

Updated Swiss Guidelines for the Treatment and Follow-Up of Cutaneous Melanoma

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Key Words

Cutaneous melanoma · Swiss melanoma guidelines

Abstract

Melanoma is the most common lethal cutaneous neoplasm. In order to harmonize treatment and follow-up of melanoma patients, guidelines for the management of melanoma in Switzerland have been inaugurated in 2001. These have been approved by all Swiss medical societies involved in the care of melanoma patients. New data necessitated changes concerning the safety margins (reduction to maximally 2 cm) and modifications of the recommendations of follow-up.

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Cutaneous melanoma not only has a high incidence, but is also the most aggressive of the cutaneous neoplasms [1]. For these reasons, treatment guidelines have been prepared under the aegis of the Swiss Cancer League (skin

cancer group) and published in 2001 [2], with the aim of providing a practical guide for all physicians (general practitioners, dermatologists, surgeons, oncologists and others) who encounter cutaneous melanoma in their daily work. The recommendations presented in these guidelines have been graded according to the amount of scientific evidence supporting them using the 'level of evidence' classification developed by the Canadian Medical Association in 1998 (table 1).

The guidelines have been discussed and approved by the Project Group 'Melanoma' of the Swiss Group for Clinical Cancer Research (SAKK) with the following members: A. Barth, Solothurn; D. Guggisberg, Neuchâtel; D. Hohl, Lausanne; P. Mäder, St. Gallen; W. Mingrone, Aarau; R. Morant, St. Gallen; N. Schaub, Basel; R. von Moos, St. Gallen.

Representatives of the following medical societies of Switzerland have approved the guidelines: A. Banic* for the Swiss Society for Reconstructive Surgery; K.W. Grätz* for the Swiss Society for Maxillofacial Surgery; T. Hardmeier for the Swiss Society for Pathology; H.-M. Hoogewoud* for the Swiss Society for Medical Radiology; R. Obrist* and P.-Y. Dietrich for the Swiss Society for Medical Oncology; T. Ruffli for the Swiss Society of Dermatology and Venereology; S. Schmid for the Swiss Society for Otorhinolaryngology; H. Steinert for the Swiss Society for Nuclear Medicine; M. Wolfensberger* for the Swiss Society for Otorhinolaryngology (* = presidents according to the FMH Swiss Medical List).

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Table 1. Level of evidence classification system (Canadian Medical Association, 1998)

Level I	Evidence is obtained from a systematic review (meta-analysis) of all relevant randomized controlled trials. The scope of the trials is large enough that the risk of false-positive or false-negative results is minor
Level II	Evidence is obtained from at least one properly designed randomized controlled trial. The risk of false-positive or false-negative results is higher than in level I
Level III	Evidence is obtained from well-designed controlled trials without randomization, from well-designed cohort or case-control analytic studies, preferably from more than one research center, or from multiple time series with or without the intervention
Level IV	Represents the opinions of respected authorities or the consensus reports of expert committees. Evidence is based on clinical experience and/or descriptive studies
Level V	Represents the opinion of the authors based on their own clinical experience

The purpose of these guidelines is to ensure the adequate treatment of melanoma patients in Switzerland. At present, patients with low-risk melanoma tend to be over-treated, whereas the follow-up procedures for patients with high-risk or metastasizing melanoma are sometimes inadequate. These guidelines were introduced in April 1999 in the Departments of Dermatology in Geneva and Lausanne, Switzerland ('Recommandations pour la prise en charge du mélanome malin', Groupe Mélanome Lémanique), and Zurich, Switzerland, and have been in use since that time. Our experience with the guidelines showed them to provide a valuable, practical basis for treating cutaneous melanoma. Drawing on the combined expertise of a multidisciplinary team, the guidelines reflect current international standards and the state of the art. Modifications of these guidelines under special clinical situations lie at the discretion of the individual practitioner.

Medical progress and new information necessitated an update of these recommendations in 2004.

Clinical Aspects and Prognosis

The incidence of melanoma continues to increase in Switzerland. Currently, approximately 1,500 new melanoma cases per year are expected (incidence 14–16/100,000/year). The lifetime risk for newborns of the year 2000 is estimated to be 1:80. Approximately 20% of all

these patients will die of melanoma. For prognostic and didactic purposes, primary cutaneous melanomas are classified into four clearly defined categories according to their clinical presentation [3, 4].

The most common form of melanoma is superficial spreading melanoma (50%). It presents an asymmetrical flat skin lesion with irregular pigmentation and border, and regression phenomena. Nodular melanoma (30%) is the next most common form. It is often a papular lesion with pigmentation changes and irregularly spreading borders. Lentigo maligna melanoma (10%) arises typically in older patients in areas of skin exposed to sunlight. The fourth type of lesion is acrolentiginous melanoma (5%), which occurs on the skin of the hands or the feet. In addition, there are several rare variants such as amelanotic, desmoplastic and polypoid melanoma, which together comprise about 5% of all cases.

A first clinical diagnosis is made using the ABCD rule, which takes into consideration the *asymmetry*, *border*, *color*, *diameter* of the skin lesions and *E (evolution)* [5] (level of evidence III). The accuracy of the diagnosis can be improved by surface microscopy, if this is carried out by an adequately trained dermatologist (level of evidence III) [3, 6].

The prognosis of the primary tumor can be estimated by measuring the tumor thickness according to Breslow (level of evidence I) [7, 8]. This is simply the distance from the outer boundary of the stratum granulosum of the epidermis to the deepest extension of the tumor, measured in an appropriately prepared histological specimen. Whereas the 10-year survival rate of patients with thin primary tumors (tumor thickness <1 mm) is higher than 90%, that of patients with a tumor thickness >4 mm is less than 50%. Patients with locoregional metastases in the lymph nodes have a 10-year survival rate of 30% and those with distant metastases one of less than 5% (level of evidence II).

The refined version of the pTNM system which includes the staging of microscopically positive lymph nodes (table 2) is the classification system of choice [9] (level of evidence IV).

Surgical Treatment of Primary Melanoma

Previously, all malignant melanomas were excised with a safety margin of 5 cm, irrespective of the individual characteristics of the lesions. Now, suspicious melanocytic lesions are first examined by excision biopsy (level of evidence IV) [3, 10]. The diagnosis of melanoma is made

Table 2. TNM classification [9]

T	primary tumor	
T _{is}	in situ	
T1	≤ 1.0 mm	a) without ulceration b) with ulceration
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
N	regional lymph nodes	
N1	1 lymph node	a) micrometastasis ^a b) macrometastasis ^b
N2	2–3 lymph nodes	a) micrometastasis ^a b) macrometastasis ^b c) in-transit metastases/ satellite metastases <i>without</i> metastatic lymph nodes
N3	≥ 4 metastatic lymph nodes, matted lymph nodes or combinations of in-transit metastases/satellite(s) or ulcerated melanoma and metastatic lymph nodes	
M	distant metastases	
M1a	Distant skin, subcutaneous or lymph node metastases (normal LDH)	
M1b	Lung metastases (normal LDH)	
M1c	All other visceral (normal LDH) or any distant metastases (elevated LDH)	

LDH = Lactate dehydrogenase.

^a Micrometastases are diagnosed after elective or sentinel lymphadenectomy.

^b Macrometastases are defined as clinically detectable lymph node metastases confirmed by therapeutic lymphadenectomy or when any lymph node metastasis exhibits gross extracapsular extension.

histologically and the thickness of the tumor determined according to Breslow. The final operative removal of the primary tumor should be carried out within 4–6 weeks following primary resection, leaving a safety margin of 1–2 cm, depending on the thickness of the tumor (table 3). Special localizations, e.g. in the face, may necessitate exceptions from standard safety margins. In these locations, radiotherapy might be considered as an alternative for lentigo maligna (melanoma) [11].

We no longer recommend elective lymph node dissection, since it has been shown to have positively influenced prognosis in only a limited subpopulation of patients (<60 years of age, tumor thickness 1–2 mm) and is associated with a significant risk of lymph edema as side effect [3]. Instead, we recommend the sentinel lymph node biopsy (level of evidence III), a procedure which requires cooperation between dermatologist-surgeon, nuclear medicine and pathologist [12]. This procedure allows a precise staging of the patient. It is not yet clear whether sentinel node biopsy can improve the prognosis of the melanoma patient [3].

Surgical Treatment of Locoregional Lymph Node Metastases

In the case of isolated locoregional lymph node metastases, surgical removal, including the surrounding lymph node region, is indicated; removal of the tumor-bearing lymph node alone is insufficient [3]. Surgical removal is also recommended in the case of an isolated metastasis in a parenchymal organ, including the central nervous system. However, before undertaking additional aggressive

Table 3. Excision safety margins and additional treatment modalities for surgical treatment of primary melanoma (pT1–4N0M0)

Tumor thickness	Excision safety margin, cm	Remarks	Level of evidence
Melanoma in situ (tumor thickness is not indicated) (pIisN0M0)	0.5	Consider superficial radiotherapy in lentigo maligna in elderly patients	III
<2mm (pT1–2N0M0)	1	Tumor thickness >1 mm sentinel lymph node dissection ¹	II IV
>2 mm (pT3–4N0M0)	2	Sentinel lymph node dissection ¹ Interferon therapy ¹	III IV III

¹ These therapies should be restricted to controlled studies at specialized centers.

local surgical treatments, a detailed staging investigation, one including imaging techniques such as CT scan or PET (positron emission tomography), is necessary to exclude the presence of further metastases.

Many randomized and nonrandomized clinical trials have investigated the impact of adjuvant treatment modalities in high-risk melanoma. However, solid evidence can only be gleaned from prospective randomized multicenter trials. These, as yet, have not been able to identify a significant increase in the length of relapse-free period or in survival rate with any of the commonly used adjuvant treatment modalities: neither elective lymph node dissection, perfusion of the extremities, radiotherapy nor chemotherapy have shown a convincing benefit to the melanoma patient collective as a whole [3]. Adjuvant treatment with *Viscum album* (Iscador®) is not recommended, since it might accelerate the disease course [13].

Adjuvant interferon α therapy in high-risk melanoma patients was shown to enhance disease-free survival in several investigations. In two studies, high-dose interferon after surgically removed high-risk melanomas (thick primary tumors, pT4N0M0) and lymph node metastases (pTxN1–2M0) demonstrated a significant impact on overall survival and disease-free survival [14, 15] but is associated with significant side effects. The optimal tim-

ing and dosing schedules and the best type of interferon (pegylated versus conventional) are not yet defined [16, 17]. Therefore, we urge that adjuvant interferon treatment is applied in the context of randomized clinical trials in specialized centers.

Therapy of Advanced Melanoma (pTxNxM1a–1c)

The optimal therapy for advanced melanoma depends to a great extent on the localization of the metastases (therapy options summarized in table 4). If an isolated locoregional metastasis is present, surgical treatment is to be recommended. If multiple metastases are found localized in one extremity, then perfusion with cytostatics and tumor necrosis factor α is a further effective treatment option [18].

Palliative therapy for advanced disease with several metastases in different anatomical regions should initially use well-tolerated cytostatics such as dacarbazine, temozolomide alone or in combination with cytokines like interferon α [19] or in case of aggressive metastatic disease polychemotherapy. Since the overall impact of systemic therapy on survival in advanced melanoma pa-

Table 4. Treatment modalities for melanoma metastases

Number and localization of the metastases	Treatment modalities for 1st choice, 2nd choice and 3rd choice	Level of evidence
In-transit metastases (few) (pTxN2cM0)	(1) Surgical removal (2) Radiotherapy	III IV
In-transit metastases (multiple, > 5) (pTxN2cM0)	(1) Perfusion of the extremity ¹ (2) Excision (systemic chemoimmunotherapy) ¹ (3) Radiotherapy (systemic chemoimmunotherapy) ¹	IV IV IV
Locoregional lymph nodes (pTxN1,2abc,3M0)	(1) Radical lymphadenectomy, in case of incomplete resection: irradiation additional interferon α treatment ¹	III IV IV
Solitary central nervous system metastases (pTxNxM3)	(1) Neurosurgical removal (2) Stereotactic irradiation ¹ (according to localization this could also be the 1st choice)	III III
Solitary lung metastases (pTxNxM1)	(1) Surgical removal (2) Chemoimmunotherapy ¹	III IV
Multiple metastases (pTxNxM1a–1c)	(1) Chemoimmunotherapy ¹	IV
Painful bone metastases (pTxNxM1a–1c)	(1) Radiotherapy	III

¹ These therapies should be restricted to controlled studies at specialized centers.

tients is poor, these patients should be preferentially treated in controlled clinical trials evaluating new approaches such as vaccination [20], antisense therapies [21], antiangiogenic therapies [22] or histamine [23] and others.

Table 5. Follow-up procedures for melanoma patients

Repeated clinical checkups (level of evidence III)
(a) Complete examination of the skin including dermatoscopy (plus computer-assisted systems, if necessary) of atypical moles
(b) Palpation of the region of the primary tumor, of all lymph node regions and the abdomen
(c) Pulmonary examination (for pleural effusion)
Imaging techniques
Ultrasound of the locoregional lymph nodes (level of evidence III) and the abdomen, chest X-ray (level of evidence IV)
PET (level of evidence IV) or CT scans of the chest and abdomen (level of evidence IV), possibly also CT scans of the skull
Blood investigations (level of evidence V)
Soluble S-100 molecule

Melanoma Follow-Up

During melanoma follow-up, patients are monitored in order to detect a relapse and to recognize additional skin tumors (level of evidence III), especially a second melanoma, as soon as possible [22, 24, 25]. The second melanoma risk is estimated to lie at 5–8% (level of evidence III); melanoma patients also have increased risks for other skin tumors. In patients with lentigo maligna melanomas, 35% of the patients developed another cutaneous malignancy within 5 years [11]. The follow-up should be prognosis oriented and include psychological care for the patients. Since patients with a thin primary melanoma have only a small risk of relapse, imaging techniques are not necessary for this patient population. In contrast, CT or whole-body PET scans [26] are recommended in the follow-up of high-risk patients: those with thick primary tumors or following treatment of metastases (level of evidence V). S-100 [27, 28] may also be useful in the follow-up of melanoma patients. A summary of the recommended follow-up procedures is found in table 5. A follow-up scheme, including recommended investigations and monitoring intervals, classified according to the Breslow tumor thickness and year since initial diagnosis, is given in table 6.

Table 6. Follow-up scheme for melanoma patients (level of evidence IV)

Tumor thickness according to Breslow	Year after the initial diagnosis	Interval of the clinical examination months	Imaging techniques (individually adapted)
< 1 mm	1–5	6	none
< 1 mm	>5 (lifelong)	12	none
> 1 mm and < 4 mm	1–3	3	annual chest X-ray, ultrasound of loco-regional lymph nodes and abdomen
> 1 mm and < 4 mm	4–5	6	annual chest X-ray, ultrasound of loco-regional lymph nodes and abdomen
> 1 mm and < 4 mm	>5 (lifelong)	12	none
≥ 4 mm and/or lymph node metastases	1–3	3	annual ultrasound of locoregional lymph nodes, PET (or CT scans) of chest and abdomen
≥ 4 mm and/or lymph node metastases	4–5	6	annual ultrasound of locoregional lymph nodes, PET (or CT scans) of chest and abdomen
≥ 4 mm and/or lymph node metastases	>5 (lifelong)	6–12	none

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