

# Cutaneous malignant melanoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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## incidence

The incidence of malignant melanoma varies from 3–5/100 000/year in Mediterranean countries to 12–20/100 000 in Nordic countries. The mortality rate is 2/100 000 for females and 3/100 000/year for males with a lesser variation with geography. Melanoma mortality has doubled in males over the last 25 years. Increased ultraviolet-B ray exposure of a genetically predisposed population seems responsible for an ongoing increase in incidence over recent decades.

## diagnosis

Suspicious lesions are characterized by asymmetry, border irregularities, color heterogeneity, dynamics (evolution of color, elevation or size) ('ABCDE rule'). Diagnosis should be based on a full-thickness excisional biopsy with a small side margin [B]. Processing by an experienced pathology institute is mandatory. The histology report should follow the WHO classification and include maximum thickness in millimeters (Breslow), level of invasion (Clark level I–V), presence of ulceration, presence and extent of regression and clearance of the surgical margins.

## staging

Physical examination with special attention to other suspicious pigmented skin lesions including head and genitalia, tumor satellites, in-transit metastases, regional lymph node and systemic metastases is mandatory. Today, many primary melanomas have a diameter of <5 mm. In low-risk melanomas (tumor thickness <1 mm) no other investigations are necessary. In higher stages imaging is recommended in order to exclude

regional or distant metastatic disease. The refined version of the ASCC staging and classification system, which includes the staging of microscopically positive lymph nodes, is the classification system of choice (Table 1).

## treatment for localized disease

Wide excision of primary tumors with a normal skin margin of 0.5 cm for *in situ* melanomas, of 1 cm for tumors with a Breslow thickness up to 2 mm and 2 cm for thicker tumors is recommended [II, B]. Modifications may be needed for preservation of function in melanomas of the fingers and toes or those of the face and the ear.

Routine elective lymphadenectomy or irradiation to the regional lymph nodes is not recommended [II, B].

Sentinel lymph node biopsy in melanoma with a tumor thickness of >1 mm is necessary for precise staging and is followed by complete clearance of regional lymph nodes, if the sentinel node was positive for micro-metastases [C]. This procedure should be performed only by skilled teams in experienced centers.

There is no generally accepted adjuvant therapy to date for patients with high-risk primary melanoma or completely resected lymph node metastases (stage III). Adjuvant immunotherapy with interferon- $\alpha$  (IFN- $\alpha$ ) leads to a significant prolongation of disease-free survival in some but not all randomized trials. Positive effects of high-dose IFN- $\alpha$  on overall survival have been demonstrated in two out of three randomized trials [C]. The optimal timing and dosing schedules and the best type of interferon (pegylated versus conventional) are not yet defined. Therefore, adjuvant interferon treatment is preferentially applied in the context of randomized clinical trials in specialized centers.

Adjuvant chemotherapies, mistletoe extracts, viscum album and hormone therapies are not beneficial. Adjuvant immunotherapy with other cytokines including interleukin-2, tumor vaccination and immunochemotherapy are experimental and not to be used outside of controlled clinical trials.

Radiotherapy for local tumor control should be considered in case of inadequate resection margins of lentigo maligna melanoma or R1 resections of melanoma metastases when re-excision is not feasible [B].

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Approved by the ESMO Guidelines Working Group: August 2002, last update September 2007. This publication supercedes the previously published version—Ann Oncol 2007; 18 (Suppl 2): ii71–ii73.

Conflict of interest: Dr Dummer has reported no conflicts of interest. Dr Hauschild has reported that he is member of the advisory board for Schering-Plough, Synta, Pfizer, BMS, Bayer and that he receives study grants from Bayer, Essex Pharma, Roche, Pharma.

Table 1

AJCC	TNM stage	10-year survival (%)	Criteria for staging
IA	T1a N0 M0	87.9	T1a = Breslow $\leq$ 1 mm, no ulceration (U-) and Clark level $\leq$ III
IB	T1b N0 M0	83.1	T1b = Breslow $\leq$ 1 mm with ulceration (U+) or Clark level $\geq$ IV
	T2a N0 M0	79.2	T2a = Breslow 1.01–2.0 mm U-
IIA	T2b/T3a N0 M0	64.4/63.8	T2b = Breslow 1.01–2.0 mm, U+/T3 = 2.01–4.0 mm U-
IIB	T3b/T4a N0 M0	53.9/50.8	T3b = Breslow 2.01–4.0 mm U+/T4 = $>$ 4.0 mm U-
IIC	T4b N0 M0	32.3	T4b = Breslow $>$ 4.0 mm U+
IIIA	Any T <sub>a</sub> N1a/N2a M0	63.0/56.9	U-, N1a = 1 lymph node microscopically +/N2 = 2–3 nodes
IIIB	Any T <sub>b</sub> N1a/N2a M0	47.7/35.9	U+, N1a = 1 lymph node microscopically +/N2 = 2–3 nodes
IIIC	Any T <sub>b</sub> N1b/N2b M0	24.4/15.0	U+, N1b = 1 lymph node macroscopically +/N2 = 2–3 nodes
	Any T N3 M0	18.4	U- or U+, N3 = $\geq$ 4 nodes, satellite or in transit metastases
IV	Any T any N M1a	15.7	M1a = nodal metastases with normal LDH; distant skin, subcutaneous metastases with normal LDH
	Any T any N M1b	2.5	M1b = lung metastases with normal LDH
	Any T any N M1c	6.0	M1c = LDH elevated and/or any non-pulmonary visceral metastases

Percentage figures are median values for disease-specific survival with a standard deviation between 1% and 7%. AJCC, American Joint Committee on Cancer; TNM, Tumor–node–metastasis; LDH, lactate dehydrogenase.

## treatment for locoregional metastatic disease

In the case of isolated loco-regional lymph node metastases, surgical removal, including the surrounding lymph node region, is indicated; removal of the tumor-bearing lymph node alone is insufficient. 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 local surgical treatments, a detailed staging investigation, including imaging techniques such as CT or positron emission tomography (PET) scans, are necessary to exclude the presence of further metastases [B].

Non-resectable in-transit metastases or inoperable primary tumors of the limbs without additional metastases may be treated with isolated limb perfusion using e.g. melphalan and tumor necrosis factor [II–III, C]. However, such treatment requires major surgery and should be restricted to a few experienced centers. Radiation therapy may be used instead [V, D], although there are no data showing a positive effect on any outcome measure.

Adjuvant systemic therapy after complete resection as mentioned above.

## treatment for systemic metastatic disease (stage IV ASCC)

Palliative therapy for advanced disease with several metastases in different anatomical regions should initially use cytostatics such as dacarbazine, vinca alkaloids, nitrosurea or temozolomide alone or in combination with cytokines like IFN- $\alpha$  or, in the case of aggressive metastatic disease, polychemotherapy [C]. Since the overall impact of systemic therapy on survival in advanced melanoma patients is questionable, these patients should be treated preferentially in controlled clinical trials evaluating new approaches. Surgery of visceral metastases may be appropriate for selected cases with good performance status and isolated tumor manifestation. In all surgically treated patients R0 resections must be the goal.

Palliative radiotherapy should be considered especially for symptomatic brain or localized bone metastases.

## patient information and follow-up

The patient and his/her family, in particular small children, should be instructed in avoidance of sunburn, extended unprotected solar or artificial ultraviolet exposure and in lifelong regular self-examination of the skin and peripheral lymph nodes. The patient must be aware that her/his family members have an increased risk of melanoma [B]. A secondary melanoma develops in 8% of all melanoma patients within 2 years of their initial diagnosis. 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.

During melanoma follow-up, patients are clinically monitored in order to detect a relapse and to recognize additional skin tumors, especially a second melanoma, as early as possible [B].

Recommendations for follow-up depend upon the risk of relapse over time. Follow-up relies primarily on clinical examinations every 3 months during the first 3 years and every 6–12 months thereafter. 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, ultrasound of lymph nodes, CT or whole body PET/PET–CT scans may be considered in the follow-up of high-risk patients, i.e. those with thick primary tumors or following treatment of metastases. However, there is currently no consensus on the use of imaging techniques or blood tests. Rising serum S100 has a higher specificity for disease progression than lactate

dehydrogenase (LDH) and therefore is the most accurate blood test in the follow-up of melanoma patients if any blood test is done at all [D].

Psychosocial guidance and rehabilitation—if needed—constitute an important task of the caring physician. Reporting follow-up results to Clinical Cancer Registries secures quality control of surgical and medical interventions.

## note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

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