European Journal of Cancer 63 (2016) 201–217

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline – Update 2016

Claus Garbe [a,*], Ketty Peris [b], Axel Hauschild [c], Philippe Saiag [d], Mark Middleton [e], Lars Bastholt [f], Jean-Jacques Grob [g], Josep Malvehy [h], Julia Newton-Bishop [i], Alexander J. Stratigos [j], Hubert Pehamberger [k], Alexander M. Eggermont [l] On behalf of the European Dermatology Forum (EDF) the European Association of Dermato-Oncology (EADO) and the European Organisation for Research and Treatment of Cancer (EORTC)

[a] *Centre for Dermatooncology, Department of Dermatology, Eberhard Karls University, Tuebingen, Germany*
[b] *Institute of Dermatology, Catholic University, Rome, Italy*
[c] *Department of Dermatology, University Hospital Schleswig-Holstein (UKSH), Campus Kiel, Kiel, Germany*
[d] *University Department of Dermatology, Université de Versailles-Saint Quentin en Yvelines, APHP, Boulogne, France*
[e] *NIHR Biomedical Research Centre, University of Oxford, UK*
[f] *Department of Oncology, Odense University Hospital, Denmark*
[g] *University Department of Dermatology, Marseille, France*
[h] *Melanoma Unit, Department of Dermatology, Hospital Clinic, IDIBAPS, Barcelona, Spain*
[i] *Section of Biostatistics and Epidemiology, Leeds Institute of Cancer and Pathology, University of Leeds, UK*
[j] *1st Department of Dermatology, University of Athens School of Medicine, Andreas Sygros Hospital, Athens, Greece*
[k] *University Department of Dermatology, Vienna, Austria*
[l] *Gustave Roussy Cancer Campus Grand Paris, Villejuif, France*

Received 13 May 2016; accepted 16 May 2016

KEYWORDS
Cutaneous melanoma;
Tumour thickness;
Excisional margins;
Sentinel lymph node dissection;

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 Organisation 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 using dermoscopy and staging

* *Corresponding author*: Center for Dermatooncology, University Department of Dermatology, Liebermeisterstr. 25, 72076 Tuebingen, Germany. Tel.: +49 7071 29 87110; fax: +49 7071 29 5187.
E-mail address: claus.garbe@med.uni-tuebingen.de (C. Garbe).

http://dx.doi.org/10.1016/j.ejca.2016.05.005

Interferon-α;
Adjuvant treatment;
Metastasectomy;
Systemic treatment

is based upon the AJCC system. CMs are excised with 1–2 cm safety margins. Sentinel lymph node dissection is routinely offered as a staging procedure in patients with tumours >1 mm in thickness, although there is as yet no clear survival benefit for this approach. Interferon-α treatment may be offered to patients with stage II and III melanoma as an adjuvant therapy, as this treatment increases at least the disease-free survival and less clear the overall survival (OS) time. The treatment is however associated with significant toxicity. In distant metastasis, all options of surgical therapy have to be considered thoroughly. In the absence of surgical options, systemic treatment is indicated. For first-line treatment particularly in *BRAF* wild-type patients, immunotherapy with PD-1 antibodies alone or in combination with CTLA-4 antibodies should be considered. BRAF inhibitors like dabrafenib and vemurafenib in combination with the MEK inhibitors trametinib and cobimetinib for *BRAF* mutated patients should be offered as first or second line treatment. Therapeutic decisions in stage IV patients should be primarily made by an interdisciplinary oncology team ('Tumour Board').

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 Organisation 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. This update has been initiated due to the substantial advances in the therapy of metastatic melanoma since 2009.

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. 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 specialities 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

Melanoma is a malignant tumour that arises from melanocytic cells and primarily involves the skin. Melanomas can also arise in the eye (uvea, conjunctiva and ciliary body), meninges and on various mucosal surfaces. While melanomas are usually heavily pigmented, they can be also amelanotic. Even small tumours may have a tendency to metastasise and thus lead to a relatively unfavourable prognosis. Melanomas account for 90% of the deaths associated with cutaneous tumours. In this guideline, we concentrate on the treatment of cutaneous melanoma (CM) [1–8].

1.3. Epidemiology and aetiology

The incidence of melanoma is increasing worldwide in white populations, especially where fair-skinned peoples receive excessive sun exposure [9–11]. In Europe the incidence rate is <10–25 new melanoma cases per 100,000 inhabitants; in the United States of America (USA) it is 20–30 per 100,000 inhabitants; and in Australia, where the highest incidence is observed, it is 50–60 per 100,000 inhabitants. In recent years there has been a dramatic increase in incidence in people over the age of 60 and especially in men in parts of Europe but the incidence in many parts of Europe continues to increase at all ages and is predicted to continue to increase for some time [12]. The commonest phenotypic risk factor is skin that tends to burn in the sun, and inherited melanocortin-1 receptor variant is the most important underlying genotype. Individuals with high numbers of common naevi and those with large congenital naevi, multiple and/or atypical naevi (dysplastic naevi) are at a greater risk and this phenotype is also genetically determined [13–16]. The inheritance of melanoma is in most cases seen in people with common lower risk susceptibility genes but; 5–10% of melanomas appear in melanoma-prone families who carry high penetrance susceptibility genes [17,18]. The most important exogenous factor is exposure to UV irradiation, particularly intermittent sun exposure [19–21].

1.4. Different subtypes of melanoma

The classical subtypes are distinguished by clinical and histopathological features. Furthermore, in recent years