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Melanoma: ESMO Clinical Practice Guidelines 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 in Nordic countries and is still rising. The mortality rate is 2–3/100 000/year with a lesser variation with geography and relatively stable over the last decade. However, the melanoma mortality rate in males but not in females has increased over the last 25 years. Increased ultraviolet light exposure of a genetically predisposed population seems to be at least in part responsible for an ongoing increase in incidence over recent decades.

diagnosis

Suspicious lesions are characterized by Asymmetry, Border irregularities, Colour heterogeneity, Dynamics (dynamics in colours, elevation or size) ('ABCD rule'). Today, many primary melanomas have a diameter of <5 mm). Dermoscopy by an experienced physician enhances the diagnostic accurancy [B].

Diagnosis should be based on a full thickness excisional biopsy with a small side margin. Processing by an experienced pathology institute is mandatory.

The histology report should follow the AJCC classification and includes the 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. However, in due time the evaluation of the Clark level is being omitted and replaced by information on the mitotic rate of the primary tumour.

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staging

Physical examination with special attention to other suspicious pigmented lesions, tumour satellites, in-transit metastases, regional lymph node and systemic metastases is mandatory.

In low-risk melanomas (tumour thickness <1 mm) no other investigations are necessary. In higher stages imaging is recommended in order to allow proper staging.

The refined version of the AJCC staging and classification system which includes a sentinel node staging is the only internationally accepted classification system (Table 1).

treatment of localized disease

Wide excision of primary tumours with safety margins of 0.5 cm for *in situ* melanomas, of 1 cm for tumours with a Breslow thickness up to 2 mm and 2 cm for thicker tumours is recommended [II, B]. Modifications may be needed for preservation of function in acral and facial melanomas.

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

Sentinel lymph node biopsy in melanoma with a tumour thickness of >1 mm is necessary for precise staging. It should be followed by a complete lymphadenectomy of regional lymph nodes, if the sentinel node was found positive for metastases [C]. However, this procedure has no proven effect on overall survival. Sentinel lymph node biopsy should be performed only by skilled teams in experienced centres.

There is no generally accepted adjuvant therapy to date for patients with high-risk primary melanoma (stage IIB/C) or completely resected lymph node metastases (stage III).

A number of prospective randomized trials have investigated adjuvant treatment with low, intermediate and high doses of interferon (IFN)-α. IFN-α therapy following the resection of the primary tumour has improved recurrence-free survival (RFS), but without confirmed significant effects on overall survival (OS).

The first trial that showed a positive effect in OS was ECOG 1684: 287 patients were enrolled to receive high-dose IFN-α for 1

Table 1. AJCC Staging system 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

year versus observation. Twenty-five per cent of the patients had to be withdrawn due to severe adverse effects. Five-year disease-free survival (FS) was 37% versus 26% and OS was 46% versus 37%. On this basis, high-dose adjuvant IFN-α won US FDA approval. A meta-analysis of several high-dose interferon trials showed no statistically significant effect on OS. It was then proposed that IFN might exert its best effect in long-term therapy.

Since PegIFN-α is suitable for long-term therapy, the European Organisation for Research and Treatment of Cancer (EORTC) has designed a large prospective randomized trial to investigate the potent positive effect of PegIFNα-2b in the adjuvant setting in patients with stage III melanoma. A total of 1256 patients with resected stage III melanoma were randomized to receive observation or pegylated IFN-α therapy. Randomization was stratified for microscopic (N1) versus macroscopic (N2) nodal involvement, number of positive nodes, ulceration and tumour thickness. RFS (primary endpoint), distant-metastases-free survival (DMFS) and OS were analysed for the intent-to-treat population.

The interferon group received an induction interferon dose of a weekly dose of 6 μg/kg for the first 8 weeks and then the dose was reduced to 3 μg/kg per week for 5 years.

At 3.8 years of median follow-up, RFS was significantly reduced by 18% in the PegIFNα-2b arm compared with observation; the 4-year RFS rate was 45.6% compared with 38.9%. DMFS was improved but non-significantly ($P = 0.11$). OS was unchanged in the two groups. In stage III-N1a (micro-metastases detected in the sentinel node) both RFS [hazard ratio (HR) 0.72; 57.7%vs 45.4%; $P = 0.01$] and DMFS (HR 0.73; 60.5% versus 52.6%; $P = 0.01$) were prolonged in the PegIFNα-2b arm, whereas in stage III-N1b (macroscopic metastases) there was no benefit.

This trial showed that a prolonged adjuvant treatment with IFN-α improved the RFS period and DMFS in a subgroup of patients with low tumour burden.

Therefore, in this patient population pegylated interferon can be recommended, if the individual patient tolerates it well [C]. Adjuvant treatment in patients with resected macroscopic node involvement is preferentially applied in the context of randomized clinical trials in specialized centres. However, high-dose interferon a2b is an approved indication for this therapeutic situation.

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

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

treatment of 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 tumour-bearing lymph node alone is insufficient. Surgical removal is also recommended in the case of an single metastasis in parenchymal organs, including the central nervous system. However, before undertaking additional aggressive local surgical treatments, a detailed staging investigation, including

imaging techniques such as CT or PET (positron emission tomography) scans, is necessary to exclude the presence of further metastases [B].

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

treatment of systemic metastatic disease

(stage IV; AJCC classification from 2002)

Patients should preferentially be treated within clinical trials. However, not for all metastasized melanoma patients clinical trials are available. In these cases palliative therapy for advanced disease with several metastases in different anatomical regions may initially use well tolerated cytostatics such as dacarbazine (DTIC), taxanes, fotemustine or others, cytokines (Interferons, Interleukin-2) or combinations. There is no standard therapy. However dacarbazine is at least considered as a reference drug in this situation. In aggressive metastastic disease multi-agent polychemotherapy [C] containing Paclitaxel and Carboplatin or Cisplatin, Vindesine and Dacarbazine produce partial response and stabilizations in a meaningful number of patients. However, since the overall impact of systemic therapy on survival in advanced melanoma patients is questionable, these patients should be preferentially treated in controlled clinical trials evaluating new treatment modalities.

There are no randomized clinical trials for IL2 monotherapy. Some centres still today use IL2 as first line therapy when disease burden is low. Several randomized trials did not show any survival benefit for the very intensive biochemotherapy including IL-2. Over the last decades several phase II clinical trials have demonstrated the feasibility of CTLA4 blockade either alone or in combination with vaccines or chemotherapy. These therapeutic approaches using CTLA4 blockade have resulted in a proportion of metastatic melanoma patients surviving up to two years and longer. These results are promising. However, they have to be confirmed by randomized phase III clinical trials (Table 2).

Surgery of visceral metastases may be appropriate for selected cases with good performance status and isolated tumour manifestations. In principal, the goal are R0-resections in these patients.

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

In general, stage IV melanoma patients need to be treated and discussed in an interdisciplinary tumour board at centres with broad experience in this disease.

patient information and follow-up

Melanoma patients should be instructed in avoidance of sunburns, extended unprotected solar or artificial ultraviolet exposure and in lifelong regular self-examinations of the skin and peripheral lymph nodes. Patients must be aware that family members have an increased melanoma risk [B].

During melanoma follow-up, patients are clinically monitored in order to detect a relapse and to recognize additional skin tumours, especially secondary melanomas, as

Table 2. Treatment modalities for melanoma metastases

Number and localization of the metastases	Treatment modalities[a]	Grade of recommendation
In-transit metastases (few) (pTXN2cM0)	1. Surgical removal	C
	2. Radiotherapy	C
In-transit metastases (multiple, >5) (pTXN2cM0)	1. Perfusion of the extremity[b]	DD
	2. Radiotherapy (systemic chemoimmunotherapy)[b]	D
Locoregional lymph nodes (pTxN1a,2a)	1. Consider trial participation	
	2. Additional Interferon alpha treatment[1]	B
Locoregional lymph nodes (pTxN2b,2c,3)	1. Radical lymphadenectomy, in case of incomplete resection: irradiation,	C
	2. Consider trial participation	C
Solitary central nervous system metastases (pTxNxM3)	1. Neurosurgical removal	D
	2. Stereotactic irradiation[b] (according to localization this could also be the 1st choice)	D
Solitary lung metastases (pTxNxM1)	1. Surgical removal	D
	2. Consider clinical trial participation	
	3. Chemotherapy/immunotherapy[b]	D
Multiple metastases (pTxNxM1a-1c)	1. Consider clinical trial participation	
	2. Chemotherapy / immunotherapy[b]	
Painful bone metastases (pTxNxM1a-1c)	1. Consider clinical trial participation	D
	2. Radiotherapy	C

[a]Given as 1st choice, 2nd choice and 3rd choice.

[b]These therapies should be restricted to controlled studies at specialized centres.

early as possible [B]. However, it is unknown if this policy leads to improved survival rates. Eight per cent of all melanoma patients develop a secondary melanoma within 2 years of their initial diagnosis. Melanoma patients also have increased risks for other skin tumours. In patients with lentigo maligna melanomas, 35% of the patients developed another cutaneous malignancy within 5 years.

There is currently no consensus on the frequency of follow-up and the use of imaging techniques. In recent series, most relapses have been detected by the patients themselves, questioning the usefulness and cost-effectiveness of follow-up visits every 3 months during the first 3 years and every 6–12 months thereafter. Above recommendations were solely based on the relapse-risk profile over time. Increased intervals between controls may reduce false positive findings and suffice for psychological support of the patients.

Since patients with a thin primary melanoma have only a small risk of relapse, routine imaging techniques are definitively not necessary for this patient population. In high risk patients, e.g. those with thick primary tumours or following treatment of metastases ultrasound of lymph nodes, CT or whole body PET/PET-CT scans may lead to an earlier diagnosis of regional or systemic relapses. However, an impact of radiological exams upon survival has not been demonstrated so far. Rising serum S-100 has a higher specificity for disease progression than LDH and therefore is the most accurate blood test in the follow-up of melanoma patients if any blood test is recommended at all [D].

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 experts.

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