Hersh et al. 2011 [482]	RCT, open label	Ipi Ipi + DTIC	37 35	11.4 months (95 % CI 6.1–15.6) vs. 14.3 months (95 % CI 10.2–18.8), n.s.	5.4 % (95 % CI 0.7–18.2) vs. 14.3 % (95 % CI 4.8–30.3), n.s.	n = 2 (1.6+/1.85+ years) vs. n = 2 (1.73+/1.76+ years)

RCT = randomized clinical trial, Ipi = ipilimumab, gp100 = vaccine, HR = hazard ratio, CI = confidence Interval, vs. = versus, sign. = significant, n.s. = not significant, NR = not reached.
*Response rate: complete remission plus partial remission (= decrease in the sum of longitudinal diameters of all measurable metastases by more than 30 %).

(10 mg/kg body weight) plus dacarbazine or only dacarbazine [481]. This trial also showed significant improvement in overall survival for ipilimumab plus dacarbazine (11.2 months) compared to monochemotherapy with dacarbazine (9.1 months). Severe (grade 3 or 4) adverse events were seen in 56.3 % of patients treated with ipilimumab plus dacarbazine and in 27.5 % of dacarbazine patients. Four cycles of ipilimumab therapy (3 mg/kg body weight IV over 90 minutes q 3 weeks) are recommended. As ipilimumab may induce severe immune-mediated adverse reactions, patient compliance is indispensable. Particularly cutaneous (rash), gastrointestinal (colitis), hepatic (hepatitis), endocrine (hypophysitis), and neurologic adverse reactions may occur. Guidelines for proper management of adverse events have been developed and may also be reviewed in the prescribing information. As response to ipilimumab may be delayed and not occur until 12 weeks or even months after treatment initiation, final assessment of tumor response should only be performed after completion of four cycles.

An overview of randomized trials on ipilimumab is shown in Table 11.

There are 2 randomized trials on specific immunotherapy in metastatic melanoma. A phase III study investigating vaccination with peptide-pulsed dendritic cells neither showed improvement in response rates nor in overall survival compared to DTIC [483]. In a recent phase III trial examining high-dose IL-2 therapy with and without peptide vaccine (gp100:209–217(210M) plus Montanide ISA-51), combination treatment revealed a significant increase in response rates und progression-free survival [484]. Significant improvement in overall survival, however, was not observed (p = 0.06).

The combination of interferon-alpha with dacarbazine or temozolomide (chemoimmunotherapy) has been analyzed in 6 randomized trials [485–489]. An older study from 1991 showed a significant increase in response rates and overall survival for 30 patients treated with DTIC plus interferon-alpha, albeit the control group contained more male patients with poorer prognosis [486]. All other trials did not manifest any survival benefit, but rather higher toxicity. Chemoimmunotherapy should therefore only be offered within the context of clinical trials.

Based on phase II trials, high-dose IL-2 therapy is alternatively available in the USA, whereas this therapeutic regimen is not used in Europe due to high toxicity and lack of data from phase III studies.

3.5.6.6 Monochemotherapy

3.5.6.6.a	Evidence-based recommendation
Grade of recommendation o	Monochemotherapy with dacarbazine is an established systemic therapy and may be offered to melanoma patients with non-resectable metastases.
Level of Evidence 1b	Systematic search of the literature *de-novo:* [458, 481, 483, 486–501]
	Strength of consensus: 85 %

Table 12 Overview of monochemotherapies in metastatic melanoma.

Agent	Dose
Dacarbazine	800–1 200 mg/m² IV day 1 every 3–4 weeks or 250 mg/m² IV day 1–5 every 3–4 weeks
Temozolomide	150–200 mg/m² PO day 1–5 every 4 weeks
Fotemustine	100 mg/m² IV day 1, 8, und 15, followed by a 5-week interval, continuation every 3 weeks
Source: S2 Guideline Melanoma, 2007	

3.5.6.6.b	Evidence-based statement
Level of Evidence 1b	The efficacy of temozolomide and fotemustine is equivalent to that of dacarbazine.
	Systematic search of the literature *de-novo:* [490, 496, 498]
	Strength of consensus: 85 %

F. Meier, C. Garbe

In randomized clinical trials, the chemotherapeutic agents dacarbazine, temozolomide, carboplatin, cisplatin, paclitaxel, vindesine, detorubicin, and fotemustine have been examined as single substances, yet without placebo-control arm. None of these agents resulted in significant prolongation of survival times. The alkylating cytostatic agent dacarbazine (DTIC) has been used most frequently and serves as standard or reference drug in patients with metastatic melanoma. Objective response rates of 5–12 % have been described in recent phase III trials, but only few patients showed a lasting response. Temozolomide is an oral alkylating cytostatic agent with the same active metabolite and a similar favorable adverse-events profile as dacarbazine. In phase III trials, temozolomide and dacarbazine have shown equivalent efficacy [496, 498]. Common adverse events of dacarbazine and temozolomide include anorexia, nausea and vomiting, leucopenia, thrombopenia, and anemia. In a phase III study, fotemustine was equivalent to dacarbazine with respect to survival and response rates [490].

An overview of monochemotherapies in metastatic melanoma is shown in Table 12.

3.5.6.7 Polychemotherapy

3.5.6.7.a	Evidence-based statement
Level of Evidence 1a	Polychemotherapy is associated with higher response rates; median overall survival is not significantly altered.
	Systematic search of the literature *de-novo:* [493, 499, 502–507]
	Strength of consensus: 85 %

3.5.6.7.b	Consensus-based recommendation
GCP	Patients with tumor progression during previous systemic therapy or initially rapid tumor progression may be offered polychemotherapy.
	Strength of consensus: 84 %

A. Pflugfelder

A systematic review from 2003 found 7 randomized studies comparing polychemotherapy to DTIC [505]. The following regimens were investigated in comparison to DTIC alone: 1. the Dartmouth regimen (dacarbazine, carmustine, cisplatin and tamoxifen), 2. a combination of vindesine and DITC, 3. a combination of vinblastine, bleomycin and cisplatin, 4. a combination of detorubicin and DTIC, 5. a combination of carmustine and vincristine, 6. a combination of carmustine, vincristine and DTIC, 7. a combination of lomustine, vincristine and DTIC, and 8. the BHD regimen (carmustine, hydroxyurea, and DTIC). The Dartmouth regimen showed significantly increased response rates (18.5 % vs. 10.2 %, p = 0.09) in one study, but none of the trials yielded significant improvement in survival. Compared to DTIC monotherapy, all other regimens exhibited markedly higher toxicity [493, 499, 502–504, 506, 507]. Thus, polychemotherapy cannot be recommended as standard first-line therapy.

Patients with high tumor load, rapid metastatic dissemination, and/or progression despite previous treatment(s) pose a particular therapeutic challenge in everyday clinical practice. In these cases, temporary disease stabilization comes to the fore. Due to high response rates during polychemotherapy, some of these patients may experience alleviation of symptoms and possibly, in case of tumor remission, at times also prolongation of survival time. This has to be weighed against high toxicity rates and the amount of time required for these therapies in a situation where lifetime is a limiting factor. Common polychemotherapy regimens are listed in table Table 13.

The CarboTax regimen has been frequently employed recently. In a randomized trial (CarboTax + sorafenib/placebo), it displayed a surprisingly long progression-free survival time of 4 months [508]. Further prospective and retrospective studies have reported median overall survival between 7 and 11 months, depending on the percentage of M1c patients. Only 2 out of 405 patients in 7 trials treated with CarboTax experienced complete remission. Common adverse events during therapy include hair loss in the days following the infusion, arthralgia, fatigue, and, particularly in the long run, sensory neuropathies. Obligate blood count changes require close monitoring and treatment. The risk for life-threatening allergic reactions to the solvent cremophor in paclitaxel as well as to carboplatin may be reduced by appropriate premedication. In summary, there is urgent need for a less toxic last-line therapy that may, however, still impart hope.

Table 13 Overview of various polychemotherapy regimens in metastatic melanoma.

Regimen	Dose
CarboTax regimen	Carboplatin AUC6 IV Paclitaxel 225 mg/m² IV d1q21, dose reduction from cycle 5 (C AUC5/P 175 mg/m²)
GemTreo regimen	Gemcitabine 1000 mg/m² IV Treosulfan 3 500 mg/m² IV d1,d8q28
DVP regimen	DTIC 450 mg/m² IV Vindesine 3 mg/m² IV Cisplatin 50 mg/m² IV d1,d8q21/28
BHD regimen	BCNU (carmustine) 150 mg/m² IV d1q56 Hydroxyurea 1500 mg/m² PO d1q56 DTIC 150 mg/m² IV d1-5q28
BOLD regimen	Bleomycin 15 mg IV d1,d4q28 Vincristine 1 mg/m² IV d1,d5q28 CCNU (lomustine) 80 mg/m² PO d1q28 DTIC 200 mg/m² IV d1–5q28

Source: S2 Guideline Melanoma, 2007
AU = area under the curve, d1q21 = d day of drug administration, q duration of cycle

An overview of various polychemotherapy regimens in metastatic melanoma is shown in Table 13.

3.5.6.8 Biochemotherapy

3.5.6.8	Evidence-based recommendation
Grade of recommendation A	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.
Level of Evidence 1a	Guideline adaptation: [509]
	Strength of consensus: 88 %

A. Pflugfelder

The above-stated recommendation regarding biochemotherapy and the present text are based on an adaptation of the source guideline "Cancer Care Ontario, Biochemotherapy for the Treatment of Metastatic Malignant Melanoma: A Clinical Practice Guideline, 2007". A total of 9 randomized trials were found and evaluated, one trial was only available as abstract. Updated research (Apr 2007–Oct 2011) found this particular study as full publication [510], but no other study for the given selection criteria.

"Six randomized controlled trials compared chemotherapy alone to chemotherapy combined with interleukin-2 and interferon, two randomized trials compared a combination of chemotherapy and interferon with chemotherapy combined with interleukin-2 and interferon, and one trial compared interferon and interleukin-2 with versus without chemotherapy. […] Only two trials [511, 512] reported statistically significant response rates favoring treatment with biochemotherapy. […] None of the nine trials detected a statistically significant survival improvement." ([508], p. 1).

The trials that compared standard chemotherapy with standard chemotherapy plus interleukin 2 and interferon were included in a meta-analysis. "All nine trials reported results on toxicity. In both arms, across the other trials, fever, chills, nausea and vomiting were the most common grade 3 and 4 adverse events. Overall, biochemotherapy regimens are more toxic than chemotherapy regimens." ([508], p. 10).

3.5.6.9 Quality of life in the stage of distant metastasis

3.5.6.9.	Evidence-based statement
Level of Evidence 1b	Insufficient indications exist that medical tumor therapy in the metastatic stage has a positive effect on the quality of life.
	Systematic search of the literature *de-novo:* [396, 489, 500, 513–525]
	Strength of consensus: 88 %

U. Trefzer

For the most part, pharmaceutical agents do not substantially influence the disease course in patients with metastatic, non-resectable melanoma. Only vemurafenib may provide a beneficial effect, yet available data is still scarce. Patients participating in a phase I trial showed a decrease in pain intensity and use of pain medication within 1–2 weeks after initiation of vemurafenib therapy.

With increasing metastasis and thus advanced tumor stage, patients display a rise in disease-associated symptoms and hence loss of quality of life. These symptoms include pain, loss of mobility, nausea, vomiting, fatigue, and diminished capabilities to participate in social and professional activities. Not only should tumor therapy therefore ideally have a positive impact on disease course, but also on patients' quality of life.

It is, however, conceivable that therapeutic agents exhibiting acceptable response rates, possibly in connection with longer progression-free intervals, also lead to enhancement of the quality of life, at least for a short while.

There is a comprehensive analysis of 13 studies on quality of life in patients receiving pharmacotherapy [516]. In these studies, various questionnaires, such as the EORTC, the EORTC QLQ 36, the QLQC30 questionnaires or the Rotterdam Checklist Symptom Questionnaire were employed. In addition, a "Hospital Anxiety and Depression Scale" was used. Low data acquisition due to low return rates of patient forms is a frequent problem in QoL trials. A comparative trial of temozolomide and DTIC showed no benefit for either treatment arm. Yet of the 305 randomized patients, only 105 filled out the baseline questionnaire EORTC QLQ-C30. After 12 weeks, only 81 patients, and after 24 weeks, only 30 patients filled out a questionnaire. Although a reliable statement is thus not possible, TMZ patients showed statistically significant improvement in physical functions (physical function subscale), less fatigue, and less insomnia after 12 weeks. Over the course of the entire trial, however, no significant benefit for either treatment arm was observed [520]. Addition of e.g. cisplatin to a chemotherapeutic regimen may result in poorer life quality. Accordingly, one study demonstrated negative effects on hearing, nausea and vomiting, appetite, and a non-significant worsening in role functions. As addition of e.g. cisplatin does not lead to improvement in response rates, one may inversely infer that patients on e.g. monochemotherapy have a better quality of life than those on combination regimens, yet similar to identical response rates and overall survival times.

Thus, as a rule and due to lack of positive trials [489, 500, 523], there is no actual improvement in the quality of life through pharmacotherapy in metastatic disease. Tumor progression per se results in deterioration of quality of life. Only in those rare cases of sustained tumor response, drug therapy may be expected to be beneficial as to quality of life. This underscores the necessity for additional supportive therapy.

3.5.7 Radiotherapy of distant metastases

3.5.7.1 Radiotherapy – fractionation

3.5.7.1	Evidence-based statement
Level of Evidence 1b	Conventional fractionation regimens show equal efficacy with respect to local tumor control in comparison to higher individual doses (>3 Gy).
	Systematic search of the literature *de-novo:* [526]
	Strength of consensus: 100 %

P. Feyer

In a palliative setting, the therapeutic decision has to take the patient's personal needs into particular consideration. Adverse events ought to be avoided, and a short treatment duration should be sought.

Two randomized controlled studies exist evaluating the effect of fractionation on skin, soft tissue, or lymph node metastases in melanoma. Sause et al. [526] compared four fractions of 8 Gy once a week versus 20 fractions of 2.5 Gy spread over 5 sessions per week. There was no significant difference in therapeutic response between the two groups.

Neither could the randomized trial by Overgaard et al. in 1985, comparing 3 × 9 Gy and 8 × 5 Gy, demonstrate a difference in therapeutic response in patients with skin and lymph node metastases. Thus, it may be concluded that various fractionation regimens provide equal efficacy regarding response to radiation therapy. In order to prevent adverse events later on, patients with a relatively favorable prognosis and life expectancy of more than 1 year should be irradiated with lower individual doses (1.8 to 2.0 Gy per fraction). (Refer to chapter 3.4.3, adjuvant radiation therapy after lymph node dissection). Especially after preceding chemotherapy, the increased risk for late toxicities should be heeded.

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

3.5.7.2.a	Evidence-based recommendation
Grade of recommendation o	In patients with acute signs and symptoms due to epidural compression in the spinal cord, radiotherapy may be performed for local symptom control.
Level of Evidence 4	Systematic search of the literature *de-novo:* [527]
	Strength of consensus: 100 %

3.5.7.2.b	Evidence-based recommendation
Grade of recommendation o	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.
Level of Evidence 4	Systematic search of the literature *de-novo:* [93, 412–414, 528–533]
	Strength of consensus: 100 %

3.5.7.2.c	Evidence-based recommendation
Grade of recommendation B	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.
Level of Evidence 4	Systematic search of the literature *de-novo:* [93, 412–414, 528–533]
	Strength of consensus: 96 %

P. Kurschat

Overall, available data on the indication for radiation therapy in distant metastatic melanoma is insufficient, as no systematic randomized multicenter trials exist. The above-mentioned recommendations are derived from altogether 18 publications that are mostly retrospective case series with a maximum Level of Evidence (Oxford) of 4. None of the studies has a control group. One explanation for the lack of larger systematic trials, which would allow for recommendations with high Level of Evidence, may be the 1930s dogma claiming that melanoma is generally not a radiation-sensitive tumor. This assessment, however, cannot be upheld according to present data.

The only study on palliative radiation therapy for epidural spinal cord compression was performed by Herbert et al. 85 % of the 26 evaluable patients showed a sustained therapeutic response until death. Stereotactic radiation therapy may be considered as alternative in this location.

There is a total of 10 case series and retrospective analyses, partly with larger patient groups, on radiation therapy in stage IV melanoma metastases to the skin, subcutis, or lymph nodes [93, 412–414, 528–533]. Frequently, however, the primary study objective was not the efficacy of radiation therapy, but rather the effect of additional measures such as hyperthermia. Two studies showed an increase in the efficacy of radiation therapy through combination with hyperthermia [412, 528]. Overgaard et al. treated 115 metastases in 36 patients with 15 to 30 Gy (single dose 5 or 10 Gy within 8 days). 53 metastases were simultaneously or subsequently (after 3 to 4 hours) subjected to local hyperthermia. 87 % of the 102 evaluable individual lesions displayed a complete or partial response.

The effect of fractionation was examined by Konefal et al. 35 patients with 67 metastases were irradiated with cumulative doses between 18 and 66 Gy. There was no correlation between response rates and cumulative doses. When individual fractions of up to 5 Gy were used, complete response rates were seen in only 9 %, whereas individual doses of > 5 Gy resulted in complete remissions in 50 % of patients. This effect was statistically highly significant. Individual doses of 5 Gy were also applied by Pyrhonen et al., who treated 89 metastases in 15 patients with cumulative doses of 40 Gy within 23 days (8 fractions with 5 Gy each). Overall response rates were 97 % (69 % CR, 28 % PR). Here as well, the size of the metastases played a crucial role. In metastases greater than 4 cm, complete remissions were achieved in only 20 %. On the other hand, in lesions smaller than 2 cm, complete responses were seen in 76 %. Similar observations were also reported by Doss et al. [534].

Radiation therapy for metastases to the skin, soft tissue, and lymph nodes has also been described in smaller patient groups by 6 further studies [93, 413, 529, 531–533]. Here, cumulative doses of mostly 30 to 40 Gy were employed yielding objective response rates between 45 % and 80 % as well as beneficial palliative effects.

The treatment of metastatic dissemination to other locations, e.g. lungs or liver, has been described in only 5 studies [93, 413, 414, 529, 532]. Seegenschmied et al. treated 19 pulmonary and 9 hepatic lesions, but they did not break down their findings according to individual sites. Generally, patients showed overall response rates (CR and PR,

Table 14 Recommended agents for patients with proven bone metastases.

Agent	Dose	Regimen
Denosumab	120 mg subcutaneously	every 4 weeks
Pamidronate	90 mg IV	over the course of at least 2 h, every 3–4 weeks
Zoledronate	4 mg IV	over the course of 15 min, every 3–4 weeks
Ibandronate	6 mg IV	over the course of 15 min, every 3–4 weeks
Ibandronate	50 mg PO	daily

measured by WHO criteria three months after conclusion of radiation therapy) of 49 %, with 2 out of 3 patients also having pulmonary metastases. 12 out of 16 patients in a study by Katz et al. (20 lesions, 9 of which were pulmonary) displayed improvement of clinical symptoms. The publications by Lobo, Rounsaville, and Konefal only reported on very few patients.

It may generally be concluded that radiation therapy for distant melanoma metastases to the skin, soft tissue, lymph nodes, and bones provides favorable local control rates and palliative effects. A positive impact on overall survival, however, has not yet been demonstrated.

3.5.8 Therapy for bone metastases

3.5.8.1 Medical therapy of bone metastases

3.5.8.1.a	Consensus-based recommendation
GCP	Patients with osseous metastases should receive amino bisphosphonates* or a RANK ligand Inhibitor**.
	Strength of consensus: 96 %

*Ibandronate, pamidronate, zoledronic acid, **denosumab

3.5.8.1.b	Consensus-based recommendation
GCP	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.
	Strength of consensus: 96 %

H. Link

Bone metastases may cause a series of problems such as

- persistent or intermittent pain,
- fractures,
- spinal compression,
- hypercalcemia.

Thus, bone metastases may decrease life quality and life expectancy and markedly increase morbidity.

There is no specific data for melanoma. Recommendations are based on the "American Society of Clinical Oncology clinical practice guideline update (ASCO)" on bone-modifying agents in metastatic breast cancer.

Treatment should be initiated upon detection of bone metastases. Oral administration of bisphosphonates is equivalent to intravenous application with respect to efficacy. If a more rapid therapeutic effect is required, intravenous application should be preferred. In patients with a creatinine clearance of more than 60 ml/min, no adaptation in dose, rate of infusion, and therapeutic interval is required. Serum creatinine levels should be checked prior to each intravenous bisphosphonate application. In patients on denosumab, who have a creatinine clearance of less than 30 ml/min or are on dialysis, frequent monitoring for hypocalcemia is recommended. All patients on bisphosphonates shall, all those on denosumab must receive supplementary calcium and vitamin D (at least 500 mg and 400 IU, respectively), except in case of hypercalcemia [536–539].

Treatment should preferably be continued long-term and adapted to disease course.

Osteonecrosis of the jaw (ONJ) is a rare (incidence < 1–2 %), but potentially serious complication when using bone-modifying agents (BMA). Prior to initiation of bisphosphonate or denosumab therapy, all patients should undergo dental/maxillary surgery evaluation and, if indicated, treatment. The incidence of ONJ may be reduced by pretherapeutic preventive dentistry.

Optimal oral hygiene is pivotal, and dental procedures that involve the jaw bone or periosteum should be avoided during BP or denosumab therapy. If such procedures, however, become necessary, prolonged perioperative, systemic antibiotic prophylaxis should be administered (Refer to S3 Guideline "Bisphosphonate-associated Jaw Necroses", AWMF).

Recommended agents for patients with proven bone metastases are listed in Table 14.

3.5.8.2 Radiotherapy in bone metastases

3.5.8.2	Evidence-based recommendation
Grade of recommendation B	In patients with osseous metastasis, radiotherapy should be performed to improve clinical signs and symptoms and to prevent local complications.
Level of Evidence 4	Systematic search of the literature *de-novo:* [529, 531, 532, 534, 535, 540, 541]
	Strength of consensus: 96 %

P. Kurschat

Radiation therapy for osseous metastases has been evaluated in 9 retrospective studies. Rate et al. conducted the largest trial with 39 metastases in 26 patients treated with palliative intention. After a cumulative dose of 11–36 Gy with individual fractions of at least 4 Gy or 27–40 Gy with fractions of up to 3 Gy, 85 % showed improvement of clinical symptoms. Seegenschmied et al. reported overall radiologic response rates of 83 % after average cumulative doses of 48 Gy. Individual fraction sizes did not matter, but cumulative doses of more than 30 Gy yielded better results. Kirova et al. treated 21 patients with bone metastases with 30 Gy (10 individual fractions) or 20 Gy (5 fractions). 67 % exhibited significant improvement of clinical symptoms. Control of clinical symptoms between 68 and 86 % was also observed in studies by Doss, Katz, Konefal, Lobo, and Rounsaville. Richtig et al. were unable to show any objective complete or partial remission through combined radiochemotherapy. Palliative effects were not reported.

In summary, radiation therapy yields distinct palliative effects as to pain control in at least two thirds of patients with osseous metastases. Consequently, this treatment should be performed in patients with clinical symptoms or imminent danger of fracture. Asymptomatic metastases or those not threatening stability do not require radiation therapy.

3.5.9 Therapy for liver metastases

T. Eigentler

Liver metastases occur in roughly 40 % of patients with visceral metastasis (own data, Central Registry Malignant Melanoma). Most patients with metastatic uveal melanoma show hepatic involvement. Almost all therapeutic trials on liver metastases include uveal melanoma patients. These trials were therefore also considered in the search and evaluation process. The statements do not differentiate between liver metastasis of cutaneous versus uveal melanoma.

3.5.9.1 Resection of liver metastases

3.5.9.1	Evidence-based recommendation
Grade of recommendation B	In patients with limited liver metastasis, the option of excision should be examined, when it can be performed as a R0-resection.
Level of Evidence 4	Systematic search of the literature *de-novo:* [476, 542–548]
	Strength of consensus: 100 %

Complete metastasectomy

The prognosis for patients after resection of liver metastases has been predominantly examined in smaller case series (in six of eight studies < 50 patients underwent surgery) [476, 542–548]. Most of the data has been retrospective (seven of eight studies). Median overall survival in patients undergoing complete metastasectomy was reported to be 22–28 months and is thus distinctly longer than in patients treated systemically. It remains unclear whether these results may be attributed to selection bias.

3.5.9.2 Local therapeutic procedures

3.5.9.2	Evidence-based recommendation
Grade of recommendation 0	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.
Level of Evidence 4	Systematic search of the literature *de-novo:* [549–566]
	Strength of consensus: 100 %

Ablation procedures

Through application of radio frequency (RFA), laser (LITT), microwaves (MW), or focused ultrasound (FUS), percutaneous or interstitial ablation procedures aim to thermally destroy tumor tissue.

Isolated hepatic perfusion

Isolated hepatic perfusion (IHP) using melphalan (± TNF alpha) has most frequently been performed [559, 560, 567, 568]. These studies include only small patient groups (up to 29 patients). Combined complete and partial response rates are between 37 % and 70 %, median overall survival between 7.5 and 12.1 months.

Hepatic intraarterial chemotherapy

Fotemustine and cisplatin have most often been used in hepatic intraarterial chemotherapy (HIAC) [556, 557, 559, 563, 564, 569–571].

Peters et al. treated 101 patients with uveal melanoma metastases to the liver by HIAC with fotemustine and were able to show objective response rates of 36 %, with median overall survival being 15 months. Becker et al. compared intraarterial hepatic application of fotemustine with its systemic application followed by subcutaneous application of interleukin-2 on day 31 and subcutaneous interferon alpha on day 36. While there were response rates of 21.7 % vs. 8 % in favor of intraarterial hepatic application, median overall survival rates were identical (12 months) for both arms. Agarwala et al., Melichar et al., and Cantore et al. employed a platinum-based regimen yielding response rates of 16–38 %. Intraarterial hepatic application of a polychemotherapy regimen [557] did not result in additional therapeutic benefit.

Hepatic intraarterial chemoembolization (syn. transarterial chemoembolization)
Chemoembolization combines local delivery of high-dose chemotherapy with embolization-induced tumor ischemia. The amount of time the chemotherapeutic agent remains within the embolized tissue is markedly prolonged through blockage of blood supply. Systemic toxicity is low, as a large portion of the chemotherapeutic agent remains in the liver and becomes metabolized on site.

Applied cytostatic agents included cisplatin, fotemustine mitomycin C, and BCNU [550, 553, 554, 558, 561, 562, 565, 566]. In the largest trial with 42 cutaneous melanoma patients with suffering from liver metastases, Ahar et al. were able to show objective response rates (complete and partial response) of 13.9 % and median overall survival of 7.69 months. The smaller studies yielded objective response rates of up to 57 % [554].

Radioembolization/selective internal radiation therapy (SIRT)
The only available study included eleven uveal melanoma patients with metastases to the liver [555]. Seven patients (63 %) exhibited an objective response. 1-year survival rates were 80 %.

3.5.10 Therapy for brain metastases

3.5.10.1 Surgery and radiotherapy for brain metastases

3.5.10.1.a	Evidence-based recommendation
Grade of recommendation B	Palliative whole-brain radiation therapy should be offered for multiple symptomatic brain metastases, if expected survival is longer than three months.
Level of Evidence 1b	Systematic search of the literature *de-novo:* [572]
	Strength of consensus: 96 %

3.5.10.1.b	Evidence-based recommendation
Grade of recommendation 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.
Level of Evidence 3b	Systematic search of the literature *de-novo:* [573–576]
	Strength of consensus: 100 %

3.5.10.1.c	Consensus-based recommendation
GCP	With acute signs and symptoms due to brain metastases, the possibility of surgery should be considered.
	Strength of consensus: 100 %

3.5.10.1.d	Consensus-based statement
GCP	The role of adjuvant whole-brain radiotherapy after local therapy has not yet been clarified.
	Strength of consensus: 100 %

R.-D. Kortmann

Prognostic factors
Cerebral metastases constitute the most common cause of death in melanoma patients with metastatic disease and pose a great therapeutic problem. They may manifest themselves through nausea, headache, unilateral neurologic symptoms, acute hemorrhage, organic brain syndrome, seizures, or cerebral nerve palsy.

With one exception [572], only retrospective analyses may be used for evaluation.

The RPA classification (recursive partitioning analysis) may be reproduced for brain metastases in melanoma as well [573, 577, 578]. In a retrospective analysis by Eigentler et al., patients with RPA classification I showed a median survival of 7 months compared to 5 months (class II) and 3 months (class III). The differences were statistically significant. Further prognostic factors are elevated LDH and S100B serum levels. In multivariate analysis, a Karnofsky performance status scale of ≥ 70, absence of elevated LDH levels as well as local therapy (stereotactic single-dose radiation or surgery) were statistically significantly associated with more favorable survival rates [573, 577]. In a multivariate analysis by Raizer et al., age, presence of extracranial metastasis, neurologic symptoms, and the number of brain metastases were significantly correlated with poorer median survival. Patients receiving surgery respectively stereotactic single-dose radiation therapy or temozolomide chemotherapy displayed more favorable survival rates [575]. In a series by the "Sydney

Melanoma Unit", advanced age presented an unfavorable prognostic factor. A long interval between primary diagnosis and occurrence of brain metastases was significantly associated with improved survival rates [574].

Exclusive whole-brain radiation therapy

Examined patient groups are very heterogeneous. The gain in median survival time was 3 months in a case series by Staudt et al. (from 1 to 4 months) and from 2.1 to 3.4 months in a series by Fife et al. [574, 577]. There was no statistically significant benefit for whole-brain irradiation in these studies. Raizer et al. were able to demonstrate a twofold rise in survival time from 2 to 4 months by whole-brain radiation therapy, without showing statistical significance [575].

76 patients were included in a phase III trial by Mornex et al., in which fotemustine alone was compared to fotemustine followed by whole-brain irradiation [572]. Response rates and overall survival were identical. There was, however, a significant difference in the time to cerebral progression for those undergoing additional radiation therapy. Prospective data on symptom control cannot be gathered from any of the available studies.

Local therapy ± whole-brain radiation therapy

Surgery and stereotactic single-dose radiation therapy (radiosurgery) have shown enhanced local tumor control as well as increased median overall survival [573–575, 577]. With respect to tumor control through local therapy (single-dose irradiation or surgery), there is conflicting data on the number of brain metastases in limited intracranial disease. In an analysis by Eigentler et al., a beneficial effect appears to be present for single respectively solitary brain metastases only. Median survival time was 9 respectively 6 months in favor of local therapy. The differences were statistically significant. If the analysis included patients with up to three cerebral metastases, there was no significant difference between stereotactic single-dose irradiation and whole-brain radiation therapy. In a retrospective analysis of the "Sydney Melanoma Unit" by Fife et al. that comprised 1237 patients, local therapy revealed a statistically significant median survival benefit as well: 3.4 months for whole-brain irradiation, 8.7 months for surgery alone [574]. In the "Sydney Melanoma Unit" study, surgery was also offered to patients with more than one lesion, if extracerebral disease was under control or surgery was deemed clinically necessary. The study by Wronski did not address the actual number of resected brain metastases per patient [576]. None of the trials examined surgery in comparison to stereotactic single-dose therapy with respect to local tumor control. Thus, an unequivocal therapeutic recommendation cannot be issued.

In retrospective analyses by Wronski et al. and Fife et al., additional whole-brain radiation therapy did not show any statistically significant difference regarding survival [574, 576]. Median survival after additional whole-brain irradiation was 9.5 months compared to 8.3 months after surgery alone. The incidence of recurrent cerebral metastases was identical for a wait-and-see approach versus whole brain radiation therapy, 56 % vs. 45.7 % [576]. In the study by Fife at al., median survival time was 8.7 months after surgery alone and 8.9 months after surgery with subsequent whole-brain irradiation [574].

If brain metastases give rise to clinical symptoms with elevated intracranial pressure or imminent blockage of cerebrospinal fluid drainage, immediate surgical intervention for symptom relief should generally be considered.

No melanoma-specific detailed recommendations can be issued with respect to radiation dose size in stereotactic single-dose and whole-brain radiation therapy.

3.5.10.2 Medical therapy in brain metastases

3.5.10.2.	Evidence-based recommendation
Grade of recommendation o	Patients with brain metastases may be offered systemic therapy analogous to the recommendations for metastasis to other visceral organs.
Level of Evidence 4	Systematic search of the literature *de-novo:* [480, 490, 501, 579–587]
	Strength of consensus: 88 %

W. Wick

In general, the same protocols are employed as in the treatment for other visceral metastases. The blood-brain barrier is most likely not intact in cerebral metastasis (accumulation of gadolinium), which is why there is no certain benefit for drugs that easily enter into the cerebrospinal fluid.

Those randomized phase III trials that included patients with cerebral metastases compared fotemustine vs. DTIC and ipilimumab with and without glycoprotein 100 (gp100) peptide vaccination vs. gp100 alone with regard to overall survival. In the fotemustine trial, only 43 of 229 patients suffered from brain metastases at the time of randomization. Fotemustine and DTIC both showed response rates of 5 % respectively. In the ipilimumab trial 82 of 676 patients exhibited brain metastases at the time of randomization. Here, ipilimumab yielded better overall survival rates compared to gp100.

Overall, available data is limited by the exclusion of patients with cerebral involvement or low case numbers. Uncontrolled phase I/II or II studies examined temozolomide alone [579, 581, 586] or in combination with sorafenib [580], thalidomide [583], lomustine [585], cisplatin [581], and docetaxel [581]. Further trials investigated DTIC in combination with

fotemustine [582], fotemustine alone [584], or thalidomide [587]. Despite frequently blurred lines between therapeutic success and failure, three of six temozolomide trials as well as two out of three fotemustine trials suggest a certain therapeutic benefit. There seems to be no relevant efficacy for thalidomide, increased doses of temozolomide, or a combination of DTIC and fotemustine or temozolomide and lomustine. As there is only limited overall efficacy of cytotoxic therapy, the potential use of one of the novel immune or individualized therapies shall be considered.

3.6 Follow-up

3.6.1 Duration of follow-up

3.6.1	Evidence-based recommendation
Grade of recommendation B	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.
Level of Evidence 1b–	Systematic search of the literature *de-novo:* [116, 300, 588–591]
	Strength of consensus: 100 %

U. Leiter

Background information on the clinical decision process
Aiming at early detection of recurrences and secondary melanomas, standardized follow-up is a pivotal component in the care of melanoma patients. Since the 1990s various proposals regarding follow-up for melanoma patients have been recommended, yet there is no international consensus [588, 590, 592]. Some authors recommend a 10-year, risk-adapted follow-up with increasing intervals between exams over the course of time.

Some groups have suggested long-term or life-long follow-up primarily because of the increased risk for secondary melanomas [593–597]. The calculation of hazard rates gives important indications as to the time until recurrences and secondary melanomas and may thus represent a rational basis in the decision making process.

Analyses of hazard rates for recurrences showed the most pronounced differences between stages I–III within the first year after primary diagnosis. The relative risk was 1 : 2 : 6.3. At stage I, hazard rates remained consistently low over a 5-year period. At stages II–III, there was an increased recurrence risk in year 1–2, which, after 3 years, again approached the same hazard rate as stage I. The highest recurrence rates were observed at stage III within the first year, followed by an approximation to stage II [590]. A more recent analysis confirmed these findings. Stage IA showed consistently low hazard rates during the entire follow-up period of 10 years. After a period of 10 years, hazard rates at stages IB–III converge with stage IA rates [300].

Analyses of stage I–II patients with negative sentinel lymph nodes after sentinel lymph node biopsy revealed recurrences in 8.9 %–10.1 %, 78 % of which occurred within 18 months [598].

In melanomas < 1.0 mm, 10% of recurrences occure ≥ 10 years after primary diagnosis. Depending on tumor thickness, the majority of recurrences even in thin melanomas (< 1.0 mm), occurred within the first years after primary diagnosis [590, 596, 599]. The risk for recurrence after 10 years is roughly 1 % [588].

Studies in stage I–III disease showed that 47 % of recurrences occurred within the first year after diagnosis, 32 % within the second year [590], respectively 80 % within the first 3 years. [588–590, 600–603]. Median occurrence of regional lymph node metastases was earlier than in locoregional or distant metastases (recurrence-free survival 17.6 months vs. 23, respectively 25.9 months) [604]. It has been reported that all locoregional metastases in stage IIIB/C disease occur within 40 months and distant metastases within 71 months. At stages IIIB and IIIC, CNS metastases emerged as first manifestation of recurrence in 7 % and 23 % of cases within 23 months. At stage IIIC, all metastases occurred within 24 months [605]. Stabilization of recurrence rates set in after 50 months. The recurrence risk never dropped below 5 % within the first 40 months. The probability for recurrence is highest within the first three years and markedly drops thereafter.

A study in primary stage I–II melanoma revealed a leveling off of survival curves 8 years after primary diagnosis [591]. Prognostic factors of the primary tumor appear to no longer exert any influence on recurrence risk after a period of more than 8 years. Approximation of recurrence rates at a low level of < 1 : 30 people per month and year sets in after about 10 years, making recurrences increasingly less likely after that time [300, 591, 600]. This data suggests discontinuation of follow-up after 10 years. Some authors also proposed potentially shorter intervals, e.g. up to 5 years [120, 600]. However, since 20 % of recurrences occur more than 5 years after primary diagnosis, it appears rational to maintain a 10-year follow-up regimen.

In order to detect late recurrences as well as late secondary melanomas, it is recommended to instruct patients in thorough self-examination, as it may henceforth be performed by him/herself [600].

Studies on the duration of follow-up with regard to secondary melanomas: long-term or life-long follow-up has been suggested by some groups primarily because of the increased risk for secondary melanomas [595–597]. However, various studies have shown that most secondary melanomas

occur within the first two years after the primary diagnosis of melanoma, with a marked drop in incidence thereafter [300, 590, 595]. On the other hand, secondary melanomas may even occur more than 30 years after the diagnosis, suggesting a need for life-long, regular dermatologic examinations [595, 597, 599]. Especially patients with individual risk factors (dysplastic nevus syndrome, family history) ought to be provided access to long-term dermatologic exams in addition to regular follow-up.

Studies on patient preferences, practical and economic aspects: Studies by Murchie and Dancey deal with patient preferences. In the first years after the diagnosis of melanoma, patients at low risk for recurrence predominantly require reassurance that no recurrence is present [606, 607]. In the study by Murchie et al., this goal was achieved by general practitioners offering phone consultations, thus avoiding frequent follow-up exams. An analysis by Dancey et al. revealed that 98 % of patients deemed hospital follow-up reasonable and expected regular examinations. 90 % benefited from reassurance, 72 % from clinical examination and getting answers to their questions. Regular follow-up diminishes the psychological morbidity associated with melanoma [606]. *Evaluation:* The findings by Murchie et al. cannot be directly applied to Germany due to differences in structure of the health care systems in the UK versus Germany, especially regarding the number of specialists. Therefore, these findings only play a marginal role in the overall evaluation of how long follow-up shall be performed (Randomized unblinded trial with comprehensible randomization system, blind setup not feasible, small patient group (142 patients).)

Summary and explanation of recommendations

Stage-adapted follow-up is recommended for early detection of recurrences and secondary melanomas. As 80 % of recurrences emerge within the first 3 years after primary diagnosis, thorough follow-up is advocated for this time period.

After 8–10 years, the risk for recurrence in stage I–III disease approximates independent of risk factors of the primary tumor, and only 5 % of recurrences occur after 10 years. Thus, a 10-year follow-up appears to be reasonable. The risk for secondary melanomas is highest within the first two years after primary diagnosis and steadily remains at a low level henceforth.

In order to detect secondary melanomas, particularly patients with individual risk factors (dysplastic nevus syndrome, family history) ought to be provided access to long-term dermatologic exams in addition to regular follow-up.

Thorough patient instruction on proper self-examinations for the detection of secondary melanomas as well as late recurrences appears reasonable, as patients will then be able to perform these exams on a life-long basis beyond the actual follow-up period.

3.6.2 Self-examination

3.6.2	Evidence-based recommendation
Grade of recommendation B	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.
Level of Evidence 3b	Guideline adaptation: [194, 348]
	Strength of consensus: 92 %

U. Leiter

Numerous guidelines view self-examinations as an essential component of follow-up. It requires informing and instructing patients on whole-body inspection as well as palpation of post-surgical scars, locoregional lymph drainage areas, and regional lymph node basins. Some centers use brochures and videos in this context, and relatives are sometimes included in the instruction process [590, 600, 608]. Numerous publications on follow-up – some retrospective, others prospective analyses of a patient group at the respective center – also try to answer the question who actually detected potential recurrences [116, 590, 600, 608]. Randomized controlled trials do not exist. Present publications yield varying results, as the percentage of recurrences detected by patients themselves ranges from 20 to 75 % [109, 116, 299, 590, 608]. One group reported that 56 % of recurrences were diagnosed by a physician, while 60 % of those detected by patients were locoregional [589]. This underscores the significance of self-examinations in combination with regular follow-up.

Present international guidelines [19, 194, 609] do not clearly define where and by whom follow-up exams shall be performed. It is widely accepted that effective self-examinations require thorough instructions. These were conveyed by physicians or specially trained nurses and comprised a list of clinical melanoma features as well as explanations regarding symptoms of recurrence (characteristics of satellite/in-transit and lymph node metastases as well as general symptoms like pain, fatigue, weight loss, nausea and vomiting, dyspnea, and headache) that should warrant consulting a physician. Furthermore, all patients received instructions on whole-body inspection and palpation of the regional lymph drainage area. Subsequently, even after these training measures, there were great differences in patients' individual ability to detect recurrences. Some patients brought early metastatic manifestations to the attention of their physician, whereas others simply ignored even large tumor masses [590].

In Great Britain, Murchie et al. designed a framework for an integrated follow-up program: patients were initially asked about their preferences with regard to follow-up conditions [610]. Most patients endorsed follow-up by a physician, although half of these patients admitted to being afraid of respective follow-up examinations. A main objective for these patients was reassurance. Other publications analyzing patients' opinions on follow-up showed that most patients deem routine follow-up as important [592, 606]. Whole-body examinations, instructions on self-examination, and provision of further information were all deemed desirable during follow-up exams [610].

3.6.3 Follow-up schedule

3.6.3	Consensus-based recommendation			
Grade of recommendation GCP	Follow-up of melanoma patients should be performed at risk-adapted intervals according to the following schedule.			
		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 resected stages			
	Strength of consensus: 100 %			

M. Weichenthal

Background information on the clinical decision process

The question at what intervals follow-up should be conducted has to be considered with respect to individual objectives of regular follow-up.

1. Early detection of recurrences respectively metastases,
2. early detection of secondary melanomas,
3. psychosocial patient support.

Here, the conditions and findings of clinical and radiologic workup for metastasis are most strongly subject to chronologic and stage-dependent influences. With regard to early detection of secondary melanomas and psychosocial support, a general frame-work may be formulated.

Examination intervals for early detection of metastasis

The issue of adequate follow-up intervals plays a crucial role as to the question whether specific workup for metastasis may be rationally employed to improve mortality, morbidity, and quality of life in affected patients.

The assumed risk for recurrence at a given point in time represents an essential parameter in these considerations. In 1988, based on their data on recurrence rates, McCarthy et al. proposed a formula for calculating aspired examination intervals [611]. It is based on two premises:

1. The relative rate of recurrences detected by follow-up is at least 50 % (as opposed to those detected by the patient, respectively by symptoms or chance).
2. The theoretical probability for the failure to detect metastasis due to a missed follow-up exam should not exceed 1 %.

In effect, these premises result in the establishment of follow-up intervals in which the calculated probability for metastasis is 2 % at most. The reverse approach – considering what probability for metastasis should at least be present for a follow-up exam to be reasonable – is not part of this discussion.

Other authors have suggested that intensified follow-up might be reasonable, as long as 95 % of expected metastases have not been detected [605]. In this analysis, the risk is broken down to the metastatic site or the region affected by the respective workup procedure (local-/in-transit, regional lymph node metastases, visceral metastases as well as brain metastases). Moreover, the given rate retrospectively refers to the relapsed subpopulation at the respective stage (IIIA/B/C), without providing information on the percentage of each particular stage among the trial population. Thus, the stated remaining risk of 5 %, e.g. with respect to lymph node recurrence in stage IIIC disease after more than one year (additionally based on the still recurrence-free population), would yield roughly 1–2 % of those patients still expected to develop lymph node metastasis as first sign of progression.

In general, cost-benefit analyses have to be taken into account as well when pondering at what point the risk for metastasis is significantly high to warrant an intensified follow-up program. Present studies primarily zero in on the cost of various procedures for metastasis detection in various schedules and patient groups [594, 612, 613]. There are no explicit cost-benefit analyses with respect to time-related threshold values for recurrence risks.

Basseres et al. showed that, in 66 % of cases, the interval between detected relapse and the previous follow-up exam was up to 4 months. This data was seen as indication that follow-up intervals in patient groups at significant risk for metastasis should not exceed 3–4 months, provided the intention to detect metastases at an early or asymptomatic stage [614].

Respective data is sketchy and prospective studies evaluating different intervals do not exist. The percentage of metastases detected by follow-up, not by symptoms or patients themselves, may constitute an indirect gauge for the adequacy of a follow-up interval.

Regarding this particular issue, a number of studies provide data that may be considered in connection with the respectively applied follow-up schedule.

Some of these authors propose that detection rates of follow-up exams should not be lower than 50 %. Romano et al. also report self-detection rates for various kinds of metastases. In-loco and in-transit metastases show relatively high self-detection rates (62.5 %), whereas detection of lymph node and visceral metastases outside follow-up proved to be markedly lower (48.6 % and 37.4 % respectively). Here, employing a trimonthly schedule, the largest percentage of metastases occurred within the first two years after primary diagnosis. This suggests that a trimonthly schedule is able to facilitate detection of more than 50 % (here 53 %) of metastases [605].

A more recent analysis evaluating the potential delay in diagnosis using two different follow-up schedules comes to the following conclusion: in stage I and II disease, the extension of follow-up intervals from 3 respectively 6 months to 6 respectively 12 months entails relevant diagnostic delays in only a small percentage of cases [615]. This study, however, assumes detection rates of 75 % by patients themselves or other persons. Analysis of the actual earliness of detection, e.g. with respect to operability of metastases, is not carried out.

Other authors have also discussed shorter intervals (review in Francken et al. 2005 [594]). Risk-benefit and cost-benefit analyses have to be addressed as well, though, when contemplating the issue of adequate follow-up intervals [594, 612, 613].

Stage-adapted intervals

The rationale to differentiate between disease stages with respect to follow-up intervals as well as type and scope of recommended procedures is derived from cumulative recurrence risks of each individual stage and their course over time.

Most recommendations are based on three stage groups with low, medium, and high risk for metastasis, thus avoiding excessive individualization of follow-up. On principle, the term "follow-up" is used for clinically tumor-free patients. This ordinarily includes patients after complete surgical resection of primary tumors and/or locoregional metastases. However, this may also include distant metastases in complete remission after resection or removal by other means (radiation therapy, pharmaceutical tumor therapy).

The objective of stage classifications is to provide a consistent and clear differentiation between various risk groups on the basis of relevant prognostic parameters. As with other solid tumors, the stage classification in melanoma presently contains four clinical stages: I (early primary tumors), II (advanced primary tumors), III (locoregional metastasis), and IV (distant metastasis). While older versions still showed consistently increasing recurrence risks according to stage progression, the present AJCC 2009 classification [17] reveals a more complex structure. The detection of very early lymph node metastases by sentinel lymph node biopsy results in a better prognosis for stage IIIA than for stage IIC. Thus, there is an overlap of stages which has to be taken into account regarding follow-up recommendations.

By adding parameters like ulceration of the primary tumor as well as mitotic rate, stage IA now shows a 10-year survival rate of more than 95 %. Annual hazard rates over time reveal no significant dynamics, either, so that these patients do not require intensified follow-up. Examination intervals are rather geared towards detection of secondary melanomas as well as psychosocial and other need for information.

With 10-year survival rates between 85 and 88 %, stage IB shows elevated recurrence rates, rendering tumor-specific follow-up rational. With respect to a common follow-up concept, it therefore appears reasonable to group stage IB patients with stage II patients.

Unlike the AJCC group (Balch et al. 2009, other studies on recurrence rates at the primary stage [299, 300, 594, 615] have not been able to confirm the markedly more unfavorable stage IIC survival rates to such an extent. Nevertheless, it seems reasonable to provide stage IIC patients with the same follow-up as stage III patients.

Various studies investigating recurrence rates over time in stage I–III disease indicate that intensified follow-up exams may frequently be discontinued after three years [116, 588–591, 598, 600, 605, 611]. Based on their more favorable cost-benefit structure, some examination methods (clinical exam and lymph node sonography) may reasonably be continued for 5 years, respectively in an intensified fashion.

Explanation of recommendations

Stage-adapted follow-up is recommended for early detection of recurrences and secondary melanomas. As 80 % of

recurrences occur within the first three years after primary diagnosis, intensified follow-up is advocated for this period. Stage IA marks the exception, since no elevated recurrence rates have been observed even within the first three years after diagnosis. Nevertheless, these patients may benefit from follow-up appointments within the first 3 years after surgery, as an increased percentage of secondary melanomas is diagnosed during this period [300], patients have an increased need for information and consultation, and postoperative follow-up is facilitated [238, 616]. Intensified follow-up includes trimonthly appointment intervals. Individual follow-up exams may be conducted in a risk-adapted fashion using various diagnostic methods. With decreasing risk, follow-up intervals may be extended from initially 6 months to 12-months.

Examination intervals for early detection of secondary melanomas

As long as proper tumor follow-up is required, whole-body inspection as integral component of follow-up is going to accomplish the task of detecting secondary melanomas. Annual preventive screening for secondary melanomas, however, should be performed by specialists on a life-long basis after discontinuation of regular follow-up. Various authors concur on this recommendation [594, 617]. DiFronzo et al. advocate permanent semiannual screenings for secondary melanomas. This course of action should at least be adopted in high-risk patients (e.g. dysplastic nevus syndrome, familial melanoma) [618].

Leiter et al. have demonstrated that an increased rate of secondary melanomas is diagnosed within the first two years after primary diagnosis. The rate levels off in the third year [300]. Other authors have also reported an increased incidence of secondary melanomas within the first 12 to 24 months after primary diagnosis. Thus, one may derive the recommendation to clinically examine all melanoma patients – independent of their risk for metastasis – on a semiannual basis for the first two years after primary diagnosis. This course of action also aims at motivating patients to perform self-examinations in a sustained manner.

Examination intervals for psychosocial support

According to current data, the reassuring aspect of negative clinical findings in particular is crucial for psychosocial support of tumor-free patients. Present literature does not provide any specific intervals for regular follow-up [606].

Considering psychosocial support even at early stages, it seems plausible to offer at least four appointments within the first two years after diagnosis, in order to do justice to patients' need for support.

3.6.4 Workup during follow-up

3.6.4.1 Physical examination during follow-up

3.6.4.1	Evidence-based recommendation
Grade of recommendation A	Physical examinations shall be performed in all melanoma patients during follow-up.
Level of Evidence 2b	Systematic search of the literature *de-novo:* [116, 612–614]
	Strength of consensus: 100 %

I. Satzger, U. Leiter

Physical examination comprises specific history taking, inspection of the entire integument as well as palpation of the primary scar, in-transit and lymph drainage areas, and lymph node basins.

Most relapses and secondary melanomas are detected during physical exams [116, 614]. In a prospective study of 2 008 patients, roughly 50 % of recurrences were picked up through history taking/physical examination [116], 80 % of which were local recurrences, in-transit metastases, and regional lymph node metastases. Early detection of secondary melanomas is equally feasible by inspection of the integument during clinical examination.

Particularly patients in whom complete surgical removal of metastases is practicable benefit from early detection of recurrences during follow-up, Basseres et al. reported that 96 % of all operable metastases were detected by clinical exams [614].

Physical examinations in stage I–III disease have proven to be the most effective procedure for early recurrence detection [612, 613].

3.6.4.2 Lymph node sonography during follow-up

3.6.4.2	Evidence-based recommendation
Grade of recommendation A	Locoregional lymph node sonography shall be performed during follow-up in melanoma patients with stage IB and above.
Level of Evidence 1a	Systematic search of the literature *de-novo:* [104, 113, 613, 619]
	Strength of consensus: 100 %

I. Satzger, U. Leiter

Sonography comprises examination of the surgical scar of the primary tumor, the in-transit area as well as locoregional lymph nodes and potentially further basins. Approximately 70 % of melanoma metastases occur

locoregionally as satellite, in-transit or locoregional lymph node metastases. The latter, if discovered early, may potentially be completely resected (R0 resection). Thus, early detection of locoregional lymph node metastases is of particular significance. In a meta-analysis of 74 trials, lymph node sonography proved to be the most sensitive and most specific procedure for the detection of locoregional lymph node metastases [104]. In addition, lymph node sonography is superior to mere palpation [104, 113, 619]. Lymph node sonography has been described as the most effective procedure for the detection of locoregional lymph node metastases [612, 613].

3.6.4.3. Measurement of S100B serum levels during follow-up

3.6.4.3	Evidence-based recommendation
Grade of recommendation B	The tumor marker S100B should regularly be measured in asympto-matic patients in stage IB or higher during regular follow-up.
Level of Evidence 1a	Systematic search of the literature *de-novo:* [118, 120, 612, 613, 620]
	Strength of consensus: 92 %

I. Satzger, U. Leiter

Serum levels of this tumor marker are dependent on the patient's tumor load. Thus, increase in S100B levels over time may portend disease progression. As delayed processing and warm storage temperatures of blood samples facilitate false-positive results, it is recommended to first repeat the test. If levels continue to be elevated, further imaging workup is recommended.

A meta-analysis of 22 studies [118] demonstrated a correlation between S100B and survival. In multivariate analysis, S100B serum levels constituted an independent prognostic parameter. As tumor marker, S100B displays a very high sensitivity (86–91 %). Its specificity has been reported to be 76–91 % [122, 448].

Not only may elevated serum S100B levels point to distant metastasis, but in 29.4 % of cases also to lymph node metastases. In-transit metastases, however, did not lead to increased S100B levels, as shown in an analysis by Egberts et al. [621]. In a comparative study, S100B was markedly superior to lactate dehydrogenase (LDH) and alkaline phosphatase (AP) [120].

In a group of 411 high-risk melanoma patients, 14 patients developed distant metastasis. In 8 of those patients (57 %), metastasis was initially detected by S100B elevation [622].

3.6.4.4 Chest X-ray during follow-up

3.6.4.4	Evidence-based recommendation
Grade of recommendation B	Chest x-ray should not be performed routinely during follow-up.
Level of Evidence 2b	Systematic search of the literature *de-novo:* [613, 623, 624]
	Strength of consensus: 77 %

I. Satzger, U. Leiter

Chest X-ray exams are inferior to computed tomography (CT) in the detection of small pulmonary metastases.

One major issue of chest X-ray exams is the high number of false-positive and false-negative findings. During a follow-up study of 1 969 patients, only 10/204 relapses were discovered by chest X-ray. The majority (7/10) of recurrences were observed in patients with stage III disease [613]. Brown et al. reported a low sensitivity of chest X-ray of 7.7 % (2 % at stage I to 11.5 % at stage III) and a specificity of 96.5 %. In a trial of 1 235 patients, 210 relapses occurred, 38 of which were detected by chest X-ray. In order to detect these 38 recurrences, a total of 4 218 (38/4218 = 0.9 %) exams were performed. On the other side, 129 (3.1 %) false-positive findings had to be worked up using further procedures [623]. Isolated pulmonary metastases amenable to surgical therapy were found in only 3/38 patients. Morton et al. only included patients with stage III disease. 23/108 developed pulmonary metastases, only 11 of which (sensitivity of 48 %) were revealed by chest X-ray. Again, there was a high number of false-positive findings in 19 patients. The specificity of this procedure was reported to be 78 % in this study [624].

3.6.4.5 Abdominal sonography during follow-up

3.6.4.5	Evidence-based recommendation
Grade of recommendation B	Abdominal ultrasound should not be performed routinely in asymptomatic patients in the follow-up of melanoma.
Level of Evidence 2b	Systematic search of the literature *de-novo:* [116, 614, 625, 626]
	Strength of consensus: 96 %

I. Satzger, U. Leiter

Parenchymal distant metastases and abdominal lymph node metastases may be detected by means of abdominal sonography. This method is limited by poor imaging of paraaortic and retroperitoneal lymph nodes, particularly in obese patients. Advantages of abdominal sonography are its simple practicability and lack of irradiation. Results, however, depend on the experience of the examiner. The sensitivity of

PET/MRT/CT is greater than that of abdominal sonography [626]. In a study by Kaufmann et al., abdominal sonography yielded a sensitivity of only 53 % in the detection of abdominal metastases, albeit a high specificity of 98 % [625].

3.6.4.6 Imaging procedures during follow-up

3.6.4.6	Evidence-based recommendation
Grade of recommendation B	Cross-sectional imaging should be performed routinely in the follow-up of melanoma patients in stage IIC or higher.
Level of Evidence 1a	Systematic search of the literature *de-novo:* [104, 441, 605, 626–628]
	Strength of consensus: 89 %

I. Satzger, U. Leiter

CT/MRI

Cerebral metastases are more readily detected by magnetic resonance imaging (MRI) than by CT or FDG-PET/CT [626]. Lack of radiation exposure represents another upside.

Magnetic resonance imaging has proven to be more sensitive and specific in the detection of soft tissue metastases or abdominal metastases (e.g. lymph nodes, liver, adipose tissue, muscle) [303, 627].

In the diagnosis of osseous metastases, MRI has shown the highest sensitivity and specificity, albeit there is no data directly comparing MRI to CT in this type of metastasis [302]. PET/CT has displayed similar diagnostic accuracy with respect to bone metastases.

Whole-body computed tomography represents a very sensitive procedure, which even allows for the detection of metastases as small as 2–4 mm [627]. In a study by Romano et al., 72 % of asymptomatic distant metastases were discovered by CT scans [605], while other trials yielded detection rates of 15–28 % [109, 116, 441, 612]. Computed tomography and whole-body MRI play a pivotal role in case of suspected metastasis (due to clinical, lab, or sonographic findings) as well as during follow-up of patients with stage IV disease or in the preoperative evaluation of metastases. In asymptomatic stage III patients, cross-sectional imaging screening should only be performed in a risk-adapted fashion, as more than 50 % of recurrences at that stage are also detected by the patient or through clinical examinations [116, 594, 600, 605].

Consistent interpretations of CT findings based on 2D and 3D measurements as well as information on tumor vascularization represent substantial benefits of this procedure [627]. Downsides to CT are its limited soft tissue contrast and radiation exposure which, depending on protocol, amounts up to 10–20 mSv. Thus, whenever possible, low-dose CT procedures should be considered.

Especially in the diagnosis of small pulmonary metastases, CT exams have shown a higher sensitivity [627] compared to MRI (66.9 vs. 2.9 %, $p < 0.0001$) and should therefore be employed as primary diagnostic method in the evaluation of these lesions.

Overall, a general recommendation on respective imaging procedures cannot be issued based on available trial data, as the studies included inhomogeneous patients groups and were characterized by low evidence levels (2b–3b). As alternative for follow-up especially in young stage III and IV patients, MRI scans of the head, neck, abdomen/pelvis may be considered to avoid radiation exposure. With respect to individual metastatic sites and possible differential use of MRI or CT, further specified recommendations cannot be issued on the basis of present data.

PET/CT and FDG-PET

Positron emission tomography (PET) is a newer procedure displaying the uptake of radioactively labeled glucose in metabolically active areas. Combination of PET and computed tomography in a PET/CT scanner represents further advancement of this technique, thus facilitating enhanced spatial mapping of metabolically active lesions and increasing the diagnostic validity of this procedure [104, 628]. PET/CT exams reveal a high sensitivity (80 %) and specificity (87 %) in the detection of distant metastases, distinctly higher than conventional CT (51 % and 69 %, respectively) [104].

3.6.4.7 Skeletal scintigraphy during follow-up

3.6.4.7	Evidence-based recommendation
Grade of recommendation B	Skeletal scintigraphy should not be performed routinely in the follow-up of melanoma.
Level of Evidence 3b	Systematic search of the literature *de-novo:* [104, 109, 140]
	Strength of consensus: 100 %

Skeletal scintigraphy

Regarding skeletal scintigraphy, only older methodologically insufficient studies exist. Since the introduction of CT in the staging workup, skeletal scintigraphy has become increasingly superseded. For melanoma, there is only scarce data on the detection of bone metastases by PET or PET/CT techniques, representing advancements of scintigraphy [626].

3.6.4.8 Follow-up schedule with recommended procedures

3.6.4.8	Consensus-based recommendation
GCP	Follow-up should be performed according to the following scheme and with the following examination methods.
	Strength of consensus: 100 %

Stage	Physical examination			Lymph node sonography			S100B			Imaging procedures		
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 Ro resected stages, **only with proper pathologic staging by SLNB, otherwise like IIC

3.6.5 Rehabilitation

3.6.5	Consensus-based recommendation
GCP	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.
	Strength of consensus: 100 %

A. Weyergraf

Medical rehabilitation of melanoma patients aims at preventing or diminishing physical, social, and professional disabilities as well as facilitating a preferably lasting reintegration into work life [629]. Moreover, it targets the advancement of participation in social life and the improvement of quality of life. The rehabilitation concept is based on a holistic perception of melanoma patients, taking into account somatic effects of the disease, including functional deficits due to surgical and drug treatment, as well as coping problems on a psychosocial level [630, 631]. Thus, only interdisciplinary treatment strategies will do justice to the complexity of oncologic symptoms [630, 632]. Involvement of psychologists and social workers in the rehabilitation team, led by the specialist as case manager, is particularly important. In addition, nurses, physical and occupational therapists as well as ecotrophology represent essential components of the rehabilitation plan [269, 633, 634].

Objectives of rehabilitation: through rehabilitation and follow-up, the rehabilitee shall be (re)enabled to practice a profession and partake in activities of everyday life, preferably in a way and to the extent deemed "normal" (typical within the context of his personal life).

These objectives may be achieved by

- complete – or at least best possible – restoration of original structure and function respectively activities and participation,
- application of "substitution strategies" using remaining function respectively activities (compensation),
- instruction on personal responsibility regarding lifestyle,
- adaptation of environmental conditions to the rehabilitee's impairment in activities respectively participation (adaptation).

The individual rehabilitation objective is determined on the basis of sociomedical assessment concerning the rehabilitee's need and ability for as well as prognosis of rehabilitation [635] (federal work group on rehabilitation). Prerequisites for medical rehabilitation in melanoma patients are the need and ability for rehabilitation, which is ascertained early on during primary hospital treatment or in an outpatient setting. The potential for active participation by the rehabilitee in the rehab process is required. The indication for medical rehabilitation measures exists, if (as described in the terms of the "International Classification of Functioning, Disability and Health" [ICF] of the WHO):

- impairment of physical structures and functions exists (e.g. postoperatively),
- impairment of everyday activities exists,
- professional and also private participation is impaired or permanently endangered,
- there is an imbalance of positive and negative contextual factors comprising the entire somatic, social, and professional background of a human being including environmental factors affecting him.

Thus, the need for rehabilitation is given, if, as consequence of disease and therapy, impairment of participation is imminent or already existing, and if permanent functional deficits cannot be sufficiently influenced by acute medical interventions [632].

Contraindications for medical rehabilitation measures in melanoma patients are:

- lack of ability or prognosis for rehabilitation,
- unfinished radiation therapy,
- unfinished surgical therapy,
- ongoing chemotherapy that offsets the ability for rehabilitation,

- addiction disorder that offsets the ability for rehabilitation,
- need for primarily acute medical intervention,
- need for rehabilitation primarily due to non-oncologic disease [632].

Unlike other rehabilitation measures, the German statutory pension insurance is usually the benefactor, irrespective of employment or retirement status. If rehabilitation is to be entered directly (i.e. within two weeks) after hospital discharge, such follow-up rehab is initiated e.g. by the hospital's social services using forms G 250 (application) and G 260 (findings report). If oncologic rehab is initiated later in an outpatient setting, the required forms are G 100 and G 1204–G 1206. There are only two exceptions to this rule: 1. insurees of the Knappschaft-Bahn-See pension insurance (form 87102) and 2. patients living in Northrhine-Westphalia (form CA 1 of the Work Group against Cancer). The sociolegal entitlement to medical rehabilitation for malignancies is based on Section 15 Social Code VI for persons in gainful employment and Section 31 Social Code VI for all other patient groups.

3.7 Supportive therapy

3.7.1 Use of complementary medicine

3.7.1	Consensus-based recommendation
GCP	After comprehensive weighing of possible risks (side effects and interactions), complementary measures may be employed in individual cases if the patient desires.
	Strength of consensus: 96 %

J. Hübner

Complementary procedures are based on various methods and agents that partly originate from nature medicine or otherwise pursue a holistic therapeutic concept.

They do not replace active antitumoral or supportive therapy, but merely constitute complementary methods enabling patients to become actively involved.

There is no universally accepted definition of complementary and alternative medicine. It is frequently differentiated from so-called Western (academic) medicine, but the lines are not drawn consistently.

Complementary therapy is grounded in the principles of scientific medicine. Its premise is that efficacy can be proven, and it is employed complementarily to Western medicine [636].

With respect to melanoma, there are no clinical studies documenting antitumoral efficacy of preparations or methods of complementary or alternative medicine.

Among preclinically tested agents are phytochemicals like flavonoids (e.g. EGCG from green tea, curcumin, quercetin) and terpenes. In-vitro and in-vivo data exists, in part showing synergistic effects with certain chemotherapies. Little is known about interactions. However, as agents influencing cytochrome p450 3A4 in particular and antioxidants in general potentially decrease the efficacy of chemo and radiation therapy as well as that of small molecules, concomitant administration in pharmacologic doses should be avoided. Ingestion via healthy fruit and vegetable diet is desirable.

In supportive therapy, various methods and agents are used concomitantly or shortly after antitumoral therapy. In this context, apart from evaluating efficacy data of a method, it is particularly important to heed negative effects (direct damage and interactions). Available pertinent data is rather sketchy. Since patient safety is paramount, preclinical findings and case reports suggesting potentially negative effects also ought to be taken into consideration during risk assessment.

Nutritional supplements are vitamins and trace elements, amino acids, fatty acids, and phytochemicals. In case of proven deficiency, specific substitution appears to be justified. There are no clinical trials that demonstrate a benefit of additional supplementation. Among preclinically tested substances are phytochemicals such as flavonoids (e.g. EGCG from green tea, curcumin, quercetin) and terpenes. In-vitro and in-vivo data exists, in part showing synergistic effects with certain chemotherapeutic agents employed in melanoma, or with radiation therapy.

Omega-3 fatty acids have been investigated in cancer cachexia with conflicting results. A 2007 Cochrane review judged available data as insufficient as to the efficacy of omega-3 fatty acids in the treatment of cancer cachexia [637]. Thus, due to inconsistent data, omega-3 fatty acids are not a component of evidence-based therapy. In no way does their prescription replace the care of an experienced physician nutrition specialist.

Unlike isolated and well-defined phytochemicals, phytotherapy deals with extracts that are multi-compound mixtures prepared according to traditional recipes. No clinical trials have been published on the efficacy of European medicinal plants in melanoma patients.

Positive effects with regard to quality of life and the immune system have been suggested for Chinese herbal mixtures in accordance with TCM (Traditional Chinese Medicine). Use outside clinical trials is not recommended [638, 639], as there have been reports of fatalities following therapy with Asian herbs.

Immunostimulants

In 4 smaller case series, thymopentin has shown immunologic effects and in some cases even tumor regressio [640–643]. As no clinical trials with melanoma patients exist, its use outside clinical studies is not advisable. There are no clinical trials involving other immunostimulants, such as medicinal fungi, echinacea, aloe, noni, fermented wheat germ extract, splenic peptides etc., that would suggest their supportive use in melanoma.

Acupuncture

A Cochrane review summarizes the evidence as follows: acupuncture-point stimulation diminishes chemotherapy-induced acute vomiting, but not acute nausea. There is no effect on delayed nausea and vomiting. Electrostimulation is ineffective [644].

If acupuncture-point stimulation is chosen as complementary therapy, adequate anti-emetic medication according to guidelines is required (as prophylaxis and rescue medication).

With regard to pain management in tumor patients, available data does not suffice for a positive recommendation.

Homeopathy

The therapeutic benefit of homeopathy as supportive melanoma therapy has not been proven. A Cochrane analysis comprises a group of very heterogeneous studies. The two studies that received positive evaluations did not include homeopathy in the strict sense. Thus, there is no study that demonstrates a benefit for homeopathy in tumor patients [645].

3.7.2 Information on complementary and alternative therapies

3.7.2	Consensus-based recommendation
GCP	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.*
	Strength of consensus: 91 %

*This includes among others ukrain, vitamin B 17 (apricot seeds, bitter almonds), insulin potentiation therapy, ketogenic diet, vitamins according to Dr. Rath, Germanic New Medicine®, self-blood cytokines, Zapper, redifferentiation therapy

J. Hübner

Looking for help, patients frequently encounter many unfounded offers. These are partially based on honest attempts by physicians not knowledgeable in recent oncologic research to support their patients. Moreover, there are numerous providers for whom economic aspects are paramount. In the context of these methods, patients are denied rational therapies. It is crucial to protect patients from these offers by taking a clear stance. Offers rapidly change, as new methods appear and those previously used for longer periods of time take a backseat. Some methods are grounded in the traditional art of healing, others employ adaptations of modern scientific branches (e.g. hyperthermia) or own interpretations of carcinogenesis and immunologic relationships (dendritic cells). Physicians not specialized in oncology may have difficulties in recognizing the dubious character of these methods.

Consultation about "complementary medicine" measures should be conducted by experienced oncologists. Important objectives are:

- strengthening the therapeutic bond between patient and physicians,
- protecting patients from potential harm resulting from unqualified application of "complementary medicine" methods,
- providing support in coping,
- fostering patients' initiatives as to a health-oriented, active, and individual role in the treatment concept [646].

Competent consultation acts as intermediary between patients' needs and interests, scientific data, aspects of consumer protection, and responsible handling of limited resources within the health care system. Competence in communicatively dealing with this subject means understanding patients' concerns and experiences as well as conveying authenticity and integrity of medical actions [647]. Harsh repudiation of "complementary medicine" procedures may diminish trust in patient-doctor relations, impair compliance, and even result in discontinuation of therapy [648–650].

Medical consultation on complementary medicine should initially inquire about the patient's interest in the subject. Doing this, it may be helpful to also clarify models about tumor genesis relevant to the patient (layman's etiology).

Apart from providing expert and profound information about benefits and also risks of complementary therapy, the goal of further consultation is to strengthen the doctor-patient relationship and to enable mutual candor.

Thus

- the patient's self-initiative and his sense of self-responsibility and self-control may be strengthened,
- the patient may be protected from dubious offers,
- harm through adverse events inflicted by uncontrolled application of complementary and alternative methods (directly or via interactions) may be avoided.

3.7.3 Psycho-oncology

3.7.3	Consensus-based recommendation
GCP	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.
	Strength of consensus: 100 %

C. Loquai, A. Werner

Psycho-oncology comprises all clinical and scientific efforts in clarifying the significance of psychological and social factors in the development and progression of malignancies. Furthermore, it deals with individual, familial, and social processes of coping as well as the systematic use of this knowledge in prevention, early detection, workup, treatment, follow-up, and rehabilitation [651].

Early detection of stress on the part of patients and relatives and its adequate treatment takes top priority.

Compared to other malignancies, the impact of melanoma on various psychosocial dimensions and the corresponding need for adequate support has not been investigated to a large extent.

Two systematic reviews have shown that one third of all melanoma patients exhibit clinically relevant distress, especially anxiety symptoms [652, 653].

Among the objectives examined in psycho-oncologic studies, quality of life was to the fore. Further issues were psychotherapeutic, educative, and psychopharmacologic interventions as well as psychosocial influences on survival, health behavior, and need and utilization of psychosocial care. The few available comparative studies have revealed that mixed groups with primarily early-stage melanoma patients on average perform better as to quality of life than those with other malignancies. Stress requiring treatment has been ascertained in 10–45 % of melanoma patients [654–659]. With advanced disease, impairment of physical and role functions [660] as well as financial and professional problems emerged. Medical care was experienced as less supportive [661].

Risk factors for increased stress in melanoma patients comprise demographic factors (female gender, younger age, absence of spouses or life partners, lower educational background), clinical factors (advanced disease, deterioration of physical status, visible defects), and psychosocial factors (negative cognitive appraisal of melanoma, lack of social support) [281, 653].

Melanoma patients with an active, problem-centered coping strategy show better coping results than those with passive or avoidance coping styles [286, 659, 662, 663].

Similar to other malignancies, some studies suggest that individual parameters may positively as well as negatively influence disease course with respect to coping.

Cognitive appraisal plays a paramount role in the adaptation process of melanoma survivors: adaptation is all the more effective, the lesser the sense of threat, the greater the sense of challenge and the higher the assessment of one's coping capability. Objective disease-related variables play a far less important role [664].

Social support is critical concerning psychological adaptation in melanoma patients and is associated with active coping and less psychological stress [282, 286, 653].

Current data is not yet conclusive, but suggests that psychosocial interventions may enhance the quality of life in melanoma patients. Early structured interventions facilitate an active cognitive coping style in melanoma patients, reduce cognitive-affective stress, and bring about a markedly improved quality of life (e.g. less depression, less fatigue, more energy) [663].

Conclusion:

Unlike other malignancies, psychosocial care in melanoma patients has not been investigated to a large extent. Improved knowledge of somatic, social, behavioral, und cognitive factors may result in the development of optimized psychosocial treatment and monitoring strategies and determination of health-promoting interventions. In order to systematically and sophisticatedly identify stress and need for care in melanoma patients as well as specific indications for psycho-oncologic measures, validated measuring tools may be helpful in addition to clinical judgment. Among these tools are basic psycho-oncologic documentation (PO-BaDo), the German version of the Hospital Anxiety and Depression Scale (HADS), the Hornheide questionnaire (HF), the distress thermometer (DT), or the questionnaire on stress in cancer patients (FBK) (Herschbach u. Weis 2010). Medical and psychosocial risk features may offer clues as to when a more intensive care, support, or possibly concomitant psychotherapeutic or psychopharmacologic treatment is useful. Psycho-oncologic interventions have to be leveled at patients' and relatives' individual needs.

3.7.4 Quality of life

D. Nashan, G. Strittmatter

Global assessment of quality of life (QL) with characterization of functional and symptomatic variables should be a standard feature and performed by means of sophisticated assessment tools over the course of the disease and around therapeutic interventions. Differentiated long-term measurements are to be ascertained by longitudinal studies using symptom-adapted validated assessment.

Methodological implementation of QL assessment is desirable in everyday clinical practice, because specific interventions may be derived. So far, there is no conclusive evidence for a verifiable benefit of interventions on survival. Interventions may positively influence certain dimensions of quality of life [236, 268].

Health-related quality of life (HRQOL) constitutes a latent construct not directly observable, but rather indirectly workable by means of indicators. QL assessment tools are unidimensional (global questions) or multidimensional and may be classified in cross-disease (generic) and disease-specific procedures. There is broad consensus that disease-related quality

of life may only be reasonably assessed from the subjective viewpoint of those affected [665].

There is no commonly accepted definition of the term "disease-related quality of life". Thus, an operational definition, as multidimensional construct, is used that includes physical, emotional, mental, social, spiritual, and behavioral components of wellbeing and functionality.

Frequently employed cross-disease QL assessment tools in melanoma patients are: "EORTC QLQ-C30", "Short Form-36" (SF-36), "Brief Symptom Inventory" (BSI), "Global Quality of Life Scale" (GLQ-8), and "Quality of Well-Being Self-administered Questionnaire" (QWB-SA). Further tools in use are the questionnaire on general disease-related quality of life in melanoma patients (FACT-M), in addition FACT-BRM for cytokine therapy and FACT-F for fatigue, "State Trait Anxiety Inventory" (STAI), and "Hospital Anxiety and Depression Scale" (HADS) for anxiety and depression [659, 666–668]. Some other instruments such as the "Cancer Therapy Satisfaction Questionaire" (CTSQ,) for QL assessment during therapy are being developed [669].

Quality of life is determined to a large extent by the presence or absence of problems subjectively experienced as burdensome. In the Hornheide questionnaire (HF), specifically developed for skin tumor patients, differentiated assessment of stress in 8 relevant areas of stress provides weighted multidimensional self-assessment and thus crucial indicators for indirect QL assessment and starting points for QL improvement. Crossing of dimension-specific stress threshold values reveals the need for care and allows for direct allocation of interventions that are aimed at relieving the individual patient and thus improving his/her quality of life [661].

Fatigue also represents a paramount criterion of quality of life in melanoma patients. Its significance is displayed by the assessment of comparable dimensions (physical, psychological, emotional, and cognitive) as well as by the incidence of cancer-related fatigue in 50–90 % of patients [670]. There are 31 different potential fatigue assessment scales [671], yet only few have been used in melanoma. The EORTC-QLQ C30 and the Common Toxicity Criteria have been primarily employed [672].

Differentiation between fatigue and depression has proven to be difficult, yet increasingly essential, as specific psycho-oncologic and pharmaceutical recommendations are being developed [673].

Corresponding to some assessments, melanoma patients do not necessarily exhibit poorer QL compared to the general population or other tumor groups [660]. Patients experience a deterioration of QL around the time of primary diagnosis, disease progression, and during systemic therapy [504, 513, 518, 652, 660, 668, 674, 675]. Predisposing factors regarding QL progression have been insufficiently validated, albeit some studies have indicated a negative correlation with female gender, preexisting depression, lower social status, and lack of coping [655, 676].

Conclusion:
The impact of quality of life on compliance, consistent implementation of therapy, and potentially more favorable disease course (recurrence-free survival) underscores the significance of QL assessment. Targeted, specific assessment is pivotal, as only this allows for adapted therapy and thus alleviation of symptoms.

3.7.5 Pain management

U. R. Kleeberg, R. Voltz

Incidence
Of all complaints expressed by tumor patients and melanoma patients in particular, pain is one of the foremost symptoms. 20 % of all out-patients receiving adjuvant and palliative treatment experience pain, 46 % of which feel insufficiently treated and 41 % insufficiently informed about adverse drug reactions (ADR) [677]. In advanced cancer, the incidence increases to 30–40 %, in the terminal phase to more than 70 % [678]. Cancer pain is always a multidimensional event arising from various pathophysiologic causes. It is affectively and cognitively modulated and entails growing impairment of physical and eventually psychosocial capabilities. Thus, successful, holistic pain management is an essential, albeit difficult, task of the oncologic team.

Etiology and pathogenesis
In patients with metastasized melanoma, repeated differential diagnosis is of particular significance. Current assessment of etiology and examination of pain characteristics are sine qua non for qualified pain management. Common causes for pain in melanoma patients are listed in table Table 15.

Pain management
Effective pain management requires correct pain classification (nociceptive, visceral, neuropathic, or mixed) as well as exploration of breakthrough pain, psychological distress, addictive disorders, and cognitive impairment [680].

Causal therapy specifically directed at the origin of tumor pain always takes precedence over merely palliative interventions. Even in patients previously already intensively treated with cytostatic agents and radiation therapy, symptom-oriented palliative chemo and or radiation therapy initially ought to be discussed in tandem with analgesic treatment on an interdisciplinary level. In doing so, therapy-related stress has to be weighed against potential

Table 15 Causes for pain in melanoma patients.

Tumor-related and tumor-associated pain (60–90 %)	Therapy-related pain (10–25 %)	Tumor-independent pain (3–10 %)
▸ Bone/soft tissue infiltration ▸ Compression and infiltration of nerves, blood and lymph vessels ▸ Tumor necrosis on skin and mucous membranes with ulceration and perforation ▸ Cerebral edema, liver capsule pain, venous thrombosis ▸ Paraneoplastic syndrome ▸ Zoster neuralgia, fungal infection	▸ Surgery ▸ Radiation therapy ▸ Lymphedema ▸ Chemotherapy	▸ Migraine ▸ Tension headache ▸ Arthralgia ▸ Back pain ▸ Positional pain, decubital ulcer

from: Kleeberg U.R.: Schmerztherapie. In: Schmoll H.J., Höffken K., Possinger K. (Hgb) Kompendium Internistische Onkologie. 5. Edition, 2010 [679]

benefits. The vast majority of patients experience effective alleviation of the complex tumor-related pain syndrome and they regain "strength for life". Only 3 % (internationally 13 %) of chronic pain patients require intermittent palliative sedation [681].

Besides somatic sensory causes, the sensation of pain is also modulated by affective and cognitive factors, which have to be reassessed at every conversation with the patient. In the process, the patient's self-image and his/her own attitude towards pain and its cause have to be addressed. Relatives and nurses have to be included. This collaboration optimizes compliance, the prerequisite for any successful intervention [682, 683].

Cancer pain is not just a physical sensation, but also always associated with psychological and vegetative reactions, as it triggers a spiral of conscious and unconscious responses: anxiety, despair, and hopelessness lead to withdrawal, isolation, and depression, but also to vegetative irritability, insomnia, exhaustion and even psychological derangement. The support and care of patients and their relatives by the oncologic team helps address these issues and provides relief.

The pain ladder introduced by the WHO (1988) comes into use in systemic pharmaceutical pain management. The distinct and usually multifactorial pathogenesis of pain requires agents with different modes of action. Through rational use of various analgesics, their efficacy can be enhanced and adverse drug reactions may be reduced.

The following groups of agents are available for drug therapy of the chronic complex pain syndrome in cancer patients. Upon exhaustion of causal interventions, these agents are usually employed in combination:

- non-opioid analgesics (non-steroidal anti-inflammatory drugs, NSAIDs),
- centrally acting analgesics (weak opioids),
- opioids and opiates,
- adjuvant agents (psychotropic and anti-seizure drugs, corticosteroids).

Analgesics of all classes are fraught with numerous adverse events that have to be addressed prophylactically. This is best achieved by slowly increasing the dose of the analgesic as well as by preventive measures and intensive support of patients and their relatives. Prevention and treatment of anorexia, nausea and vomiting, upper abdominal discomfort, constipation, drowsiness, and vertigo are paramount.

Rare ADR include allergies, serotonin-syndrome (serotonergic overstimulation of the central nervous system [CNS] with tremor, sweating, fever, diarrhea) and, depending on tumor location and interventions in the lesser pelvis, urinary retention. Through specific use of all treatment methods available, pain management in melanoma may be optimized in a way that patients do not have to suffer pain at any stage of their disease [679].

3.7.6 Antiemetic therapy

P. Feyer

Vomiting and especially nausea are still among the most commonly feared adverse events during chemo and radiation therapy [684]. Sufficient antiemetic prophylaxis and therapy are therefore a basic prerequisite for successful treatment. In order to achieve maximum efficacy, available antiemetic gents like 5-HT3 receptor antagonists (5-HT3 RA), neurokinin-1 receptor antagonists (NK1 RA), and steroids should be employed in accordance with guidelines.

Definitions

Vomiting/nausea as consequence of chemo/radiation therapy is classified into 3 variants with respect to chronologic

occurrence. In everyday clinical practice, the first two forms play the leading role:

Acute: occurring within the first 24 hours after chemo/radiation therapy, primarily by serotonin release from enterochromaffin cells of the small intestine.

Delayed: occurring 24 hours to 120 hours after chemo/radiation therapy, primarily mediated by substance P.

Anticipatory: only occurring after nausea and vomiting related to previous chemo/radiation therapy. Consequence of classic conditioning, not sufficiently treatable with drug therapy.

Risk factors for nausea and vomiting

The emetogenic potential of chemotherapy constitutes the main risk factor for vomiting induced by cytostatic agents. Individual chemotherapeutic agents are accordingly classified into 4 risk classes (Table 16, 17). Patient-related risk factors for vomiting have to be taken into account, such as regular low alcohol consumption, female gender, age < 35 years, preexisting motion sickness, anxious personality, and previous chemotherapy as well as preexisting nausea.

Antiemetic therapeutic strategy

The recommendations for antiemetic prophylaxis are oriented towards the updated MASCC/ESMO Guidelines 2011 (Multinational Association of Supportive Care in Cancer – www.mascc.org) and the guideline update of the ASCO ("Antiemetics Clinical Practice Guidelines ASCO 2011" – www.asco.org/guidelines/antiemetics) (Table 18).

Radiation therapy induced nausea and vomiting

In patients receiving radiation therapy, the emetogenic risk should also be ascertained on the basis of risk categories (Table 19). Prophylaxis and therapy should be initiated in accordance with guidelines (Table 20).

In patients receiving combined radiation/chemotherapy, the emetogenic risk is usually defined by chemotherapy, unless the risk by radiation therapy is greater.

Among the newer antiemetics recently approved by the EMA are:

- *fosaprepitant 150 mg*, the NK1 antagonist as single dose for treatment of acute and delayed vomiting over the course of 3 days,
- *granisetron, transdermal system*, a patch continuously releasing granisetron over the course of 5 days and regarded as option for multi-day chemotherapy and high to moderate emetogenic radiation therapy,
- *ondansetron ODT as oral lozenge*, corresponding to the range of indications of 5-HT3 RA.

The combination of a 5-HT3 RA plus corticosteroids is also recommended in pediatric patients receiving highly or moderately emetogenic chemotherapy. Due to differences in pediatric pharmacokinetic parameters, higher weight-adapted doses of 5-HT3 RA may be required compared to adults.

Conclusion:

Determination of the therapeutic emetogenic potential should be done by reference to the ascertained risk category. The cytostatic agent respectively radiation therapy exhibiting the highest emetogenic potential is critical in determining adequate therapy. The individual risk profile should be taken into account. Prophylactic application of antiemetics is indispensible, given respective risk factors. If nausea/vomiting continues, differential diagnoses should be considered.

3.7.7 Lymphedema

D. Nashan, J. Hübner

Relevant types of lymphedemas in melanoma are due to obstruction of lymph drainage by the tumor or secondarily as a result of treatment [685] such as e.g.

- surgery, especially lymph node dissection [686],
- radiation therapy [687],
- isolated limb perfusion [688].

If left untreated, chronic persistent lymphedema may develop.

The therapeutic goal is optimal regression of the increased accumulation of interstitial tissue fluid as well as preservation and optimization of bodily functions.

With respect to history taking and diagnostic measures, please refer to the guideline "Diagnosis and Therapy of Lymphedemas" (http://www.awmf.org/leitlinien/detail/ll/058-001.html). A possible clinical stage classification includes:

- *stage I*: soft edema, elevation reduces swelling
- *stage II*: edema with secondary tissue changes, elevation without effect
- *stage III*: elephantiasis, hard swelling, frequently lobular form with typical skin changes

Conclusion:

Basic therapeutic procedures include complex physical decongestive therapy, manual lymphatic drainage, compression therapy, and decongestive exercises. Skin care and psycho-oncologic support should be integrated into the therapeutic concept.

Improvement of symptoms through complex physical decongestive therapy has been demonstrated following inguinal lymph node surgery in melanoma patients [689].

Well-instructed postoperative physical activity neither results in the development of additional lymphedemas nor does it worsen existing lymphedemas.

Table 16 Emetogenic potential of intravenously applied cytostatic agents (ASCO 2011).

Emetogenic potential of intravenously applied cytostatic agents	
High (risk for emesis without antiemetic prophylaxis > 90 %)	
Carmustine, BCNU	Lomustine
Cisplatin	Mechlorethamine
Cyclophosphamide (> 1 500 mg/m²)	Pentostatin
Dacarbazine, DTIC	Streptozotocin
Dactinomycin, Actinomycin D	
Moderate (risk for emesis without antiemetic prophylaxis 30–90 %)	
Altretamine	Ifosfamide
Carboplatin	Irinotecan
Cyclophosphamide (< 1 500 mg/m²)	Melphalan IV
Cytarabine (> 1 g/m²)	Mitoxantrone (> 12 mg/m²)
Daunorubicin	Oxaliplatin
Doxorubicin	Treosulfan
Epirubicin	Trabectedin
Idarubicin	
Low (risk for emesis without antiemetic prophylaxis 10–30 %)	
Asparaginase	Mitoxantrone (< 12 mg/m²)
Bortezomib	Paclitaxel
Cetuximab	PEG-asparaginase
Cytarabine (< 1 g/m²)	Pemetrexed
Docetaxel	Teniposide
Etoposide IV	Thiopeta
5-Fluorouracil	Topotecan
Gemcitabine	Trastuzumab
Methotrexate (> 100 mg/m²)	
Minimal (risk for emesis without antiemetic prophylaxis < 10 %)	
Bleomycin	Interferons
Bevacizumab	Mercaptopurine
Busulfan	Methotrexat (< 100 mg/m²)
Chlorambucil	Thioguanine
Cladribine	Vinblastine
Cytarabine (< 100 mg/m²)	Vincristine
Fludarabine	Vinorelbine
Hormone	
Hydroxyurea	

Table 17 Emetogenic potential of orally applied cytostatic agents (ASCO 2011).

Emetogenic potential of orally applied cytostatic agents	
High (risk for emesis without antiemetic prophylaxis > 90 %)	
Hexamethylmelamine	Procarbazine
Moderate (risk for emesis without antiemetic prophylaxis 30–90 %)	
Cyclophosphamide	Temozolomide
Etoposide	Vinorelbine
Imatinib	
Low (risk for emesis without antiemetic prophylaxis 10–30 %)	
Capecitabine	Fludarabine
Minimal (risk for emesis without antiemetic prophylaxis < 10 %)	
Chlorambucil	Melphalan
Erlotinib	Methotrexate
Gefitinib	Sorafenib
Hydroxyurea	Sunitinib
L-phenylalanine mustard	6-Thioguanine

Table 18 Antiemetic dose by chemotherapy risk categories (ASCO 2011).

Risk category	Dose on the day of chemotherapy	Dose on the following days
High emetogenic risk (HEC)[1]		
NK-1 antagonist		
Aprepitant	125 mg PO	80 mg PO day 2 and 3
Fosaprepitant	150 mg IV	
5-HT3 antagonist		
Granisetron	2 mg PO; 1 mg or 0.01 mg/kg IV	
Ondansetron	8 mg PO twice daily; 8 mg or 0.15 mg/kg IV	
Palonosetron	0.50 mg PO or 0.25 mg IV	
Dolasetron	100 mg PO (IV not recommended)	
Tropisetron	5 mg PO or 5 mg IV	
Ramosetron	0.3 mg IV (available only in Japan)	
Corticosteroid[2]		
Dexamethasone	12 mg PO or IV	8 mg PO or IV; day 2–3 or day 2–4
Moderate emetogenic risk (MEC)[3]		
5-HT3 antagonist		
Palonosetron	0.50 mg PO or 0.25 mg IV	

Table 18 Continued.

Risk category	Dose on the day of chemotherapy	Dose on the following days
Corticosteroid		
Dexamethasone	8 mg PO or IV	8 mg; day 2 and 3
Low emetogenic risk		
Corticosteroid		
Dexamethasone	8 mg PO or IV	

Note: For patients receiving multi-day chemotherapy, the emetogenic risk of the respective chemotherapeutic drugs first has to be determined. Patients should receive the agent with the highest therapeutic index daily during chemotherapy and 2 days after discontinuation of chemotherapy. Instead of daily application of serotonin antagonists, patients may be alternatively offered a granisetron transdermal patch, which releases the agent over the course of several days.
5-HT3 = 5-hydroxytryptamine 3; IV = intravenously; NK1 = neurokinin-1, PO = orally
1Contains the combination anthracycline and cyclophosphamide.
2The dexamethasone dose stated is directed at patients receiving the recommended triple combination of highly emetogenic chemotherapy. If patients do not receive aprepitant, the dexamethasone dose should be adapted to 20 mg on day 1 and 16 mg on days 2 and 3.
3If no NK1 antagonist is applied, the dose should be the same as for highly emetogenic chemotherapy. It is important to apply the corticosteroid only on day 1 (12 mg of dexamethasone).

Table 19 Emetogenic risk by irradiation site (ASCO 2011).

Emetogenic risk by localization of radiation therapy	
High	▸ Whole-body radiation therapy ▸ Total nodal radiation therapy
Moderate	▸ Upper abdomen ▸ Upper body radiation therapy
Low	▸ Brain ▸ Craniospinal axis ▸ Head/neck ▸ Lower thorax ▸ Pelvis
Minimal	▸ Extremities ▸ Chest

3.7.8 Hematologic adverse events

H. Link

3.7.8.1 Anemia

Tumor-related or chemotherapy-induced anemia presents a particular challenge. Anemia is significant with respect to performance capability and quality of life and should be compensated, if symptomatic, and brought up to an Hb level of 12 g/dl. Treatment of the underlying dysfunction is implemented after proper diagnosis and depends on the underlying disease or the specific cause for anemia. There is conflicting data on the impact of anemia on survival (http://www.krebsgesellschaft.de/ download/ll_o_05.pdf). Transfusions or eythropoetin constitute possible treatment options for anemia. According to guidelines by the German Medical Association, transfusions are indicated at an Hb level of 8 g/dl or below. In chronic iron-deficiency anemia (nutritive or bleeding-related), oral application of Fe-II compounds (100–300 mg/d) is indicated. Alternatively, in case of intolerance or absorption disorders (short bowel etc.), parenteral application of Fe(III) complex is an option. In acute blood loss, the indication for transfusion of packed red blood cells (PRBC) has to be examined at Hb levels < 8 g/dl. In chronic anemia, markedly lower Hb levels between 6 and 8 g/dl may be tolerated without symptoms, Thus, there is no mandatory indication for RBC transfusion in these cases. However, patients with coronary heart disease, COPD, or imminent risk for impaired cerebral perfusion, should receive transfusions at Hb levels < 10 g/dl. Tumor patients treated with chemo or radiation therapy may be started on erythropoietin from Hb levels < 10 g/dl. In patients with Hb levels below 9 g/dl, potential transfusions in addition to erythropoietin should be considered. RBC transfusion risks have to be taken into account.

Treatment with erythropoietin should be contemplated in asymptomatic anemic patients with Hb levels < 11 g/dl, in order to prevent a further drop in hemoglobin. Prophylactic

Table 20 Antiemetic dose by radiation therapy and risk category (ASCO 2011).

Risk category	Dose	Regimen
High emetogenic risk (HEC)		
5-HT3 antagonist		
Granisetron	2 mg PO; 1 mg or 0.01 mg/kg IV	5-HT3 antagonist prior to each fraction during radiation therapy, continued until 24 h after discontinuation of radiation therapy
Ondansetron	8 mg PO twice daily; 8 mg or 0.15 mg/kg IV	
Palonosetron[1]	0.50 mg PO or 0.25 mg IV	
Dolasetron	100 mg PO (IV not recommended)	
Tropisetron	5 mg PO or 5 mg IV	
Corticosteroid		
Dexamethasone	4 mg PO or IV	During fractions 1–5
Moderate emetogenic risk (MEC)		
5-HT3 antagonist	Each agent mentioned under HEC is accepted. There is no preferred option.	Prior to each fraction during radiation therapy
Corticosteroid		
Dexamethasone	4 mg IV or PO	During fractions 1–5
Low emetogenic risk		
5-HT3 antagonist	Each agent mentioned under HEC is accepted. There is no preferred option.	5-HT3 either as rescue therapy or as prophylaxis. If rescue therapy is used, continued treatment should be performed until discontinuation of radiation therapy
Minimal emetogenic risk		
5-HT3 antagonist	Each agent mentioned under HEC is accepted. There is no preferred option.	Patients should, if required, receive rescue therapy. If rescue therapy is used, continued treatment should be performed until discontinuation of radiation therapy
Dopamine receptor antagonist		
Metoclopramide	20 mg PO	
Prochlorperazine	10 mg PO or IV	

5-HT3 = 5-Hydroxytryptamine-3; IV = intravenously, PO = orally
[1]There is currently no available data on recommended dose frequency for palonosetron in this setting. The Up-date Committee recommends: application q 2 or 3 days may be adequate.

application of erythropoietin for anemia prevention is not recommended in patients with normal or almost normal Hb levels prior to chemo and/or radiation therapy. Before discontinuation of treatment Hb levels should preferably be around 12 g/dl, and patients should experience improvement of symptoms. The evidence-based EORTC guidelines on EPO therapy for anemia can be found in detail at www.onkosupport.de and the guidelines of the German Society of Hematology and Oncology (DGHO) at www.dgho.de/onkopedia/Supportiv [690–693].

3.7.8.2 Platelet transfusion

Text from cross-sectional guidelines of the German Medical Association 2008 (1) and DGHO (http://www.dgho-onkopedia.de, http://www.baek.de/downloads/Querschnittsleitlinie_Gesamtdokument-deutsch_07032011.pdf)

Indication for platelet transfusion

In adults with disease or therapy-related temporary thrombopenia following chemotherapy of hematologic malignancies, a threshold value of 10 000 platelets/µl is recommended

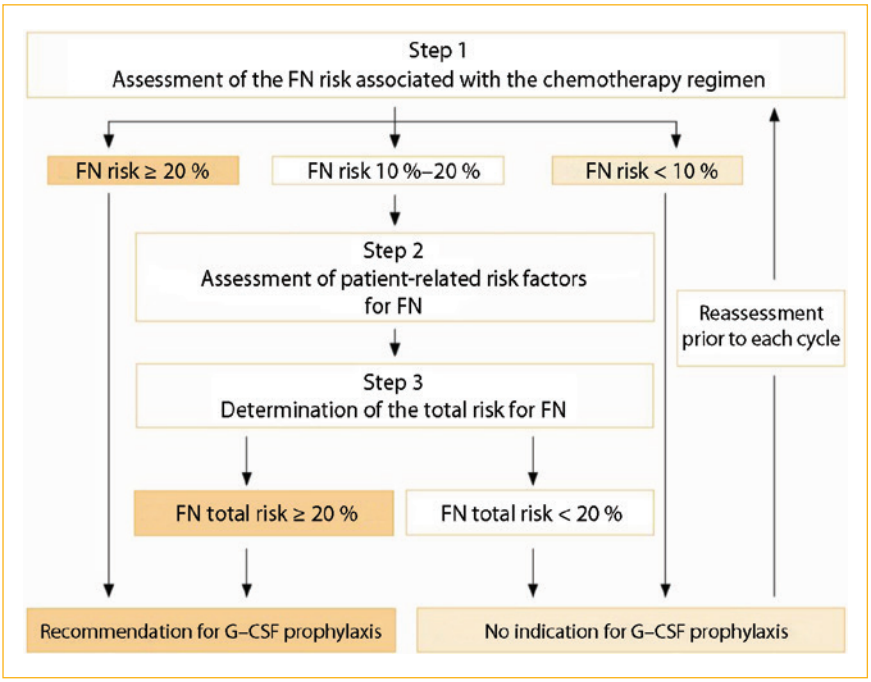

Figure 6 Indication for G-CSF prophylaxis during chemotherapy modified according to EORTC [694].

for prophylactic platelet transfusion, unless there are concomitant circumstances relevant to bleeding. This has been primarily investigated in patients with acute leukemia.

In patients with solid malignancies and thrombopenia after radiation or chemotherapy, the same threshold value for transfusion applies as mentioned in the previous paragraph. Prospective studies are missing. In the presence of manifest hemorrhagic complications (e.g. necrotizing solid primary tumors), higher platelet numbers potentially become necessary (> 50 000/µl).

Platelet transfusion is recommended for patients with acute disorders of platelet formation in:

- adults with acute leukemia, prophylactically only at platelet levels ≤ 10 000/µl or in case of manifest hemorrhage,
- patients with solid malignancies without additional risk for bleeding only at platelet levels ≤ 10 000/µl or in case of manifest hemorrhage.

Patients with acute disorders of platelet formation without additional hemorrhagic risks

This group includes patients of the above-mentioned group with additional hemorrhagic risk. In hematologic disorders, but also in patients with solid tumors and chemotherapy-associated thrombopenia, certain risk factors for severe hemorrhagic complications have emerged.

Risk factors for hemorrhagic complications in thrombopenia:

- infections
- clinical signs of hemorrhage (e.g. petechial bleeding)
- fever above 38 °C
- leucocytosis
- plasmatic (pro-hemorrhagic) coagulation disorder
- steep drop in platelet number
- preexisting areas of necrosis

Prophylactic administration of platelet concentrates is usually recommended in thrombopenic cancer patients with one or more of these risk factors, if platelet numbers drop ≤ 20 000/µl.

Platelet transfusion is recommended in hematologic-oncologic and oncologic patients with an acute disorder of platelet formation and additional hemorrhagic risks in:

- patients with additional risk factors, if platelet levels are < 20 000/µl,
- in case of manifest hemorrhage.

Platelet concentrates (PC) are either obtained from whole blood donations or by thrombapheresis from healthy blood donors. Two preparations are available. Pool PC contains 240 to 360 × 109 platelets in 200 to 350 ml plasma or plasma substitute, depending on the number of pooled units (4–6 donors). Apheresis platelet concentrate usually contains 200 to 400 × 109 platelets in roughly 200 to 300 ml plasma from a single donor.

3.7.8.3 Neutropenia, febrile neutropenia, infections

Current recommendations by the DGHO, DKG, NCCN, ASCO, and EORTC to already administer G-CSF, if the risk for febrile neutropenia is ≥ 20 %, are based on randomized

Table 21 Patient-related risk factors for febrile neutropenia.

High risk	Increased risk	Other factors
Age > 65 years	Advanced disease	Poor performance status
	Previous FN episode	Poor nutritional status
	No antibiotic prophylaxis	Female gender
	No use of G-CSF	Hb < 12 g/dl
		Liver, kidney, or cardiovascular disease

controlled trials, which have shown that patients with a ≥ 20 % risk for febrile neutropenia (FN) significantly benefit from G-CSF. If a chemotherapy is planned that harbors a moderate FN risk (10–20 %), guidelines recommend assessment of the individual FN risk prior to each treatment cycle, thereby taking patient-related respectively tumor-related risk factors into account (http://www.dgho.de/onkopedia/Supportiv) [694–696] (Table 21).

Infections

Due to the risk for antibiotic resistance, routine antibiotic prophylaxis is not recommended for chemotherapy protocols employed in melanoma. The following definitions are taken from the DGHO guideline cited as short version in the guidelines of the German Cancer Society (www.dgho-infektionen.de). Further details may be found at the aforementioned web address. Neutropenia (granulocytopenia) is defined by the following values:

Neutrophil granulocytes (segmented and banded) < 500/mm³ or < 1000/mm³ with an expected drop < 500/mm³ within the next 2 days. Moreover, patients are assigned to respective risk categories, depending on the expected duration of neutropenia and respective risk factors; e.g. low-risk group with a duration of neutropenia ≤ 7 days. Fever of unknown origin (FUO) is defined as new fever without clinical or microbiologic signs of infection occurring once without detectable cause ≥ 38.3 °C or for at least one hour ≥ 38.0 °C, or twice within 12 hours. This fever has to be regarded as sign of infection. Therapy must be commenced within 2 hours and workup must not delay its initiation [697–701]. An algorithm is shown in Figure 7.

Risk factors precluding outpatient therapy in standard risk patients (duration of neutropenia ≤ 7 days):

- ECOG performance score > 2,
- evidence for CNS infection, severe pneumonia, venous catheter infection,
- signs of sepsis or shock,
- contraindications for oral therapy: marked abdominal discomfort (diarrhea), IV supportive therapy (e.g. nutrition), dehydration, recurrent vomiting,
- necessity for continuous and close monitoring (e.g. uncontrolled diabetes mellitus, hypercalcemia),
- oral quinolone prophylaxis or therapy within the past 4 (–7) d,
- medical care not assured (various options); patient lives alone, patient/roommates have no phone; hospital experienced in treating neutropenic patients cannot be reached within 1 hour; patient not fully alert, no comprehension of risks of outpatient therapy,
- compliance not to be expected for oral medication.

3.7.9 Palliative medicine

3.7.9	Consensus-based recommendation
GCP	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.
	Strength of consensus: 100 %

J. Gärtner, U. Kleeberg, R. Voltz

Stage IV melanoma patients show a median survival time of 6–9 months, 5-year survival is below 5 % [702]. Despite the use of all available surgical, chemo, and radiation therapy measures, the disease will result in deterioration of patients' general condition in the foreseeable future, and eventually in death. To some extent, patients suffer from pronounced symptoms (e.g. pain, dyspnea) and psychosocial impairment [703, 704].

In order to prepare patients and their social milieu for this situation, the WHO recommends early involvement of services specialized in palliative medicine [705]. The reasons for this are (I) best possible alleviation of symptoms and quality of life through joint interdisciplinary treatment, (II) optimized, need-oriented, cross-specialty care, (III) comprehensive care of patients and their relatives concerning psychosocial and spiritual issues, (IV) strengthening of

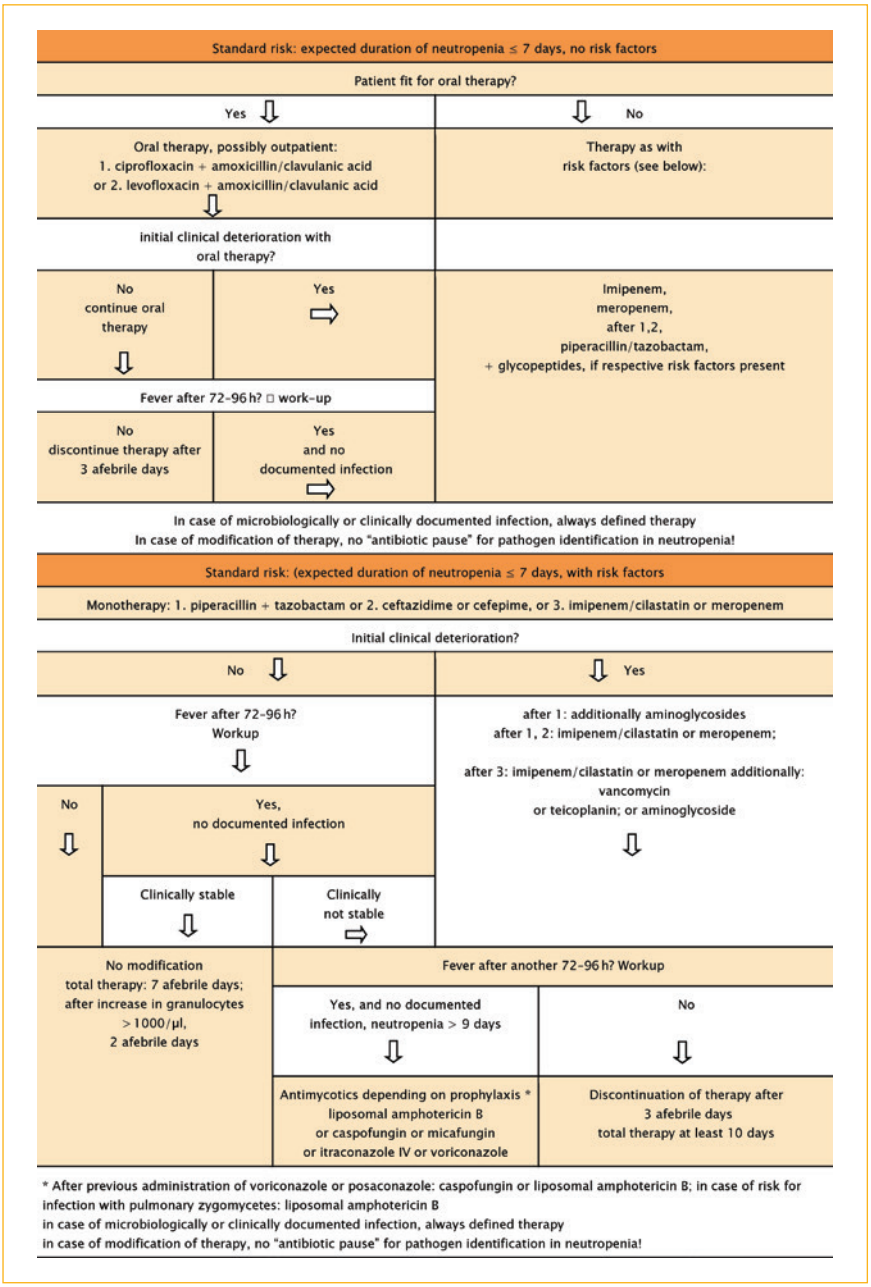

Figure 7 Algorithm for infection prophylaxis in neutropenia during chemotherapy.

trust and imparting assurance vis-à-vis the interdisciplinary treatment team through coordination of tumor-specific and palliative medicine measures, (V) support in the care and management of patients with well-advanced disease through coordination of inpatient and specialized outpatient palliative care [706].

With respect to optimum care, it is crucial to inform patients and relatives early on about the potential for comprehensive, multi-professional, palliative care [707]. As recommended by ASCO, NCCN, and WHO, a first discussion should take place at the time of systemic metastasis, if no curative interventions remain feasible [708–712]. The Work Group for Palliative Medicine of the DKG (APM) has adopted the ASCO recommendation [713]. Ideally, the initial patient contact with palliative medicine should take place in familiar surroundings. The goal should be proper integration of supportive therapeutic, palliative therapeutic as well as palliative medicine measures.

3.8 Structures of care and QM

3.8.1 Skin cancer centers

C. Garbe

Skin cancer centers have been established in Germany since early 2009, the first in Heidelberg. In the meantime, 21 centers have been certified (as of mid 2012). Certification occurs in 2 phases:

- Review of the survey form Skin Tumor Centers (download www.onkozert.de) by two specialized auditors, return of the form to the respective center noting deviations or suggestions for improvement (evaluation of the survey form).
- Audit performed by the same 2 auditors who evaluated the survey form. Not only is the respective center visited, but also cooperating departments.

The interdisciplinary skin tumor conference represents the centerpiece of each skin cancer center. As many therapeutic decisions as possible should be made there. Implementation of a skin tumor conference/board mainly comprising participants from dermatology, oncology, surgery, radiology, and radiation oncology constitutes an essential step towards establishment of such a center. Written agreements with key treatment partners and other treatment partners have to be made. Minimum numbers of skin cancer patients are required.

Another crucial issue is tumor documentation. All skin cancers have to be electronically recorded and documented. Patient pathways and SOPs (Standard Operational Procedures) for treatment modalities (sentinel lymph node, chemotherapy, etc.) are presented. A good cooperation with referring physicians, psycho-oncology, and social services has to be ensured.

The goal is coordination of management and interdisciplinary care of skin cancer patients according to current medical knowledge. Implementation of the present S3 guideline plays an essential role in this regard.

3.8.2 Clinical trials

3.8.2	Consensus-based recommendation
GCP	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.
	Strength of consensus: 96 %

C. Czeschik, D. Schadendorf

Interdisciplinary cooperation substantially contributes to enhanced communication of all specialties involved as well as to quicker decision-making. The interdisciplinary tumor board comprises competent colleagues with proven experience in their particular decision field. Continuous external review of treatment pathways und decision trees further contributes to quality enhancement.

"The clinical trial is an instrument designed to assess the effectiveness of potentially new or altered interventions that involve a wide range of clinical activity.

Trials frequently involve drug therapy, but may address new devices, surgical procedures, treatment by external instrumentation (e.g. radiotherapy), or psychosocial aspects of clinical management.

Commonly, the study question is whether a new treatment is better than the old one. It is customary to compare each new treatment group with a control group, the members of which must be offered treatment matching the best standard currently available for their consideration before joining the trial.

The randomised clinical trial (RCT), which involves random allocation of patients to their treatment or control group, is becoming the "gold standard" for assessment of new management processes.

Clinical trials involve significant funding and require the informed consent from patients and frequently, the involvement of a number of centres and health professionals to obtain an appropriate number of subjects to ensure sound statistical power [714, 715].

The conduct of trials by cooperative groups of trialists is the most likely way to advance evidence-based medicine through well-designed protocols and rigorous evaluation.

However, in our community some people are concerned about RCTs, believing that patients involved in such trials may be at risk from factors that would not occur in treatment outside a trial. On the other hand, others see participation in an RCT as being of benefit to the trial subject and probably an optimal way of receiving the best contemporary care and clinical oversight.

A recent Cochrane Review [715] assessed the effect of participation in RCTs (trial effects) independent both of the effects of the clinical treatments being compared (treatment effects) and any differences between patients who participated in RCTs and those who did not. The outcome of this review led its authors to conclude that there is no greater risk from participating in RCTs than there is from being treated outside an RCT. The authors considered that the belief or assertion that results of RCTs cannot be applied to usual practice is challenged by the review.2 This outcome would appear to provide a sound basis for clinicians to offer participation in RCTs to their patients.

Any uncertainty about the effects of treatment can best be resolved through a randomised trial as long as the eligibility criteria for the trial match the patient population seen in

usual practice, or the trial treatment is applied only to patients who match the eligibility criteria [716].” ([19], p. 127).

Thus, clinical trials substantially contribute to uninfluenced acquisition of knowledge and represent a critical building block of evidence-based medicine.

3.8.3 Quality indicators

M. Follmann, S. Wesselmann

Quality indicators (QI) are exactly defined measurable elements meant to allow for evaluation of the quality of care. They facilitate depiction of structural and procedural as well as outcome quality [717].

Using the strong S3 guideline recommendations (evidence- and consensus-based), the Guideline Program in Oncology pursues the goal to derive relevant and practicable QI that exhibit the potential for advancement of oncologic care. These indicators have to be implemented in everyday clinical practice and at the same time coordinated with existing requirements for documentation and data collection.

Ergo, in the beginning of the QI development process, a review of national and international QI and other key figures, which already exist within the realm of the respective guideline, is conducted. If there already are results of measured and analyzed QI on the respective subject matter, they are taken into consideration in the QI development process. Based on the aforementioned items, evaluation of and final consensus on the set of quality indicators is performed in the context of de-novo preparation respectively revision of the guideline in a formal process described below.

The following data available in Germany was considered in the derivation respectively development of quality indicators for the present guideline:

- basic data set of clinical cancer registries with the organ-specific addition of melanoma
- data set of the melanoma registry
- basic melanoma data set ADO (Work Group Dermatologic Oncology)

as well as

- measuring parameters identified by systematic research (ref. methodology)
  1. from the USA (National assessment of melanoma care using formally developed quality indicators. Journal of Clinical Oncology. Karl Y. Bilimoria, Mehul V. Raval, David J. Bentrem, Jeffrey D. Wayne, Charles M. Balch, and Clifford Y. Ko)
  2. from Great-Britain [609]

Generating new quality indicators from the present guideline was implemented as follows:

1. Review: compilation and analysis of the above-mentioned sources (national/international).
2. Using the strong present guideline recommendations, indicators were derived with a definition for numerator and denominator. Evidence-based as well as consensus-based recommendations were considered.
3. In a meeting of members of the guideline commission and representatives of clinical cancer registries and the certification system on May 8, 2012, existing national requirements for documentation were taken as potential basis for the QI to be developed in this guideline. Then, the above-mentioned compilation of guideline recommendations (ref. 2.) was screened and it was decided, whether a potential QI might be generated from a respective recommendation. Exclusion criteria of the first screening can be found in the guideline report.
4. This preselected set of potential QI was evaluated by an interdisciplinary panel of the guideline group using a standardized form, according to the modified Qualify Procedure (http://www.bqs-institut.de/images/stories/doc/106-qualify-down.pdf). Indicators with at least 75 % approval for each criterion (rather true, true) were considered accepted * (Table 22).
5. After written evaluation, a moderated phone conference ensued, in which evaluation results were discussed and the final set of guideline QI was defined.

12 indicators were accepted with an approval of at least 75 % per criterion.

The indicators are to be regarded as temporary. Final evaluation may only be performed after pilot testing and data collection. Pilot testing is planned, among others, by adoption of indicators into the requirements catalog of skin cancer centers. Thus, data is generated which may be used in the final evaluation during guideline updating (Table 23).

Table 22 Evaluation table of potential quality indicators.

Your evaluation	1 Not true	2 Rather not true	3 Rather true	4 True
Criterion 1: Significance of the quality feature assessed by the QI with respect to the health care system. The following statement is evaluated: "The indicator accounts for essential aspects of quality of life, morbidity, or mortality respectively denotes essential processes of care and structures of care."				
Criterion 2: Clarity of definitions. The following statement is evaluated: "The indicator is defined clearly and unequivocally."				
Criterion 3: Controllability of indicator manifestation. The following statement is evaluated: "The quality indicator refers to an aspect of care that may be influenced by the evaluated factors."				
Criterion 4: Evidence and consensus basis of the indicator. The following statement is evaluated: "The presence of the gauged process leads to an improved result." *Please note: As only strong recommendations were adopted, the strength of consensus is generally high. Please only evaluate the strength of evidence (quality of trial results with respect to the association of recommended intervention and patient-relevant outcome)!*				
Criterion 5: Consideration of potential risks/adverse effects. Partial aspect: "Are there risks for mismanagement?" The following statement is evaluated: "There are no known risks for an incentive for mismanagement or known or presumed risks of employing the indicator are described and taken into account, if necessary.		Yes		No

Table 23 Accepted quality indicators after final evaluation (Basic prerequisite for the definition of QI: the numerator is always a subset of the denominator).

	Content of recommendation (wording, LoE, GR); Quality objective	Indication of the melanoma guideline with regard to *evidence basis*
QI 1: Surgical margins (1 cm) during radical excision		
N: Patients undergoing radical excision with surgical margins of 1 cm D: Patients with primary cutaneous melanoma and curative radical excision (tumor thickness ≤ 2 mm)	**Recommendation Nr. 3.2.3.1.a** In melanoma, radical excision with respective surgical margins shall be performed with curative intent, in order to prevent local recurrence of the tumor. LoE 1a, GR A Stage, tumor thickness, surgical margins: pT1, pT2, ≤ 1 mm–2.0 mm, 1 cm pT3, pT4, 2.01–≥ 4.0 mm, 2 cm	Systematic search of the literature *de-novo:* [63]
QI 2: Surgical margins (2 cm) during radical excision		
N: Patients undergoing radical excision with surgical margins of 2 cm D: Patients with primary cutaneous melanoma and curative radical excision (tumor thick-ness > 2 mm)	**Recommendation Nr. 3.2.3.1.a** In melanoma, radical excision with respective surgical margins shall be performed with curative intent, in order to prevent local recurrence of the tumor. LoE 1a, GR A Stage, tumor thickness, surgical margin: pT1, pT2, ≤ 1 mm–2,0 mm, 1 cm pT3, pT4, 2.01–≥ 4.0 mm, 2 cm	Systematic search of the literature *de-novo:* [63]

Table 23 Continued.

	Content of recommendation (wording, LoE, GR); Quality objective	Indication of the melanoma guideline with regard to *evidence basis*
QI 3: Locoregional lymph node sonography		
N: Patients receiving locoregional lymph node sonography D: Patients with melanoma ≥ IB–IIIC	**Recommendation Nr. 3.2.6.4** Locoregional lymph node sonography shall be performed in patients with the primary diagnosis of melanoma at tumor stage IB and above. LoE 1a, GR A	Systematic search of the literature *de-novo:* [113]
	Recommendation Nr. 3.4.1.3 Locoregional lymph node sonography shall be performed in patients with suspected locoregional metastasis of melanoma or evidence thereof. LoE 1a, GR A	Systematic search of the literature *de-novo:* [104, 108, 113]
QI devised from two recommendations.		
QI 4: Sentinel lymph node biopsy		
N: Patients undergoing SLNB D: Patients with primary cutaneous melanoma (tumor thickness ≥ 1 mm) and without evidence for locoregional or distant metastasis	**Recommendation Nr. 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. LoE 1a, GR A	Systematic search of the literature *de-novo:* [144–150]
QI 5: Therapeutic lymph node dissection		
N: Patients undergoing therapeutic LND at stage IIIB and IIIC D: Patients with stage IIIB and IIIC melanoma	**Recommendation Nr. 3.4.2.2.a** Therapeutic LND shall be performed in case of proven lymphogenic metastasis (cytologic or histologic evidence, lymph node sonography, CT, PET/CT) without evidence for distant metastases (stage IIIB and IIIC). GCP	
QI 6: Postoperative radiation therapy		
N: Patients undergoing radiation therapy with 50–60 Gy in conventional fractionation (5 x 1,8–2,5 Gy/week) D: Patients with melanoma undergoing postoperative radiation therapy of the lymph drainage area	**Recommendation Nr. 3.4.3.c** If there is an indication for irradiation of the lymphatic drainage area, radiation therapy shall be performed using 50–60 Gy in conventional fractionation (5 x 1.8–2.5 Gy/week). LoE 2b, GR A	Systematic search of the literature *de-novo:* [336–345]
QI 7: Adjuvant systemic therapy		
N: Patients undergoing adjuvant systemic chemotherapy/ dacarbazine D: Patients with stage I–III melanoma	**Recommendation Nr. 3.4.4.1** Dacarbazine shall not be administered in the adjuvant therapy of melanoma LoE 1a, GR A Quality objective: 0 %	Guideline adaptation: [194, 348]

Table 23 Continued.

	Content of recommendation (wording, LoE, GR); Quality objective	Indication of the melanoma guideline with regard to *evidence basis*
QI 8: Adjuvant isolated limb perfusion		
N: Patients undergoing adjuvant isolated limb perfusion D: Patients with stage I–IIIB melanoma	**Recommendation Nr. 3.4.4.3** Adjuvant isolated limb perfusion with melphalan shall not be administered in the adjuvant therapy of melanoma. LoE 1b, GR A Quality objective: 0 %	Guideline adaptation: [194]
QI 9: LDH measurement		
N: Patients receiving LDH measurement D: Patients with stage IV melanoma	**Recommendation Nr. 3.5.2.7** As part of the current AJCC classification, LDH shall be measured in patients with suspected distant metastases or evidence thereof. LoE 1b, GR A	Systematic search of the literature *de-novo:* [17, 447, 448]
QI 10: BRAF inhibitor therapy		
N: Patients receiving BRAF inhibitor therapy D: Patients with stage IV melanoma exhibiting BRAF inhibitor-sensitive BRAF mutation	**Recommendation Nr. 3.5.6.3** In case of BRAF inhibitor-sensitive BRAF mutation, therapy with a BRAF inhibitor shall be administered. LoE 1b, GR A	Systematic search of the literature *de-novo:* [458]
QI 11: Locoregional lymph node sonography during follow-up		
N: Patients receiving locoregional lymph node sonography D: Tumor-free melanoma patients during follow-up (stage ≥ IB–IIIC)	**Recommendation Nr. 3.6.4.2** Locoregional lymph node sonography shall be performed during follow-up in melanoma patients at stage IB and above. LoE 1a, GR A	Systematic search of the literature *de-novo:* [104, 113, 613, 619]
QI 12: Presentation to skin tumor board		
N: Patients with stage IV melanoma presented to an interdisciplinary skin tumor board D: Patients with stage IV melanoma	**Recommendation Nr. 3.8.2** Patients with metastasized melanoma (stage III and above) shall be presented to an interdisciplinary tumor board, in order to determine further workup and therapy. Potential inclusion into clinical trials should be considered in each case. GCP	

3.9 Abbreviations

A.	artery
ADR	adverse drug reaction
AHB	follow-up treatment
AR	follow-up treatment measure
ASCO	American Society of Clinical Oncology
AUC	area under the curve
BCG	Bacillus-Calmette-Guérin
BSA	body surface area
BSI	Brief Symptom Inventory
CI	confidence interval
CCOPGI	Cancer Care Ontario Practice Guidelines Initiative
CLND	complete lymph node dissection
CLSM	confocal laser scanning microscopy
CNS	central nervous system
CR	complete response
CT	computed tomography
CTSQ	Cancer Therapy Satisfaction Questionnaire
DFI	disease-free interval

DFS	disease-free survival
DNCB	dinitrochlorobenzene
DCP	diphencyprone
DSS	disease-specific survival
DT	distress thermometer
DTIC	dacarbazine
ECT	electrochemotherapy
EK	erythrocyte concentrate
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
ERND	extended radical neck dissection
FAMMM	familial atypical multiple mole-melanoma
FBK	questionnaire on stress in cancer patients
FDG	fluoro-deoxyglucose
FN	febrile neutropenia
FUS	focused ultrasound
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GLQ	Global Quality of Life
Gp100	Glycoprotein 100
Gy	Gray
HADS	Hospital Anxiety and Depression Scale
HDI	high dose interferon
HDR	high dose rate
HE	hematoxylin & eosin
HF	Hornheide questionnaire
HIAC	hepatic intraarterial chemotherapy
HR	hazard ratio
HRQL	health related quality of life
ICF	International Classification of Functioning, Disability and Health
IDI	intermediate dose interferon
IFN	Interferon
IHP	isolated hepatic perfusion
Il-2	interleukin 2
ILI	isolated limb infusion
ILP	isolated limb perfusion
ITT	intent to treat
LDH	lactate dehydrogenase
LDI	low dose interferon
LITT	laser-induced thermotherapy
LM	lentigo maligna
LMM	lentigo maligna melanoma
LN	lymph node
LND	lymph node dissection
M.	muscle
MIA	melanoma inhibitory activity
MM	malignant melanoma
MPT	multiphoton laser tomography
MRND	modified radical neck dissection
MRI	magnetic resonance imaging
MSLT	Multicenter Selective Lymphadenectomy Trial
mSv	Millisievert
MW	microwaves
N.	nerve
NCIC	National Cancer Institute of Canada Clinical Trials Group
NK1-RA	Neurokinin1-Rezeptorantagonisten
NSAIS	non-steroidal anti-inflammatory substances
n.s.	not significant
OCT	optical coherence tomography
OR	odds ratio
OS	overall survival
QI	quality indicator
QWB-SA	Quality of Well Being Self-administered Questionaire
PCR	polymerase chain reaction
PET	positron emission tomography
p.i.	per infusion
PO	orally
PO-BaDo	basic psycho-oncologic documentation
QL	quality of life
R1	microscopic residual tumor (acc. to R classification)
R2	macroscopic residual tumor (acc. to R classification)
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	radio frequency ablation
RFS	relapse-free survival, recurrence free survival
rhTNF	recombinant human tumor necrosis factor
RND	radical neck dissection
RPA	recursive partitioning analysis
RR	relative risk
RSCL	Rotterdam Symptom Checklist
RT	radiation therapy
s.c.	subcutaneous
SDD	sequential digital dermoscopy
SD	Stable Disease
SIRT	selective internal radiation therapy
SND	selective neck dissection
SLN	sentinel lymph node
SLNB	sentinel lymph node biopsy
SPECT	Single-Photon-Emission computed tomography
STAI	State Trait Anxiety Inventory
Sv	Sievert
TACE	trans-arterial chemoembolization
TCM	Traditional Chinese Medicine
TD	total dose
TLND	therapeutic lymph node dissection
TMZ	temozolomide
TNF	tumor necrosis factor
V.	Vena
vs.	versus
WHO	World Health Organization

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