European Dermatology Forum

Diagnosis and Treatment of Melanoma.

European Consensus-based Interdisciplinary Guideline

Developed by the Guideline Subcommittee of the
European Dermatology Forum

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Abstract
Cutaneous melanoma (CM) is potentially the most dangerous form of skin tumour and causes 90% of skin cancer mortality. A unique collaboration of multi-disciplinary experts from the European Dermatology Forum, the European Association of Dermato-Oncology and the European Organization of Research and Treatment of Cancer was formed to make recommendations on CM diagnosis and treatment, based on systematic literature reviews and the experts' experience. Diagnosis is made clinically and staging is based upon the AJCC system. CMs are excised with one to two centimetre safety margins. Sentinel lymph node dissection is routinely offered as a staging procedure in patients with tumours more than one millimetre in thickness, although there is as yet no resultant survival benefit. Interferon-α treatment can be offered to patients with more than 1.5 millimetre in thickness and stage II to III melanoma as an adjuvant therapy, as this treatment increases the relapse free survival. The lack of a clear survival benefit and the presence of toxicity however limit its use in practice. In distant metastasis, all options of surgical therapy have to be considered thoroughly. In the absence of surgical options, systemic medical treatment is indicated, but with, to date, low response rates. Therapeutic decisions should be made by the melanoma team and the informed patient after full discussion of the options.

Key words:
Cutaneous melanoma; tumour thickness; excisional margins; sentinel lymph node dissection; interferon-α; adjuvant treatment; metastasectomy; systemic medical treatment.

1. Introduction

1.1 Purpose

These guidelines have been written under the auspices of the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC) in order to help clinicians treating melanoma patients in Europe, especially in countries where national guidelines are lacking. It is hoped that this set of guidelines will assist health care providers of these countries in defining local policies and standards of care, and to make progress towards a European consensus on the management of melanoma. It is not intended to replace recent national guidelines accepted in their original country. The guidelines deal with aspects of the management of melanoma from diagnosis of the primary melanoma through palliation of advanced disease. Prevention issues are not addressed. The guidelines are also intended to promote the integration of care between medical and paramedical specialties for the benefit of the patient.

These guidelines reflect the best published data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to deviate from these guidelines in the interest of specific patients or under special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, deviation from them should not necessarily be deemed negligent.

1.2 Definition

Malignant melanoma is a malignant tumour which arises from melanocytic cells and primarily involves the skin. Throughout these guidelines, the terms malignant melanoma and melanoma will be used interchangeably, because there are no benign melanomas.[1-6] Melanomas can also arise in the eye (uvea, conjunctiva and ciliar body), meninges and on various mucosal surfaces. While melanomas are usually heavily pigmented, they can be also amelanotic. Even small tumours have a tendency towards metastasis and thus a relatively unfavorable prognosis. Melanomas account for 90% of the deaths associated with cutaneous tumours.

1.3 Epidemiology and Etiology

The incidence of melanoma is increasing worldwide in white populations, especially where fair-skinned peoples receive excessive sun exposure. [7-10] In Central Europe the incidence rate is 10-14 per 100,000 population and in Southern Europe the incidence is 6-10 per 100,000; in the USA 10-25 per 100,000; and in Australia, where the highest incidence is observed, 50-60 per 100,000. Individuals with large numbers of common naevi and those with congenital naevi, multiple and/or atypical naevi (dysplastic naevi) are at greater risk.[11-14] The inheritance of melanoma is polygenic; 5-10% of melanomas appear in melanoma-prone families.[15;16] In addition to these genetic and constitutional factors, the most important exogenous factor is exposure to UV irradiation, particularly intermittent sun exposure.[17-19]

1.4 Clinical Features and Histology

Four main different subtypes of melanomas can be identified clinically and histologically:[20-22]

Superficial spreading melanoma (SSM) begins with an intraepidermal horizontal or radial growth phase, appearing first as a macule that slowly evolves into a plaque, often with multiple colours and pale areas of regression. Secondary nodular areas may also develop. A characteristic histologic feature is the presence of an epidermal lateral component with pagetoid spread of clear malignant melanocytes throughout the epidermis.

Nodular melanoma in contrast is a primarily nodular, exophytic brown-black, often eroded or bleeding tumour, which is characterized by an aggressive vertical phase, with a short or absent horizontal growth phase. Thus, an early identification in an intraepidermal stage is almost impossible. When present, an epidermal lateral component is observed histologically within three rete ridges at the maximum.

Lentigo maligna melanoma arises often after many years from a lentigo maligna (melanoma in-situ) located predominantly in sun-damaged faces of elderly individuals. It is characterized histologically by a lentiginous proliferation of atypical melanocytes at the dermo-epidermal junction and histological features of chronic sun exposure (solar elastosis).

Acral lentiginous melanoma is typically palmoplantar or subungual. In its early intraepidermal phase, there is irregular, poorly circumscribed pigmentation; later a nodular region reflects the invasive growth pattern.
In addition to these main types, there are several rarer variants of melanoma, such as desmoplastic, amelanotic and polypoid melanomas, which constitute less than 5% of cases.
1.5 Prognosis and Staging
About 90 % of melanomas are diagnosed as primary tumours without any evidence of metastasis. The tumour-specific 10-year-survival for such tumours is 75-85 %. The most important prognostic factors for primary melanoma without metastases as reflected in recent studies are [23;24]:

- Vertical tumour thickness (Breslow's depth) as measured on histological specimen with an optical micrometer
- Presence of histologically recognized ulceration. Melanoma ulceration is defined as the combination of the following features: full-thickness epidermal defect (including absence of stratum corneum and basement membrane), evidence of host response (i.e. fibrin deposition, neutrophils), and thinning, effacement or reactive hyperplasia of the surrounding epidermis. [25].
- Mitotic activity appears as an independent prognostic factor in several population studies
- Invasion level (Clark`s level) is only of independent significance for thin tumours ($\leq$ 1 mm thickness)

Melanomas can metastasize either by the lymphatic or hematogenous route. About two-thirds of metastases are originally confined to the drainage area of regional lymph nodes. A regional metastasis can appear as:

- Micrometastasis in the regional lymph nodes identified via sentinel lymph node biopsy.[26;27] In contrast to macrometastasis, micrometastasis is not clinically recognizable neither by palpation nor by imaging techniques. Isolated tumour cells exclusively identified by immunohistochemistry or by PCR-based techniques are classified as N0.
- Satellite metastases (up to 2 cm from the primary tumour),
- In-transit metastases (located in the skin between 2cm from the site of the primary tumour and the first draining lymph node),
- Clinically recognizable regional lymph node metastases.

The 10-year-survival is 30-70% for patients with micrometastasis, 30-50 % for patients with satellite and in-transit metastases and 20-40% for those with clinically apparent regional lymph node metastases.[23]
Distant metastases have a grim prognosis with a median survival in untreated patients being only 6-9 months, although there is considerable variation depending on internal organ involvement and serum levels of lactate dehydrogenase (LDH, Table 3).
In 2001, the AJCC proposed a new TNM classification and staging for melanoma; it has now also been accepted by the UICC.[28] This new system now forms the cornerstone for classifying melanomas and is summarized in Tables 1-4.

Table 1. T classification of primary tumour for melanoma

T classification	Tumour thickness	Additional prognostic parameters

Tis		Melanoma in situ, no tumour invasion
Tx	No information	Stage cannot be determined*
T1	< = 1.0 mm	a: No ulceration, Level II-III b: Ulceration or Level IV- V
T2	1.01-2.0 mm	a: No ulceration b: Ulceration
T3	2.01-4.0 mm	a: No ulceration b: Ulceration
T4	> 4.0 mm	a: No ulceration b: Ulceration

* Tumour thickness or information on ulceration not available or unknown primary tumour

Table 2. N classification of the regional lymph nodes for melanoma

N classification	Number of involved lymph nodes (LN)	Extent of lymph node metastases
N1	1 LN	a: Micrometastases b: Macrometastases
N2	2-3 LN	a: Micrometastases b: Macrometastases c: Satellite or in-transit metastases
N3	$\geq$ 4 LN, satellite or in-transit metastases plus node involvement	

Table 3. M classification of distant metastases for melanoma

M classification	Type of distant metastasis	LDH
M1a	Skin, subcutaneous tissue or lymph node	Normal
M1b	Lungs	Normal
M1c	All other distant metastases Any distant metastasis	Normal Elevated

Table 4. Staging of melanoma

Stage	Primary tumour (pT)	Regional lymph node metastases (N)	Distant metastases (M)
0	In situ tumour	None	None
IA	≤ 1.0 mm, no ulceration	None	None
IB	≤ 1.0 mm with ulceration or Clark Level IV or V	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 tumour thickness, no ulceration	Micrometastases	None
IIIB	Any tumour thickness with ulceration	Micrometastases	None
	Any tumour thickness, no ulceration	Up to three macrometastases	None
	Any tumour thickness ± ulceration	None but satellite and/ or in-transit metastases	None
IIIC	Any tumour thickness with ulceration	Up to three macrometastases	None
	Any tumour thickness ± ulceration	*Four or more macrometastases, or lymph node involvement extending beyond capsule, or satellite and/or in-transit metastases with lymph node involvement*	*None*
IV			Distant metastases

2. Diagnostic Approach

2.1 Clinical and Dermoscopic Diagnosis

In most instances, the clinical appearance of melanoma varies according to the melanoma subtypes (see above). Typical features are asymmetry of the lesion, irregular borders, variability in colour, diameter of 5 mm and more, growth of nodules and regression of lesional components. The sensitivity of clinical diagnosis of experienced dermatologists is about 70%.[2]

Dermoscopy should be involved in clarifying the differential diagnosis of pigmented lesions. In order to apply this technique, training and expertise are required. A meta-analysis of 22 studies showed that when experts employed dermoscopy, they achieved an increase in diagnostic accuracy over the clinical diagnosis alone in questionable lesions and thus reached a sensitivity of 89% and a specificity of 79%.[29]

In high risk patients, mainly in the case of patients with atypical mole syndrome, the detection of changes in the lesions or newly appearing lesions by follow-up examination with digital dermoscopy and total-body photography is also helpful.[30;31]

The differential diagnosis involves other pigmented melanocytic lesions (congenital, atypical, common melanocytic naevi and actinic lentigo) and non-melanocytic pigmented lesions (seborrheic keratosis, hemangioma and pigmented basal cell carcinoma) and other non-pigmented tumours (hemangioma, basal cell carcinoma, squamous cell carcinoma). In patients with an established diagnosis of melanoma, physical examination in regular intervals remains essential to identify second primary tumours, as well as skin metastases.[32]

2.2 Histopathologic Diagnosis

Whenever a suspicious skin lesion is removed a histological examination is warranted. Difficulties in the clinical diagnosis of melanoma can also be encountered on a histologic level. The specimen should be entrusted to a dermatopathologist experienced in the interpretation of pigmented lesions. The histopathologic report should include the following information:[24]

1. Diagnosis and clinicopathologic type; when there is uncertainty about malignancy it should be clearly stated in the report conclusion.

2. Tumour thickness in mm (Breslow depth)

3. Presence or absence of ulceration

4. Level of invasion (Clark level), especially for thin melanomas $\leq$1mm in thickness.

5. Microsatellites (if present)

6. Lateral and deep excision margins

Besides these absolutely necessary histologic features, additional informations can be provided, including:

- Number of mitoses per mm² (in hot spots). The mitotic activity can inform about the risk of relapse and, in some series, the probability of sentinel node positivity.

- Growth phase (horizontal or vertical)

- Presence or absence of established regression

- Presence or absence of a dense tumour infiltrating lymphocytes (TIL) infiltrate

- Lymphatic emboli

- Vascular or perineural involvement

In some instances, when the histologic diagnosis is unclear, immunohistochemical stains may be helpful (i.e. S-100 protein, HMB45 and Melan-A for the confirmation of the melanocytic nature of the tumour, HMB45 as an additional feature of malignancy when there is an inverted positive gradient, MIB-1 as a proliferation marker).

It is advised to use standardized pathology worksheets. An example of such a standardized pathology worksheet can be downloaded at www.melanomagroup.eu.

2.3 Further Staging Examinations

The value of additional staging examinations in patients with primary melanomas is controversial.[3] It is widely agreed upon that in low-risk patients staging can be omitted and in high-risk patients staging examinations should be performed. However, definitions of low- and high-risk patients vary. Useful staging examinations should include: sonography of regional lymph nodes, chest x-ray, as well as an abdominal sonography including the pelvis and retroperitoneum. In higher-risk patients, other procedures such as computerized tomography with or without positron emission tomography (PET) and magnetic resonance imaging may be indicated depending on the clinical

findings. LDH and serum protein S100 are routinely used as markers of relapse in some countries.[33;34]

3. Surgical Therapy

3.1 General Principles

The primary treatment of melanoma is surgical excision.[5;35;36] An excisional biopsy is preferred, both to give the dermatopathologist/pathologist an optimal specimen and to allow evaluation of the excision margins for residual tumour. Incisional biopsies should not be performed when an excisional biopsy is technically possible. On occasion they are necessary to confirm the diagnosis, such as when dealing with a large lentigo maligna on the face, or with acral or mucosal lesions. Incisional biopsies are more difficult to interpret histologically, and carry the risk of not sampling the worst area of the tumour. Large studies have shown that incisional biopsies do not worsen prognosis as compared with immediate complete excisional biopsy.[36;37]

3.2 Primary Melanoma

The definitive surgical excision should be performed with satety margins preferentially within 4-6 weeks after initial diagnosis. The recommendations below are consistent with evidence that smaller excision margins are appropriate; the values given below are in concordance with the American and Australian recommendations.

Table 5. Recommended excision margins for melanoma

Tumour thickness (Breslow)	*Excision margin*
In situ	0.5 cm
≤ 2.0 mm	1 cm
> 2.0 mm	2 cm

The current recommendations are based on both prospective, randomized studies and international consensus conferences.[1] There are limited data to suggest that margin has an effect on loco-regional recurrence, but there are no data to support an impact of margin on survival.

3.3 Lentigo maligna

Lentigo maligna is a slowly growing melanoma in situ, which occurs typically in UV-exposed areas like the face. Typically, lentigo maligna requires narrower margins for safety when it is excised, and micrographic control of excision margins may be involved in order to safe tissue particularly in the face.[38;39] Surgical procedures should respect the anatomy of the face as well as aesthetic and functional aspects. In elderly patients a radiation therapy is a good alternative for facial lentigo maligna. Several retrospective analyses and phase II trials have also ruled out a role for topical imiquimod as a potential alternative to surgery. The complete response rate is in a range of 75 to 88% after this non-invasive procedure.[40-42] However, patients should be informed that both, radiation therapy and imiquimod, will not allow a histological evaluation of the tumor area and the side margins.

3.4 Acral and mucosal melanomas

Lentiginous acral and mucosal (i.e. anogenital) melanomas are often poorly defined and multifocal with discrepancies between the clinically visible and histopathologic margins. Local recurrences are more frequent in these types of melanoma. Therefore, removal can be achieved with increased safety margins (at least 1cm) or by narrow margins with micrographic control.[43;44] Micrographic surgery based on paraffin-fixed tissue often allows a reduced safety margin and conservation of tissue, especially on the face. Similarly on the hands and feet, the micrographic technique serves to conserve tissue by making smaller margins possible.

3.5 Elective Lymph Node Dissection (ELND) / Sentinel Lymph Node Dissection (SLND)

No therapeutic advantage for ELND has been established.[1] The SLND was introduced in order to allow the evaluation of the first draining lymph node in the regional lymphatic system.[26] The procedure is appropriate for patients in whom neither palpation nor lymph node sonography has suggested the presence of lymph node metastases. Multicentre studies have shown that the recurrence-free and overall survival time correlates clearly with the status of the sentinel lymph

node.[27;45] SLND and radical lymph node dissection in patients with positive SLN prolongs disease-free survival but does not affect overall survival.[27]
The evaluation of the SLN is not well-standarized, and the risk of missing a micrometastasis depends heavily on the techniques employed (number of sections; H & E stain; immunohistochemical stains). Various studies have shown that a detection accuracy of 90% is first obtained after roughly 50 procedures have been performed. Thus, it seems appropriate to concentrate SLNB in larger centres where such experience can be acquired. This leads to both standardized surgical and histopathological procedures.
SLND has been established as a valuable staging tool and may become of considerable importance in the future in identifying patients for whom adjuvant therapies are indicated. The positivity rate for melanomas < 1mm is so low that it is normally not recommended for patients in this group unless there are additional poor prognostic features (e.g. ulceration, Clark IV, vertical growth phase).

3.6 Procedure in Patients with negative SLN

No further lymph node surgery is required.

3.7 Procedure in Patients with Micrometastases in SLN

Studies have not confirmed that radical lymph node dissection improves survival. The analysis of the MSLT-1 trial comparing survival in patients undergoing delayed lymph node dissection vs. those who underwent a complete lymph node dissection (CLND) because of a positive SN is exploratory in nature and therefore non-conclusive. Moreover the claimed benefit is not reflected in the overall survival analysis of the primary endpoint of the trial (survival after wide excision (WE) alone vs WE+SNLD).[27] Nonetheless when the SLND shows micrometastases, radical lymph node dissection is recommended as approximately 5 – 12 % of patients will have involvement of non-sentinel nodes. Moreover CLND might be replaced by lymph node ultrasound follow-up, a method that can detect early recurrences in the regional basin and prompt a CLND only in patients with such evidence. The practice of completion lymphadenectomy compared with ultrasound screening after SNLD to detect clinical recurrences is currently being investigated in the Multicenter Selective Lymphadenectomy Trial-2 trial.

3.8 Clinically-identified Lymph Node Metastases

If lymph node metastasis is diagnosed clinically or by imaging techniques, radical lymph node dissection is considered standard therapy.[46]

3.9 Skin Metastases

The treatment of choice for skin metastases is surgical, but systemic therapies should be considered if numerous or extensive lesions are not amenable to surgery. For multiple lesions on a limb, isolated limb perfusion with melphalan +/- tumour necrosis factor (TNF) has palliative value.[47] In stage III patients with satellite/intransit metastases the procedure can be curative, as indicated by the reported 5 and 10 years survival rates of 40 and 30 %, respectively. Isolated limb infusion is a modification of this technique and is used in some centres. Alternative options include cryotherapy, laser therapy and experimental approaches such as intralesional/topical IL-2, electrochemotherapy, miltefosine, interferon-α or imiquimod.

3.10 Distant Metastases

If technically feasible, then operative removal of distant metastases should be seen as therapy of choice. With brain metastases, stereotactic radiation therapy is equally effective. Many studies show that excision of solitary or few metastases can be associated with a good outcome for Stage IV patients.[48;49] The possibility of neoadjuvant therapy followed by surgical excision of metastatic lesions can be considered.[50]
The value of debulking procedures must be viewed critically, as there is no evidence that they improve survival. In some circumstances there is a value for palliation, particularly in combination with postoperative radiotherapy for local disease control.

4. Radiation Therapy

4.1 Primary Melanoma

Radiation therapy of the primary tumour is very rarely indicated, performed exclusively in patients in whom surgery is impossible or not reasonable.

Even though excision is the treatment of choice for lentigo maligna, radiation therapy may achieve adequate tumour control with good cosmetic and functional results in difficult areas on the face, especially in elderly individuals.

4.2 Regional Lymph Nodes

There is no role for prophylactic radiotherapy of draining lymph nodes after excision of the primary melanoma.

When lymph node dissection is not complete or metastatic lymph nodes are inoperable, radiation therapy of the regional lymph nodes may be recommended.[51] When the tumour is extensive, a debulking procedure may be performed prior to radiation therapy paying special attention to sparing vessels and nerves. In some instances, hyperthermia may also be employed.

4.3 Skin Metastases

In-transit metastases, which are too extensive for a surgical approach, may be effectively controlled by radiation therapy alone.[52] Depending on the extent and location, hyperthermia may be added.[53]

4.4 Bone Metastases

Bone metastases can be effectively palliated with radiation therapy. The response rate (CR + PR) is 67-85%.[54-57] The major indications are pain, loss of structural stability (fracture risk), and compression of the spinal canal with or without neurological symptoms.

4.5 Brain Metastases

Melanoma has a marked propensity to metastasize to the brain. Patients with brain metastases have a life expectancy of only 3 to 5 months. With radiation therapy, the neurologic deficits may be improved in 50-75% of cases, an effect which is usually associated with an overall improvement in health.[57-59] Headache responds to radiation therapy in about 80% of cases. Treatment with dexamethasone should be additionally applied in order to reduce edema surrounding the metastatic lesions and improve neurological symptoms.

Both stereotactic single-dose radiation therapy (gamma knife) and surgical resection are appropriate for solitary or few (typically up to 3), up to 3 cm in diameter large lesions. Treating individual lesions (surgery or stereotactic radiation) may prolong survival, although this has never been proven.[58;60;61]

5. Adjuvant Therapy

5.1 General Principles

Adjuvant therapy is offered to patients without evidence of metastases but at high risk for further tumour spread.[62-64] Since adjuvant therapy can considerably reduce the quality of life, its indications and administration must be carefully considered.[65] In published trials usage was predominantly in patients with tumours thicker than 1.5mm but using AJCC staging the most equivalent is stage II and III melanoma.

5.2 Adjuvant Chemotherapy

A number of controlled trials with adjuvant chemotherapy in stage II and III patients did not demonstrate any therapeutic advantage. There is no indication for adjuvant systemic chemotherapy for melanoma outside the context of controlled studies.[66]

A large prospective, randomized multicentre study showed that adjuvant limb perfusion following the excision of primary high-risk melanoma did not increase the overall survival. Thus, this toxic therapy should no longer be used in the adjuvant setting.[67]

5.3 Adjuvant Immunotherapy with Various Non-Specific Immunostimulatory Agents

Prospective randomized studies using various non-specific immunostimulatory agents (Bacille Calmette Guerin/BCG, corynebacterium parvum, levamisol, mistletoe extract), cytokines (interferon-γ, interleukin-2, GM-CSF) and melanoma specific vaccines did not show any therapeutic efficacy. In summary, none of the above-mentioned agents can be recommended for adjuvant therapy except in the setting of controlled studies.[66]

5.4 Adjuvant Immunotherapy with Interferon-α

Interferon-α is the first substance in the adjuvant therapy of melanoma which has shown a significant improvement of disease-free survival and in some prospective randomized trials, of overall survival.There are, however, conflicting results from different clinical trials. A recent metaanalysis showed a significant improvement of disease-free survival (odds ratio of 0.78, $p < 0.0001$) and a trend towards improved overall survival (odds ratio of 0.90, $p = 0.09$, see Tables 6 A

and B).[68] Thus, patients treated with adjuvant interferon-α may benefit from this treatment and cure may occur in a small percentage of patients (3-5 %). Therefore, this treatment may be offered to high-risk melanoma patients along with information on the expected risk reduction of mortality and morbidity, and on the expected toxicity.

Two studies with low-dose interferon-α have been performed in patients with primary melanoma thicker than 1.5 mm without clinical evidence of lymph node involvement.[69;70] In both studies interferon-α 3 million IU were given thrice weekly for 6-18 months. All studies showed a significant increase in the recurrence-free survival time. In the largest study with treatment lasting for 18 months, there was also a trend towards prolonged overall survival time ($p = 0.056$).[69] Today, we recommend to initiate risk-adapted adjuvant interferon-α treatment based on the results of randomized trials in patients with ≥ 1.5 mm tumour thickness, although the current TNM classification defines a threshold of tumour thickness at 2 mm.

A variety of randomized studies with different interferon-α dosages has been conducted in patients with lymph node metastases. All patients underwent initial surgery to remove the involved lymph nodes, so that interferon-α therapy was truly adjuvant. The clearest results were demonstrated for high-dose interferon-α therapy. Two prospective, randomized studies showed a prolongation of recurrence-free survival time with and without an overall survival benefit in comparison to untreated controls.[71;72]

Although high-dose IFN therapy has been approved in the USA and Canada as standard adjuvant therapy for patients with lymph node metastases, other IFN regimens are still being considered in some European countries, because of the considerable toxicity of high-dose therapy and the fact that only a small number of patients clearly benefits.[73]

In summary, there are presently no generally accepted recommendations for adjuvant treatment with interferon-α. There is clear benefit from treatment in terms of increased relapse free survival but not overall survival and at the cost of toxicity.

Table 6: Metaanalysis of randomized trials on the adjuvant treatment with interferon-alpha in stage II and III melanoma patients.[69-78]

A: Disease-free survival

Study	Treatment	Control	OR 95% CI	OR (fixed) 95% CI
High-dose				
Creagan, 1995	77/131	85/131		0.77 [0.47, 1.27]
Kirkwood, 1996	90/143	103/137		0.56 [0.33, 0.94]
Kirkwood, 2000	114/215	127/212*		0.76 [0.51, 1.11]
Z = 2.64 (P = 0.008)	281/489	315/480		0.70 [0.54, 0.91]
Intermediate-dose				
Eggermont, 2005	596/1109	164/279		0.81 [0.62, 1.06]
Z = 1.51 (P = 0.13)	596/1109	164/279		0.81 [0.62, 1.06]
Low-dose				
Grob, 1998	100/244	119/245		0.74 [0.51, 1.05]
Pehamberger, 1998	37/154	57/157		0.55 [0.34, 0.91]
Kirkwood, 2000	122/215	127/212*		0.88 [0.60, 1.29]
Cameron, 2001	32/46	35/49		0.91 [0.38, 2.21]
Cascinelli, 2001	162/225	158/219		0.99 [0.66, 1.50]
Garbe, 2004	86/146	104/147		0.59 [0.36, 0.96]
Hancock, 2004	211/338	215/336		0.94 [0.68, 1.28]
Z = 2.73 (P = 0.006)	750/1368	815/1365		0.80 [0.69, 0.94]
Total	1627/2966	1167/1912		0.78 [0.68, 0.90]
Z = 4.26 (P < 0.0001)			0.2 0.5 1 2 5 Interferon-α Control	

Disease-free survival
* 3-armed study

B: Overall survival

Study	Treatment	Control	OR 95% CI	OR (fixed) 95% CI
High-dose				
Creagan, 1995	68/131	72/131		0.88 [0.54, 1.44]
Kirkwood, 1996	81/143	90/137		0.68 [0.42, 1.11]
Kirkwood, 2000	98/215	93/212*		1.07 [0.73, 1.57]
Z = 0.84 (P = 0.40)	247/489	255/480		0.90 [0.70, 1.16]
Intermediate-dose				
Eggermont, 2005	535/1109	146/279		0.85 [0.65, 1.10]
Z = 1.22 (P = 0.22)	535/1109	146/279		0.85 [0.65, 1.10]
Low-dose				
Grob, 1998	59/244	76/243		0.70 [0.47, 1.04]
Pehamberger, 1998	17/154	21/157		0.80 [0.41, 1.59]
Kirkwood, 2000	96/215	93/212*		1.03 [0.70, 1.51]
Cameron, 2001	31/46	36/49		0.75 [0.31, 1.81]
Cascinelli, 2001	146/225	138/219		1.08 [0.74, 1.60]
Garbe, 2004	62/146	85/147		0.54 [0.34, 0.86]
Hancock, 2004	151/338	156/336		0.93 [0.69, 1.26]
Z = 1.89 (P = 0.06)	562/1368	605/1363		0.86 [0.73, 1.01]
Total	1344/2966	913/1910		0.90 [0.81, 1.02]
Z = 1.70 (P = 0.09)			0.2 0.5 1 2 5 Interferon-α Control	

Overall survival
* 3-armed study

Table 7. Dosage schedules for adjuvant therapy of melanoma with interferon-α

Schedule	*Dose*	*Frequency*	*Duration*	*Indication*
Low dose	*3 million IU s.c.*	*Days 1,3 & 5 every week*	*18 months*	*Stage II – III*
High dose				
– Initiation	*20 million IU/m2 iv. rapid infusion*	*Day 1-5 every week*	*4 weeks*	*Stage III*
– Maintenance	*10 million IU/m2 s.c.*	*Days 1,3 & 5 every week*	*11 months*	*Stage III*
Pegylated				
– Initiation	*6 µg/kg body weight s.c.*	*Day 1 every week*	*8 weeks*	*Stage III*
– Maintenance	*3 µg/kg body weight s.c.*	*Day 1 every week*	*Total 5 years*	*Stage III*

A large-sized adjuvant trial on stage III melanoma patients treated with pegylated interferon α2b compared to observation alone was conducted by the EORTC Melanoma Group. Patients with microscopically or macroscopically positive lymph nodes have been stratified for the clinical trial outcome. The dose of pegylated interferon α2b was 6 µg/kg body weight for the first 8 weeks and 3 µg/kg for the rest of 5 years. Dose reductions according to the general performance status of treated patients have been performed. The results indicate a statistically significant prolongation of relapse-free survival (RFS) for all patients and a significant benefit of distant-metastasis free survival (DMFS) for microscopically lymph node positive melanoma patients.[79] However, there was no significant benefit in terms of overall survival for interferon-treated patients. Since the predominant effect was detected in sentinel node-positive patients, pegylated interferon α2b should be discussed as a new treatment alternative after the European approval.

6. Chemotherapy and Chemoimmunotherapy

6.1 General Principles

The major indications for systemic chemotherapy and chemoimmunotherapy are inoperable recurrent tumours, inoperable regional metastases and distant metastases (stage IV). Since treatment in such situations is primarily palliative, the effect of any regimen on quality of life must be carefully weighed.[66]

In stage IV disease with distant metastases, complete responses and a cure of these patients is rarely achieved by medical treatment. Thus, there are two other main goals:

- Prolongation of survival
- Reduction of tumour size or load with a resultant increase in symptom-free course or a decrease in symptoms

6.2 Single Agent Treatment with Cytotoxic Agents and Cytokines

A number of agents with comparable effectiveness are available for systemic chemotherapy of advanced melanoma. Chemotherapy can lead to regression of tumours and a reduction in tumour-related symptoms. The best established monotherapy agent is dacarbazine (DTIC). Objective remissions (more than 50% reduction in tumour mass) are achieved in 5.3-28.6% of patients. Recent multicentre trials, however, have demonstrated that remission rates are in the range of only 5-12%.[80;81]

Many studies have also evaluated the effectiveness of cytokines in advanced disease. Both IFN and IL-2 can achieve objective remission rates comparable to cytostatic agents. Treatment with high dose IL-2 resulted in prolonged complete remissions in 5% of patients in a selected series of phase II trials. High dose IL-2 treatment is associated with high toxicity and careful patient selection is required. Treatment schedules and expected response rates are summarized in Table 8.

Table 8. Monotherapies for advanced cutaneous melanoma described in prospective randomized trials or phase II studies (*) if phase III trials were not available

Medication	Dose	Response rate
Dacarbazine Ringborg 1989, Middleton 2000[80;82]	250 mg/m^2 i.v. daily for 5 days every 3-4 weeks	12.1-17.6%
Chiarion Sileni, 2001, Young 2001[83;84]	800 – 1200 mg/m^2 i.v. daily on one day every 3-4 weeks	5.3-23%
Temozolomide Bleehen 1995, Middleton 2000[80;85]	150 - 200 mg/m^2 p.o. daily for 5 days every 4 weeks	13.5-21%
Fotemustine Jacquillat 1990, Mornex 2003[86;87]	100 mg/m^2 i.v. on days 1, 8 and 15; then 5 week pause, then repeat single dose every 3 weeks	7.4-24.2%
Vindesine Nelimark 1983, Carmichael 1982[88;89]	3 mg/m^2 i.v. every 14 day	12-26 %
Interferon-α* Robinson 1986, Miller 1989[90;91]	9-18 million IU/m^2 s.c. 3 x weekly	(13-25 %)
Interleukin-2* Dorval 1992, Legha 1996, Atkins 1999[92-94]	600,000 IU/kg as 15 min. infusion i.v. every 8 hours for 5 days (total of 14 doses). Repeat every 2 weeks.	(16-21.6 %)

6.3 Polychemotherapy and Chemoimmunotherapy

The combination of cytostatic agents and cytokines produces an increase in the objective response rate. No study, however, has shown a significant improvement in the overall survival time.[95;96] The tolerability of monochemotherapy is worsened when interferon-α or IL-2 is added.

The combination of multiple chemotherapeutic agents (polychemotherapy) or of multiple chemotherapeutic agents and cytokines (polychemoimmunotherapy) also achieves higher remission rates than monotherapy (12.7-45%), but, once again, it does not improve the overall survival (Table 9). Polychemotherapy is much more toxic than monochemotherapy. Therefore, monochemotherapy or immunotherapy alone should be preferred over polychemotherapy or poly-immuno-chemotherapy, unless the latter are conducted in the setting of clinical trials, or are motivated by palliative purposes in individual cases.

In principle all stage IV patients should be preferably treated in the context of clinical trials, since no treatment options with a proven effect on overall survival are available.

Table 9. Polychemotherapy and chemoimmunotherapy of advanced cutaneous melanoma from prospective randomized trials or phase two trials (*), if no phase III trials are available

Regimen	Dose	Response rate
DTIC (Temozolomide) + Interferon-α Bajetta 1994, Falkson 1998, Kaufmann 2005[97-99]	DTIC 850 mg/m^2 i.v. Day1 (or temozolomide 150 mg/m^2 p.o. Day 1-5) Interferon-α2a/b 3 million IU/m^2 s.c. days 1-5; then Interferon-α2a/b 5 million IU/m^2 s.c. 3x weekly in weeks 2-4 ; repeat every 4 weeks	14-27.7 %
Vindesine + Interferon- Smith 1992[100]	Vindesine 3 mg/m^2 i.v. day 1 Interferon-α2a/b 5 million IU /m^2 s.c. 3x weekly; repeat every 2 weeks	24 %
BHD Carter 1976, Costanzi 1982[101;102]	BCNU 150 mg/m^2 i.v. day 1 in every other cycle; Hydroxyurea 1500 mg/m^2 p.o. days 1-5 DTIC 150 mg/m^2 i.v. days 1-5 every 4 weeks	12.7-30.4 %
BOLD Seigler 1980, York 1988[103;104]	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 Gunderson, 1987, Pectasides 1989, Jungnelius 1998[105-107]	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 Verschraegen 1988[108]	DTIC 450 mg/m^2 i.v. days 1+8 Vindesine 3 mgm^2 i.v. days 1+8 Cisplatin 50 mgm^2 i.v. days 1+8 every 3-4 weeks	24%
DBCT McClay 1987, Chapman 1999, Creagan 1999[109-111]	DTIC 220 mg/m^2 i.v. days 1-3 BCNU 150 mgm2 i.v. day 1 of every other cycle. Cisplatin 25 mg/m^2 i.v. days 1-3 Tamoxifen 2 x 10 mg p.o. daily every 3-4 weeks	18.5-31.9%
CarboTax Rao 2006[112]	Carboplatin AUC6 i.v. day 1, after four cycles reduce to AUC4 Paclitaxel 225 mg/m^2 i.v. day 1 every 3 weeks, after four cycles reduce to 175 mg/m^2	(12.1% second line)

6.4 Special Case: Metastatic Uveal Melanoma

Melanomas of the eye involve the uvea, ciliary body or the retina. They have a different pattern of metastasis than cutaneous melanomas. Since the eye does not have a lymphatic system, almost all metastases are found in the liver. For this reason, the prognosis of metastatic ocular melanoma is in general much worse than that of cutaneous lesions. On the other hand, when patients with liver metastases from eye and skin melanomas are compared, there are no prognostic differences. Because of the preferential metastasis to the liver, patients with ocular melanoma and liver metastases may be candidates for local-regional therapeutic measures. Few systemic schedules have been reported with objective responses. (Table 10)

Table 10. Chemotherapy for advanced uveal melanoma

Medication	Dose
Fotemustine Leyvraz 1997, Egerer 2001, Siegel 2007[113-115]	Induction cycle 100 mg/m^2 intraarterial (hepatic artery) over 4 hours weekly for 4 weeks; then 5 week pause; then repeat every 3 weeks
Treosulfan/ Gemcitabine Pföhler 2003[116]	Treosulfan 5 g/m^2 i.v. day 1 Gemcitabin 1 g/m^2 i.v. day 1 Repeat every 3 weeks

6.5 Experimental Therapies

Although DTIC is the best-established treatment for metastatic disease it has never been shown to improve survival over supportive care. Patients with metastatic disease should be considered for entry into appropriate clinical trials and, where necessary, referred to specialized centres offering access to such studies. Single arm studies of experimental treatments, including phase I/II trials, may be reasonably offered as first line or second-line treatment.[66]

7. Follow-up

7.1 General Principles

The frequency and extent of follow-up examinations depends on the primary tumour characteristics. The first 5 years following surgery are most important, as 90% of all metastases occur during this time period. Late metastasis does however occur in melanoma and indicate the relevance of a follow-up beyond 5 years. Finally, patients who have had a history of melanoma have an increased risk of a secondary melanoma primary, adding increased importance to regular clinical re-examinations. Follow-up of melanoma patients has the following goals:

1. Identifying tumour recurrence or disease progression at the earliest stage,

2. Looking for atypical naevi and second primary melanomas (occurs in about 10 % of patients with cutaneous melanoma) and non-melanoma skin cancers,

3. Offering psychosocial support,

4. Providing patient education and instructions for self- skin examination,

5. Documenting the disease course,

6. Administering and monitoring adjuvant therapy, where appropriate.

7.2 Recommendations for Structured Follow-up

Follow up examinations are variable across Europe, ranging in frequency from 2 to 4 times per year for 5 to 10 years.[32;117] There is considerable variation in follow up approaches and few data to support them. In stage I to II melanoma, the intent is to detect early loco-regional recurrence so that the frequency of follow up examination is usually every 3 months for the first five years, whereas for the 6th to 10th year period investigations every 6 months seem to be adequate. In patients with thin CM (≤ 1mm) six monthly intervals may be sufficient. Clinical follow up is the the standard procedure but there are data to support the additional use of ultrasonography. Staging by CAT scan is usual for stage III disease but, presently, there is no established role for subsequent regular imaging in the absence of effective systemic therapies for melanoma.

8. Consensus-building Process and Participants

These guidelines originate from contributors who were involved in the development of their national guidelines. These national guidelines were elaborated by the different specialities involved in the

management of melanoma patients (dermatology, medical oncology, surgical oncology, radiotherapy, pathology).
These guidelines were prepared under the auspices of the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC). The basis for the elaboration of these guidelines was an English translation of the interdisciplinary melanoma guideline of the Dermatologic Cooperative Oncology Group (DeCOG) from Germany. In a first round dermatologists were involved who participated in national guideline development processes. In a second round the EORTC selected experts from different specialities who contributed to this guideline. Professor Claus Garbe, Tübingen, coordinated the activities of the the selected experts and the final authors. These guidelines are planned to be updated every three years.
Finalized: May 2009
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SOP for creation of European Dermatology Guidelines

Step	Responsible	Task	Months duration
1	EDF Guidelines Committee (EDF-GC) *	Decision of topic of specific guideline	∅
2	EDF Board	Confirmation of the choice and level of guideline (S1, S2 or S3) plus suggestion to the Guideline Committee of potential chairmen and subcommittee members.	0,5
3	EDF-GC	Foundation of subcommittee for specific guidelines. Nomination of EDF members (50 %) as well as identification of possible EADV members (25 % of members for the subcommittee) who could work within the subcommittee. Chairman of EDF guideline committee asks EADV president for approval. Finally nomination of a chairperson of the subcommittee by the group.	at EDF Meeting
4	EDF Guidelines Subcommittee (EDF-GSubC)	Development of a business plan (see attachment)	1
5	EDF Board	Confirmation of business plan and signature of the contract for financial support of guideline	1
6	EDF-GSubC	Identify all existing guidelines for the specific guideline (active process: literature survey plus contact to Dermatological Societies)	1
7	EDF-GSubC	Select the guidelines with highest quality. Criteria for selection: 1. Availability of strength of evidence 2. Availability of strength of recommendation 3. Evidence of mechanics of literature review (adhere to the recommendations of the Cochrane collaboration. These standards should assure high quality for the systematic literature search as well as for the critical appraisal of the papers. For further information see http://www.cochrane.org/crgprocedures/chapter4/1.htm and documents available at EDF Guidelines Secretariat (Mrs. Janine Schweiger, janine.schweiger@charite.de)	1
8	EDF-GSubC	Identification/nomination of additional 50 % EDF members for the EDF-GSubC from amongst the authors of the best guidelines	0,5
9	Chairperson of EDF-GSubC	Consider involvement of other disciplines and patients´ organisations	1
10	EDF-GSubC	Meet 1. to decide the author of the first draft (normally the chairperson of the subcommittee) and to discuss the present guidelines, their strengths and weaknesses 2. 6 months later to discuss the draft (consensus conference)	6
11	Chairperson of EDF-GSubC	Circulate the guideline draft to national dermatological societies for comments (actual list of societies and their presidents at EDF guidelines secretariat)	2
12	EDF-GSubC	Circulate final version for approval among members of the guideline subcommittee	1
13	EDF-GSubC	Deliver final version to EDF guideline committee chairperson, who forwards it to the EDF-GC	∅
14	EDF-GC	Review and comment guideline	1
15	Chairperson of EDF-GSubC	Send final version to EADV Board and to UEMS for approval	2
16	Chairperson of EDF-GSubC	Send guideline for official approval to UEMS (formal approval)	1
17	EDF secretary	Distribute guideline for in advance information to EDF members and National Dermatological Societies	1
18	EDF	Publication 1. on EDF homepage (by Prof. Lajos Kemeny, responsible for the website) 2. in European dermatological journals (normally in EJD, if already published in another journal, a written permission must be obtained to publish in EJD) 3. If publication in other national and international journals is requested by the respective society, this will be encouraged by the EDF	6

The normal expiry date of a guideline is 3 years after finishing point 17. In well defined exceptions the expiry date may be prolonged up to 5 years.

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* The Guideline Committee consists of the founding members of the EDF guideline work as well as of chairpersons of guidelines subcommittees.