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ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of cutaneous malignant melanoma

Incidence

- The crude incidence of malignant melanoma in the European Union is 10/100 000 per year. The incidence increases with latitude, i.e. with increasing prevalence of less pigmented skin types, from 3–5/100 000 per year in Mediterranean countries to 12–17 in Nordic countries. The mortality is 2.4/100 000 per year with a lesser variation with geography. Increased ultraviolet-B ray exposure seems responsible for an ongoing increase in incidence over recent decades.

Diagnosis

- Suspicious lesions are characterized by asymmetry, border irregularities, color heterogeneity, diameter >6 mm, and recent evolution of color, elevation or size ('ABCDE rule').
- Diagnosis should always be based on a full thickness excisional biopsy with a recommended margin of 2 mm of normal skin around the lesion. 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 levels I–V), clearance of the surgical margins, presence of ulceration, and presence and extent of regression.

Staging and risk assessment

- Physical examination with special attention to tumor satellites, in-transit metastases, regional lymph node and systemic metastases *[V, D]*.
- To exclude metastatic disease, chest X-ray, blood count, LDH, and alkaline phosphatase are recommended *[V, D]*.
- Sonography of the abdomen and regional lymph nodes is recommended only in patients with melanoma of >1 mm thickness or suspicious clinical findings. Further radiological tests only as clinically indicated *[V, D]*. PET-scanning is not useful for initial staging of clinically localized melanoma *[III, B]*.
- Risk assessment according to the sixth edition of the AJCC staging system (2002) may guide therapeutic decisions and is based on Breslow levels of the primary tumor and the presence of ulceration and of locoregional or systemic metastases, as shown in Table 1.

Treatment for localized disease

- Wide excision of primary tumors with a normal skin margin of 0.5 cm for *in situ* melanoma, of 1 cm for tumors with a Breslow thickness of 1–2 mm and 2–3 cm for thicker tumors is mandatory *[II–III, A]*. Modifications may be needed for preservation of function in melanomas of the fingers and toes or those of the ear.
- Routine elective lymphadenectomy or irradiation to the regional lymph nodes are not recommended *[II, B]*.
- Sentinel lymph node biopsy with selective complete clearance of regional lymph nodes, if the sentinel node was found positive, may be useful but should be performed only by skilled teams in experienced centers.
- There is no standard adjuvant therapy to date for patients with high-risk melanoma. Adjuvant immunotherapy with high-dose interferon results in a significant prolongation only of disease-free survival but not overall survival. This result has to be balanced against the toxicity of this treatment *[III]*. Adjuvant chemotherapies and hormone therapies have still not proven to be beneficial. Adjuvant immunotherapy with other cytokines including interleukin-2, tumor vaccination, and immunochemotherapy are controversial *[III]* and not to be used outside of protocols.
- Radiotherapy should be considered in case of inadequate resection margins of primary when re-excision is not feasible, such as in head and neck melanoma.

Treatment for locoregional metastatic disease

- Complete resection of positive regional lymph nodes must be conducted for all patients tolerating surgery *[II–III, C]*.
- In-transit metastases or inoperable primary tumors of the limbs 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]*.
- Adjuvant systemic therapy after complete resection as mentioned above. There is no standard adjuvant therapy.

Treatment for systemic metastatic disease

- There is no proof that systemic treatment results in a significant prolongation of survival. Palliative chemotherapy with single agents (e.g. dacarbazine, vindesine, temozolomide) may be given to patients with preserved performance status *[II, C]*, otherwise best supportive care should be considered. Until now, combination chemo- or chemo-/immunotherapy has not been proven consistently superior to dacarbazine in phase III trials.

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Table 1. Risk assessment using the AJCC staging system

AJCC	TNM Stage	10 yr survival	Criteria for staging
I A	T1a No M0	87.9 %	T1a = Breslow ≤ 1 mm, no ulceration (U−) and Clark level ≤ III
I B	T1b No M0	83.1 %	T1b = Breslow ≤ 1 mm with ulceration (U+) or Clark level ≥IV
	T2a No M0	79.2 %	T2a = Breslow 1.01 – 2.0 mm U−
II A	T2b / T3a N0 M0	64.4 / 63.8 %	T2b = Breslow 1.01–2.0 mm, U+ / T3 = 2.01 – 4.0 mm U−
II B	T3b / T4a N0 M0	53.9 / 50.8 %	T3b = Breslow 2.01–4.0 mm U+ / T4 = > 4.0 mm U−
II C	T4b N0 M0	32.3 %	T4b = Breslow > 4.0 mm U+
III A	Any Ta N1a / N2a M0	63.0 / 56.9 %	U−, N1a = 1 lymph node microscopically + / N2 = 2–3 nodes
III B	Any Tb N1a / N2a M0	47.7 / 35.9 %	U+, N1a = 1 lymph node microscopically + / N2 = 2–3 nodes
III C	Any Tb 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 = ≥ 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%.

- Surgery of visceral metastases may be appropriate for selected cases with good performance status and isolated tumor manifestation.
- Palliative radiotherapy should be considered especially for symptomatic brain or localized bone metastases.

Follow-up for localized or locoregional disease

- There is currently no consensus on the frequency of follow-up and recommendations for surveillance testing. There is insufficient data to recommend regular blood tests, radiological examinations including ultrasound or PET scanning outside of adjuvant treatment or follow-up protocols in patients able and willing to undergo experimental therapy. The following recommendations were judged adequate for most patients by the experts and ESMO faculty:
- Patients with sporadic or familial dysplastic naevus syndrome have a high risk and should be followed for life. Sunburns during childhood and unprotected ultraviolet exposure (solar or artificial UV-B rays) are additional risk factors.
- Follow-up for 5 years for localized melanoma of ≤1.5 mm Breslow thickness and for 10 years for others is deemed sufficient despite the rare occurrence of later relapses.
- History, physical examination including regional lymph nodes, skin inspection and palpation of primary tumor location every 3 months for 2 years and every 6–12 months thereafter are recommended.
- The patient should be instructed in avoidance of sun burns, extended unprotected solar or artificial ultraviolet exposure and in lifelong regular self-examination of the skin and peripheral lymph nodes.

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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Coordinating authors for the ESMO Guidelines Task Force: L. M. Jost[1], S. Jelic[2] & G. Purkalne[3]

[1]Invited author and member of the task force, Oncology, Kantonsspital, CH-4101 Bruderholz/BL, Switzerland; [2]Assigned task force member, Institute of Oncology and Radiology of Serbia, Department of Medical Oncology, Pasterova 14, 11000 Belgrade, Serbia; [3]Assigned task force member, P. Stradins University Hospital, Radiation & Chemotherapy Center, Pilsonu Str. 13, 1002 Riga, Latvia

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Correspondence to:
ESMO Guidelines Task Force
ESMO Head Office
Via La Santa 7
CH-6962 Lugano
Switzerland