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Diagnosis and treatment of Merkel Cell Carcinoma. European consensus-based interdisciplinary guideline

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Abstract Merkel cell carcinoma (MCC) is a rare tumour of the skin of neuro-endocrine origin probably developing from neuronal mechanoreceptors. A collaborative group of multidisciplinary experts form 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 MCC diagnosis and management, based on a critical review of the literature, existing guidelines and expert's experience. Clinical features of the cutaneous/subcutaneous nodules hardly contribute to the diagnosis of MCC. The diagnosis is made by histopathology, and an incisional or excisional biopsy is

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mandatory. Immunohistochemical staining contributes to clarification of the diagnosis. Initial work-up comprises ultrasound of the loco-regional lymph nodes and total body scanning examinations. The primary tumour should be excised with 1–2 cm margins. In patients without clinical evidence of regional lymph node involvement, sentinel node biopsy is recommended, if possible, and will be taken into account in a new version of the AJCC classification. In patients with regional lymph node involvement radical lymphadenectomy is recommended. Adjuvant radiotherapy might be considered in patients with multiple affected lymph nodes of extracapsular extension. In unresectable metastatic MCC mono- or poly-chemotherapy achieve high remission rates. However, responses are usually short lived. Treatment within clinical trials is regarded as a standard of care in disseminated MCC.

1. Introduction

These guidelines have been written under the auspices of the European Dermatology Forum (EDF) and the European Association of Dermato-Oncology (EADO) in order to assist clinicians in treating patients with Merkel cell carcinoma (MCC) in Europe. The paper was initiated due to advances in the histological diagnosis and the prognostic classification of MCC with implications for treatment selection. The guidelines address aspects of MCC management, from the clinical and histological diagnosis of primary tumour to the systemic treatment of advanced or metastatic disease. It is hoped that this set of guidelines will assist healthcare providers in managing their patients according to the current standards of care and evidence-based medicine. It is not intended to replace national guidelines accepted in their original country. 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 modify the conclusions or recommendations in this report. In addition, it may be necessary to deviate from these guidelines for individual 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.

2. Methods

To construct this EDF–EADO–European Organization for Research and Treatment of Cancer (EORTC) guideline, an extensive search with terms 'Merkel cell carcinoma' using the PubMed, EMBASE and Cochrane Library databases was conducted (until 31st December 2014). Articles included systematic reviews, pooled analyses and meta-analyses. The search was restricted to English-speaking language publications. We also searched for existing guidelines on Merkel cell carcinoma in the databases mentioned above as well as in relevant websites (national agencies, medical societies). A subgroup among the authors produced a working draft that was extensively discussed at a consensus meeting and thereafter through email communication. In addition, the panel looked for concordances and differences among recently published guidelines (see Appendix A). Previous recommendations on distinct items (epidemiology, diagnosis, prognosis, treatment and follow-up) were discussed extensively in view of the available evidence-based data. Items that were agreed upon by our expert panel were adapted within our guideline proposal with appropriate reference. Items that differed from previously published guidelines or were originally recommended by our working group were clearly stated as proposed by the EADO consensus group. The guideline draft was circulated between panel members from EADO, EDF and EORTC before reaching its final form.

3. Definition

Merkel cell carcinoma (MCC) is a rare highly aggressive primary cutaneous carcinoma of the skin with epithelial and endocrine features. Its origin – neuroendocrine – is probably skin mechano-receptors; pluripotent stem cells or even lymphoid cells are likewise debated [3].

3.1. Epidemiology and aetiology

MCC annual age standardised incidence rate per million ranges from 2 to 4 in Europe and in the United States (US) to 8/million PY in Australia. It increased from 1980 to 2000 in US and in Europe [4–7]. This can be related to a true increased incidence by itself or caused by ageing of the population, increased sun exposure and/or improvement of diagnostic immunohistochemical tools as well as improved registration. MCC predominates in men (61.5%) and in the elderly with a median age at diagnosis around 76 years, 71.6% of patients being older than 70 [5,7]. MCC is an aggressive disease with an overall 10-year survival for patients estimated to 57.3% in US [7] and 47% in Europe [5].

The main factors known to be involved in MCC pathogenesis are:

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