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Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline – Update 2012

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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 (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization of Research and Treatment of Cancer (EORTC) 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 (SLND) is routinely offered as a staging procedure in patients with tumours more than 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

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an adjuvant therapy, as this treatment increases at least the disease-free survival (DFS) 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. BRAF inhibitors like vemurafenib for *BRAF* mutated patients as well as the CTLA-4 antibody ipilimumab offer new therapeutic opportunities apart from conventional chemotherapy. 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 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. 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. 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

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 towards metastasis and thus a relatively unfavourable prognosis. Melanomas account for 90% of the deaths associated with cutaneous tumours. In this guideline, we concentrate on cutaneous melanoma (CM).[1–7]

1.3. Epidemiology and aetiology

The incidence of melanoma is increasing worldwide in white populations, especially where fair-skinned peoples receive excessive sun exposure.[8,9] In Europe the incidence rate is <10–20 per 100,000 population; in the USA 20–30 per 100,000; and in Australia, where the highest incidence is observed, 50–60 per 100,000. Individuals with high numbers of common naevi and those with large congenital naevi, multiple and/or atypical naevi (dysplastic naevi) are at greater risk.[10–13] The inheritance of melanoma is in most cases polygenic; 5–10% of melanomas appear in melanoma-prone families.[14,15] In addition to these genetic and constitutional factors, the most important exogenous factor is exposure to UV irradiation, particularly intermittent sun exposure.[16–18]

1.4. Different subtypes of melanoma

The classical subtypes are distinguished by clinical and histopathological features. Furthermore, in recent years these subtypes have been associated with epidemiological parameters and particular patterns of mutation.

Four main classical subtypes of melanomas can be identified clinically and histologically[19–21]:

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 characterised 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