REVIEW ARTICLE

Treatment of Melanoma

Claus Garbe, Patrick Terheyden, Ulrich Keilholz,
Oliver Kölbl, Axel Hauschild

SUMMARY

Introduction: The incidence of melanoma has increased fivefold during the past three decades. Melanoma can no longer be classified as rare; rather, it is now one of the more frequent tumors.

Methods: Recommendations for the diagnosis and treatment of melanoma are laid out in the interdisciplinary S2 guidelines of the German Cancer Society, upon which the present review is based. The goal of this article is to present the clinical core recommendations for treatment in all disease stages.

Results: The operative management of primary melanoma usually takes place in two steps. A complete excisional biopsy with a safety margin of about 2 mm is performed in order to establish the histopathological diagnosis. Definitive surgical excision is performed with a safety margin of 1 cm in tumors up to 2 mm thick, 2 cm in thicker tumors. In tumors more than 1 mm thick, sentinel lymph node biopsy should be performed to aid in tumor staging. Radiotherapy is indicated in inoperable tumors of all stages. Adjuvant immunotherapy with interferon alpha is recommended in tumors of thickness >2 mm and in locoregional metastasis. If distant metastasis is present and R0 surgery is not an option, the treatment should primarily comprise monotherapy or alternatively the patient should be enrolled in a clinical trial.

Conclusion: The recommendations presented here are based predominantly on the results of prospective randomized trials.

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Malignant melanoma is a malignant tumor that originates from the melanocytes and manifests mainly on the skin. Rarely, melanomas can occur on the eye (conjunctiva and uvea), the meninges, and the mucosa in different locations. Melanomas are usually strongly pigmented, but amelanotic forms have been observed. Relative to the tumor mass, melanomas have an early tendency to metastasize; the prognosis is therefore poor. Malignant melanoma is responsible for about 90% of skin cancer related mortality (1).

The incidence of melanoma in white populations worldwide is increasing, especially in light skinned people with sun exposure. In central Europe, the incidence is 10 to 15 cases per 100 000 head of population per year, and in the US, 15 to 25 cases. The highest incidence rates have been reported from Australia, at 50 to 60 cases per 100 000 per year (2). Melanomas are rare in populations with pigmented skin (Asians, Africans) and almost always located on the mucosa or on the palms of the hands or the soles of the feet.

The most important etiological factor for the development of a melanoma is UV radiation; white skinned persons are not protected against this to a sufficient degree. Even in childhood, the influence of UV radiation results in the development of benign melanocytic neoplasms, in the form of melanocytic nevi (3, 4). These are indicators of acquired mutations in the melanocytic system. The more melanocytic nevi someone has, the higher their risk of developing melanoma. Melanomas develop primarily in sites with the highest numbers of melanocytic nevi.

Clinically and histologically, four different subtypes of melanoma can be distinguished (*table 1*), which have different patterns of mutation (5). The criteria of the ABCD rule are the main diagnostic criteria (*box*). Staging is important for selecting the best therapeutic approach (6, 7). Details of the different stages of melanoma are summarized in *table 2*.

The following therapeutic guidelines are consistent with the current interdisciplinary short version of the German S2 guideline for melanoma of 2008 (8) and the S2 long versions of 2007 and 2008. In the latter, the detailed recommendations are supported by numerous literature citations (9–11).

Surgical treatment

Excision biopsy is still the gold standard in diagnosing malignant melanoma. The current German guideline recommends safety margins based on the risk of metastasis for excision and re-excision of melanomas (*table 3*)

Sektion Dermatologische Onkologie, Universitäts-Hautklinik, Eberhard-Karls-Universität Tübingen: Prof. Dr. med. Garbe

Klinik für Dermatologie, Allergologie und Venerologie, Universitätsklinikum Schleswig-Holstein, Campus Lübeck: Dr. med. Terheyden

Medizinische Klinik III, Hämatologie, Onkologie und Transfusionsmedizin, Charité, Campus Benjamin Franklin, Berlin: Dr. med. Keilholz

Klinik und Poliklinik für Strahlentherapie der Universität Regensburg: Prof. Dr. med. Kölbl

Klinik für Dermatologie, Venerologie und Allergologie, Universitätsklinikum Schleswig-Holstein, Campus Kiel: Prof. Dr. med. Hauschild

TABLE 1

Clinical histological subtypes of cutaneous malignant melanomas in the German speaking countries

Type	Abbreviation	Proportion (%)	Median age
Superficially spreading melanoma	SSM	57.4%	51 years
Nodular melanoma	NM	21.4%	56 years
Lentigo maligna melanoma	LMM	8.8%	68 years
Acral lentiginous melanoma	ALM	4.0%	63 years
Unclassifiable melanoma	UCM	3.5%	54 years
Other		4.9%	54 years

Results of the central malignant melanoma registry of the German dermatological society, 1983–1995 (n = 30 315) (9)

(8). The safety margins are notably reduced compared to earlier years and are based on the results of prospective randomized trials. The risk of satellite metastases in the immediate vicinity of the primary tumor seems to increase in proportion to increasing tumor thickness, but surgical measures do not seem to influence the development of distant metastases and thus the overall survival rate (12).

These days, most procedures on the primary tumor can be undertaken in one or two steps under local or tumescence anesthesia. The defects can be closed with primary closure or loco-regional flaps. Using split-thickness or full-thickness grafts is necessary only in selected locations.

Studies from the Tübingen dermatology clinic have led to a critical reassessment of the safety margins in patients with facial melanomas and acral lentiginous melanoma (13). Histographic, three-dimensional histology seems to enable a reduction in the safety margins without an increased risk for the patients treated in such a way (14). Especially for acral melanomas, e.g. subungual melanoma, this means that no amputations are required for locally resectable tumors. Conservative surgical measures that maintain functioning and yield better esthetic results are therefore possible in most melanomas in acral locations.

The substitution of elective lymph node dissection by sentinel node biopsy—which nowadays can be performed mostly under tumescence anesthesia—is another example of increasingly less aggressive surgical measures for melanoma. In sentinel node biopsy, the first draining lymph nodes of the regional lymphatic system

are initially captured via lymphatic drainage szintigraphy, in order to enable subsequent selective resection (15). The sentinel node is marked with a technetium-labelled nano-colloid (radioactive tracer) and additionally with patent blue. Double marking is a standard that nowadays yields a detection rate of 95% of all sentinel nodes. Since the sentinel node is skipped in less than 5% of cases, this method has become established worldwide.

Multicenter studies have shown unequivocally that the recurrence-free survival correlates to the state of the sentinel node (presence of micrometastases) (16). The sentinel node is therefore an excellent prognostic factor. The operation further guarantees good loco-regional tumor control because total lymphadenectomy will be performed if the sentinel node biopsy yields a positive result.

Since sentinel node biopsy was introduced, the number of patients who are diagnosed with clinically manifest lymph node metastasis has fallen drastically. Clinically manifest metastases in the lymph nodes represent a poor prognosis, but curative treatment options are still available, depending on the number of lymph nodes affected. For this reason, the German guidelines recommend radical lymphadenectomy as standard treatment in this scenario.

In 2006, results from the randomized multicenter study MSLT-1—of sentinel node excision or exclusive observation—were published; the study included more than 1000 patients (17). Prolonged recurrence-free survival after resection of the sentinel node was found compared with controls. Where micrometastases were found, complete lymphadenectomy was the better option. No differences were seen in terms of overall survival time and the cure rate. It therefore cannot be assumed that sentinel node excision in itself is a curative approach.

According to the guidelines, surgery should be performed in patients with single distant metastases if R0 resection is intended (10). This usually relates to metastases in the lungs or brain. A finding of single metastases has shown a good prognosis in many retrospective studies investigating the value of surgery for metastases in stage IV tumors. By rendering the patient clinically tumor free, some 5% of all melanoma patients with distant metastases are cured. If R0 is not an option then surgery is indicated if the metastases are symptomatic and surgery is therefore used to support palliative treatment.

Radiotherapy

Radiotherapy for malignant melanoma is only indicated for functionally inoperable tumors (10). It is clearly inferior to surgery in respect of local control rates; however, in a retrospective study, radiotherapy for macroscopic melanoma tissue (median tumor volume 18 cm³) resulted in complete remission in 64% of patients. The recommended radiation dose in macroscopic tumors is 70 Gy, five radiotherapy sessions per week with two individual doses of 2 Gy each. In patients with microscopic tumor remnants (R1 resection) or

BOX

ABCD rule to diagnose malignant melanoma (9)

- A = Asymmetry
- B = Border irregularity
- C = Color uneven
- D = Diameter >5 mm

TABLE 2

Tumor staging of malignant melanoma—TNM (9)

Stage	Primary tumor (T)	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 Clark level IV or V 1.01–2.0 mm, no ulceration	None None	None None
IIA	1.01–2.0 mm with ulceration 2.01–4.0 mm, no ulceration	None None	None None
IIB	2.01–4.0 mm with ulceration > 4.0 mm, no ulceration	None None	None None
IIC	> 4.0 mm with ulceration	None	None
IIIA	Any tumor thickness, no ulceration	Micrometastases	None
IIIB	Any tumor thickness, with ulceration Any tumor thickness, no ulceration Any tumor thickness ± ulceration	Micrometastases Up to 3 macrometastases None but satellite metastases and/or in-transit metastases	None None None
IIIC	Any tumor thickness, with ulceration Any tumor thickness ± ulceration	Up to 3 macrometastases 4 or more macrometastases or capsule transgressing lymph node metastases, or satellite and/or in-transit metastases affecting the lymph nodes	None None
IV			Distant metastases

questionably tumor-free tissue, a radiation dose of 60 Gy should be aimed for, again administered in individual doses of 2 Gy. In order to ensure the homogenous distribution of radiation in the affected area and in order to spare the surrounding normal tissues, three-dimensional radiation planning should be undertaken.

In-transit metastases that are too extensive for surgical intervention or untreatable by isolated limb perfusion can be controlled exclusively by radiotherapy. Three-dimensional planning is again recommended in this scenario. The total dose should be 50–60 Gy if conventional fractions are used.

In patients with regional lymph node metastases, the indication for radiotherapy of the affected regions is usually defined in case of inoperability or surgery on non-healthy tissue (R1 or R2 resection). Individual doses between 1.8 Gy and 2.0 Gy, with a total target volume dose of 50–54 Gy, are recommended. In a prospective phase II study, the local control rate after complete resection of lymph node metastases and additional adjuvant radiotherapy was 91% (19). However, randomized studies that show an advantage of adjuvant radiotherapy after complete resection of the lymph nodes are thus far lacking.

In metastases, radiotherapy is used for palliative purposes, most often for bone metastases. An indication for radiotherapy exists when patients are in pain and/or the vertebral column stability is threatened, or in patients with compression of the spinal canal with or without neurological symptoms. Response rates for palliative radiotherapy, independent of the site, are 67% to 85% (20). A retrospective study showed that for 114 irradiated metastatic sites (75 bone metastases, 26 subcutaneous

metastases, 10 visceral metastases, 3 combinations) symptoms went into complete remission in 9% of patients and partial remission in 75% of patients (21). The duration of responsiveness to therapy correlated with the radiation dose that was administered. For longer term success, biologically effective doses of more than 39 Gy are required. In individual cases and in patients with clearly limited life expectancy and no static risk, single doses of 8 Gy can be administered to shorten the overall duration of treatment.

In patients with single brain metastases, operative resection or stereotactic single radiotherapy may be used. In a prospective study, the local control rate was improved after resection of a solitary brain metastasis by applying radiotherapy to the entire brain; the risk of dying from neurological complications was reduced simultaneously. The combination of stereotactic radiotherapy with irradiation of the brain can also increase the intracerebral control rate (22). Using only stereotactic, single dose radiotherapy is less toxic than the combination with radiotherapy of the entire brain and the treatment is shorter (*figure*). In multiple brain metastases, radiation of the whole brain is indicated.

TABLE 3

Recommended safety margins (10)

Tumor thickness according to Breslow	Safety margin
In situ	0.5 cm
Up to 2 mm	1 cm
More than 2 mm	2 cm

Figure:

- a) The axial level in the NMR shows a solitary cerebral metastasis in a patient with malignant melanoma
- b) After stereotactic individual radiotherapy (the red line represents the 18 Gy isodose), the NMR control investigation after 3 months shows complete remission of the cerebral metastasis (with permission from Professor O. Kölbl, Regensburg)

The recommended dose is 30 Gy in 10 fractions over two weeks. Higher dosages seem to prolong the median survival; in individual cases, local saturation with higher doses may therefore be considered.

Adjuvant therapy

The fact that melanomas are extremely prone to metastasize and that the therapeutic options for inoperable tumor stages are limited have forced the development of adjuvant therapeutic approaches. Numerous prospective randomized studies have shown unequivocally that systemic chemotherapy, e.g., as monotherapy with dacarbazine, is not beneficial. Prospective randomized studies have found a significant therapeutic advantage for interferon alpha only, owing to prolonged recurrence-free survival. A recent meta-analysis of more than 6000 patients from 13 randomized interferon protocols based on individual patient data has found not only a highly significant advantage for prolonging the recurrence-free survival interval but also for total survival (even though the effect was small). The risk of death was reduced by 3% after five years when interferon therapy was administered. This therapeutic advantage applied particularly to ulcerating primary tumors, but no clear relation to the interferon dosage or duration of therapy was found (23).

Currently, the main distinction is made between low-dose treatment and high-dose treatment with interferon alpha (table 4). Treatment with pegylated interferons is a new approach that—in contrast to the options mentioned earlier—has not been licensed by the drug authorities. Low-dose therapy has been evaluated for melanomas of more than 1.5 mm thickness and without proved lymph node metastases in three randomized studies (23). A significantly prolonged recurrence-free survival interval was seen; a single study investigating an 18 month treatment period also found a trend towards prolonged overall survival. The indication for low-dose therapy should therefore be defined for melanomas of more than 2 mm thickness (stage IIA), especially if these are ulcerating (stages IIB and IIC).

Two prospective randomized studies on high-dose treatment with interferon alpha have unequivocally shown an advantage for recurrence-free survival in patients with confirmed lymph node metastases compared with untreated controls. High-dose therapy is indicated for metastases in the region of the sentinel lymph nodes (stage IIIA) and manifest lymph node metastases (stages IIIB and IIIC); the decisive factor is the balance between expected benefits and the relatively high toxicity, which has to be judged on an individual basis. Since high-dose therapy is not suitable for all patients, treatment with low-dose interferon alpha for two years should also be considered.

Pegylation enables once-weekly administration and avoidance of peak concentrations in the blood; the objective is to improve patients' quality of life and clinical efficacy. At the latest congress of the American Society for Clinical Oncology (ASCO), the interim

TABELLE 4

Adjuvant treatment with interferon alpha: therapeutic schemes (8)

Scheme	Dosage	Indication
Low-dose interferon alpha-2	3m IU s.c. 3×/week over 18–24 months	Stages II/III
High-dose interferon alpha-2b		
Initial treatment	20m IU/m ² i.v., days 1–5 over 4 weeks	Stage III
Maintenance treatment	10m IU/m ² s.c., 3×/week over 11 months	
Pegylated interferon alpha-2b		
Initial treatment	6 µg/kg/week over 8 weeks	Stage III
Maintenance treatment	3 µg/kg/week up to the end of 5 years	

analysis of a large study of treatment using pegylated interferon alpha-2b over five years was presented (EORTC 18991 study). In this study, patients with lymph node metastases (stages IIIA–C) were compared with untreated controls. The patients who were treated with pegylated interferon alpha-2b showed a 7% improved recurrence-free survival rate over four years (328 recurrences versus 368 recurrences, $n = 1256$); overall survival was not affected.

When using interferon of any galenic formulation, the balance between long-term use and tolerability needs to be weighed up. Interferon induces acute flu-like symptoms and widespread hematological and nonhematological organ toxicity, dose-dependent fatigue/anorexia, and neuropsychiatric side effects that may endanger compliance over the course of several years of therapy. Knowledge about specific side effects and about how to manage the specific side effect mechanism may help counteract this (24). Further developments aim to identify patient subgroups that may benefit from biomarkers.

Chemotherapy and chemoimmunological treatment in palliative indications

The principal indications for systemic chemotherapy and chemoimmunotherapy are inoperable recurring tumors, inoperable regional metastases, and distant metastases (stage IV) (11). Since treatment is administered under palliative aspects, therapeutic attempts have to be critically evaluated for the extent to which they maintain quality of life for patients.

In stage IV, limited disease is distinguished from extensive disease. Patients with limited disease (metastases affecting skin, soft tissues, lymph nodes, lungs) usually respond better to the different therapeutic schemes and have better prognoses than patients with extensive disease (metastases in liver, skeleton, brain, or general visceral metastases).

For the systemic monotherapy of advanced melanoma, several substances are available whose clinical efficacy is comparable (8). Palliative monotherapy can shrink tumors and thus achieve a reduction in tumor-related symptoms. The recommended medical drugs for monotherapy are listed in *table 5*.

Objective response rates can be improved by combining cytotoxic drugs with cytokines. However, none of the studies conducted thus far has found a significantly prolonged overall survival period (25). The subjective and objective tolerability of monotherapy is worsened if interferon or interleukin-2 are added.

In the same way, the combination of different chemotherapeutic drugs (polychemotherapy) or cytotoxic agents with cytokines (polychemoimmunotherapy) occasionally yields substantially higher remission rates without prolonging overall survival. The toxicity of combined chemotherapeutic regimens is significantly higher than for monotherapy. Polychemotherapy or polychemoimmunotherapy can, however, be of palliative use in individual cases and can provide effective treatment

TABLE 5

Monotherapy of advanced cutaneous melanoma (8)

Drug	Dosage	Response rate (%)
Dacarbazine	250 mg/m ² i.v., days 1–5 every 3–4 weeks or 800–1200 mg/m ² i.v., day 1 every 3–4 weeks	12.1–17.6% 5.3–23%
Temolozomide	150–200 mg/m ² oral, days 1–5 every 4 weeks	13.5–21%
Fotemustine	100 mg/m ² i.v. days 1, 8, and 15, followed by 5 week interval, to be repeated every 3 weeks	7.4–24.2%
Vindesine	3 mg/m ² i.v. every 14 days	12–26%
Interferon alpha	9m–18m IU/m ² s.c. 3×/week continuous administration	13–25%
Interleukin-2	600 000 IU/kg as 15 minute short infusion i.v. every 8 hours on days 1–5 (maximum 14 individual doses), repeat cycle day 14	16–21.6%

TABLE 6

Polychemotherapy and chemoimmunotherapy of advanced cutaneous melanoma (8)

Scheme	Dosage	Response rate (%)
BHD scheme	BCNU 150 mg/m ² i.v. day 1, only every 2 nd cycle Hydroxyurea 1500 mg/m ² oral days 1–5 DTIC 150 mg/m ² i.v. days 1–5 every 4 weeks	12.7–30.4%
BOLD scheme	Bleomycin 15 mg i.v. days 1 + 4 Vincristine 1 mg/m ² i.v. days 1 + 5 CCNU 80 mg/m ² p.o. day 1 DTIC 200 mg/m ² i.v. days 1–5 every 4–6 weeks	22–40%
DVP scheme	DTIC 250 mg/m ² i.v. days 1–5 Vindesine 3 mg/m ² i.v. day 1 Cisplatin 100 mg/m ² i.v. day 1 every 3–4 weeks	31.4–45%
DVP scheme	DTIC 450 mg/m ² i.v. days 1 + 8 Vindesine 3 mg/m ² i.v. days 1 + 8 Cisplatin 50 mg/m ² i.v. days 1 + 8 every 3–4 weeks	24%
CarboTax scheme	Carboplatin AUC6 i.v. day 1, after 4 cycles reduce dose to AUC5 Paclitaxel 225 mg/m ² i.v. day 1 every 3 weeks	12.1% (second-line)
GemTreo scheme	Gemcitabine 1000 mg/m ² i.v. days 1 + 8 Treoosulfan 3500 mg/m ² i.v. days 1 + 8 every 4 weeks	33.3% (PR + SD, Uveal melanoma)

AUC, "area under the curve" (creatinine clearance)
PR, partial remission
SD, stable disease

for tumor-related symptoms. The therapeutic schemes that have become established for melanoma are listed in *table 6*. Since polychemotherapeutic regimens are potentially toxic, intensive supportive treatment is crucial for the patient's quality of life. Schemes using dacarbazine require intense antiemetic treatment. In patients with bone metastases, bisphosphonates should also be administered; recommendations for protecting teeth need to be heeded before starting treatment so as to avoid jaw necroses.

It is likely that in future, more complex combinations of cytotoxic drugs and newer inhibitors of molecular target structures will be used. However, it is already clear that in patients with distant metastases, these combinations will lead to prolonged survival periods without offering any curative advantage for most patients. On this background, metastatic melanomas should be treated if possible in the context of well-controlled, randomized clinical studies.

Conflict of interest statement

Professor Garbe has received honoraria for advisory work and third party support for research and studies from Hoffmann La Roche AG, Essex-Pharma AG, Bayer Healthcare, Pfizer, Bristol Myers Squibb AG, Genta Incorporated, and Sigma Tau GmbH.

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Key messages

- The diagnosis of melanoma should be confirmed histopathologically by complete excision biopsy
- Surgical intervention for the primary tumor currently uses smaller safety margins of 1 cm (up to 2 mm tumor thickness) and 2 cm (more than 2 mm tumor thickness).
- For primary tumors ≥ 1 mm tumor thickness, sentinel lymph node biopsy is recommended as part of diagnosing the spread of disease.
- In primary tumors with a higher risk of metastasis (from 2 mm tumor thickness) and if lymph node metastases are present, adjuvant therapy with interferon alpha should be given.
- If distant metastases are present and R0 resection is not an option, monotherapy should be given as first line treatment; more aggressive schemes did not show a therapeutic advantage in studies, only higher toxicity.

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Corresponding author

Prof. Dr. med. Claus Garbe
Sektion Dermatologische Onkologie
Universitäts-Hautklinik
Liebermeister Str. 25
72076 Tübingen, Germany
claus.garbe@med.uni-tuebingen.de