European Journal of Cancer (2013) 49, 1324–1334

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.info

Low- and high-grade esthesioneuroblastomas display a distinct natural history and outcome

Gabriel G. Malouf [a,b,*], Odile Casiraghi [b], Eric Deutsch [a], Joel Guigay [c], Stéphane Temam [d], Jean Bourhis [a,*]

[a] Department of Radiotherapy, Institut de Cancérologie Gustave Roussy, Villejuif, France
[b] Department of Pathology, Institut de Cancérologie Gustave Roussy, Villejuif, France
[c] Department of Medicine, Institut de Cancérologie Gustave Roussy, Villejuif, France
[d] Department of Otorhinolaryngology-Head and Neck Surgery, Institut de Cancérologie Gustave Roussy, Villejuif, France

Available online 10 January 2013

KEYWORDS
Esthesioneuroblastoma
Outcome
Grading
Chemotherapy
Surgery
Leptomeningeal metastasis
ONB
Olfactory neuroblastoma

Abstract ***Purpose:*** Esthesioneuroblastomas, also called olfactory neuroblastomas (ENB) represent a rare sinonasal neurectodermal tumour which prognostic factors are unsteadily described.

Patients and methods: Clinical and pathological characteristics were analysed in patients treated at Gustave Roussy Institute between 1979 and 2009.

Results: Out of 63 patients, 19 patients were reclassified and 44 patients were eligible for the analysis. Multivariate analysis revealed that T staging of the modified Dulguerov TNM staging and Hyams grade > III (that we termed high-grade ENB) were the only independent prognostic factors for overall survival (OS). As compared to patients with low-grade ENB (Hyams grade ⩽ III), patients with high-grade ENB have higher T4 staging ($p = 0.02$), have frequent lymph node involvement ($p = 0.009$) and are more often unresectable ($p = 0.005$). Resected patients with high-grade ENB frequently displayed mainly leptomeningeal metastasis ($n = 4/6$) in contrast to patients with low-grade ENB who typically experience late locoregional recurrence ($n = 10/25$). With a median follow-up of 9.6 years, median DFS and OS for resected low-grade ENB were 5.4 and 20.5 years, respectively. Conversely, median DFS and OS for high-grade ENB were 1.5 and 2.5 years, respectively.

Conclusion: Low and high-grade ENB display distinct patterns at presentation and relapse, leading to different prognosis. Therefore, they may be regarded as distinct entities.

* *Corresponding author*s. Address: Department of Radiotherapy, Institut de Cancérologie Gustave Roussy, Villejuif, France (J. Bourrhis); Department of Pathology, Institut de Cancérologie Gustave Roussy, Villejuif, France (G.G. Malouf). Tel.: +33 1 42 11 49 31; fax: +33 1 42 11 53 00.
E-mail addresses: gabriel.malouf@gmail.com (G.G. Malouf), jean.bourhis@igr.fr (J. Bourhis).

0959-8049/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejca.2012.12.008

1. Introduction

Esthesioneuroblastoma, also called olfactory neuroblastoma (ENB) is a rare neuroectodermal tumour arising from the olfactory mucosa of the upper nasal tract, in the region of the cribriform plate of the ethmoid bone. The first case was reported by Berger in 1924 as *an* "*esthésioneuroblastome olfactif*"[1]. So far, no precise epidemiological studies have been reported, but ENB has a peak incidence between the 5th and 6th decade of life, although some authors have reported two peaks, the first between 11 and 20 years and the second between 50 and 60 years.[2,3] Since the first description of this entity, there are two classification systems commonly used in the literature, aiming to better predict a disease-free status and overall survival (OS).[4,5] Kadish and co-workers, from the Massachusetts General Hospital proposed a classification system based on their experience of 17 cases of ENB diagnosed between 1941 and 1971.[4] ENB were classified into three groups: A (extension to the nasal cavity only), B (extension to the nasal and paranasal cavity) and C (extension beyond the paranasal cavity). This simple classification gained tremendous success which led to its use in most reported series of ENB. However, the inadequacies of this classification have been pointed out by several authors.[5–9] Based on their experience of 26 cases treated at UCLA over 30 years ago, Dulguerov and Calcetta proposed a new classification system based on TNM staging in 1992.[5] The advantage of this classification is that tumours are classified taking into account lymph node involvement and distant metastasis. This work prompted the conduct of a meta-analysis comparing outcomes after different treatment modalities.[8] In contrast to the 5-year survival rate of around 70% in the largest series, surprisingly this meta-analysis found a 5-year survival rate of 45%.[8]

It has been emphasised that some patients present with advanced tumours with an indolent evolution, while others die within a year of the diagnosis. Local recurrence rates vary widely in the literature from 16% to 40%, and distant metastasis from 0% to 60%.[8–11] These discrepancies led to a lack of consensus regarding optimal treatment management. An explanation might be related to the inclusion of patients with different histopathological grades of ENB and/or with other misdiagnosed tumours such as sinonasal undifferentiated carcinomas (SNUC) or sinonasal endocrine carcinomas (SNEC), especially before the introduction of immunohistochemistry in the early 80s.

At the histopathological level, ENB typically presents as a lobulated tumour surrounded by sustentacular cells, with rosettes, pseudo-rosettes, calcifications and a fibrillar matrix in some areas. All these histopathological features were taken in account by Hyams who proposed a histological grading system for ENB in 1976.[12] A limitation of this grading system is its semi-quantitative nature and the fact that it relies on a four-tier grading scale based on lobular architecture, mitosis, nuclear pleomorphism, neurofibrillary matrix, necrosis, calcifications, rosettes and pseudo-rosettes. It is complex to use, especially in borderline cases encompassing grade III and IV. This is one reason why, in order to correlate the grade with outcomes, many studies tend to separate ENB into low-grade (Hyams I and II) and high-grade (Hyams III and IV) lesions thereby hampering optimal clinical management.[8,10,13,14]

The optimal treatment of ENB remains controversial. Surgery followed by radiotherapy is considered by most expert centres as the standard of care, but the impact of neoadjuvant and adjuvant chemotherapy remains unknown.[15,16] Moreover, the relevance of regional lymph node dissection and/or radiotherapy remains controversial.[10,17,18]

To better understand the clinico-biological behaviour of ENB, we undertook a retrospective analysis of all cases treated at the Gustave Roussy Cancer Institute over the last 30 years. Our methodology is different from the previous reports, since our aim was to describe the kinetics, patterns of recurrence and the outcome of ENB with pathologically confirmed diagnoses and grading according to Hyams histologic system. In addition, we propose a new classification system based on a revision of Hyams histological grading system. In this study, tumours are divided into two subtypes, low-grade and high-grade ENB, according to both kinetics and patterns of relapse and OS.

2. Patients and methods

2.1. Patient selection

We searched the Gustave Roussy Cancer Institute pathology database for all ENB treated at our institution since the 1st January 1979 until 30th June 2009 ($n = 84$). All medical reports were reviewed for the following clinical data: age, diagnosis, risk factors, symptoms at presentation, previous medical history, surgery, chemotherapy, radiotherapy, kinetics and patterns of relapse and outcome. All the cases with missing clinical data ($n = 3$) or unavailable material for histopathological reassessment of the tumour were excluded ($n = 18$). The radiotherapy fields and the chemotherapy regimens were also extracted.

2.2. Pathology selection

All available Haematoxylin–Eosin (HE) or Haematoxylin–Eosin–Safran (HES) slides of the 63 patients who fulfilled criteria were reviewed by an expert Head and Neck (O.C.) pathologist, who was unaware of the clinical outcome and lesions were scored based on Hyams histological grading system.[12] In all atypical