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MAIN ARTICLE

Olfactory event-related potentials: a new approach for the evaluation of olfaction in nasopharyngeal carcinoma patients treated with chemo-radiotherapy

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Abstract

Objective: Olfactory dysfunction is a possible side effect of chemo-radiotherapy performed in patients affected by nasopharyngeal carcinoma. Self-rating measurements and olfactory event-related potentials were used and compared in order to evaluate the impact of this treatment on the olfactory system.

Methods: Nine patients underwent subjective evaluation of olfactory function (using visual analogue scales for olfactory symptoms and quality of life, and a six-item Hyposmia Rating Scale), and a quantitative and objective measurement (olfactory event-related potentials).

Results: Spearman's rank correlation analyses highlighted significant relationships between the clinical scales and olfactory event-related potentials. Inter-group analyses showed significant differences in the latency and in the amplitude of olfactory event-related potentials between patients and controls.

Conclusion: Taking into account the small sample size and the lack of pre-treatment assessment, olfactory event-related potentials seemed to allow a more objective diagnosis of unilateral and bilateral olfactory loss. Moreover, olfactory event-related potentials and subjective scales results were concordant.

Key words: Somatosensory Evoked Potentials; Radiotherapy; Chemotherapy; Nasopharyngeal Carcinoma; Olfactory Perception

Introduction

Nasopharyngeal carcinoma (NPC) arises from the epithelium of the nasopharynx.[1] The worldwide average incidence of NPC is less than 1 per 100 000 population.[2] However, in some areas of China, its incidence is 20 per 100 000.[3–5]

Radiotherapy is considered the 'gold standard' treatment for patients affected by NPC because of the anatomical site of the nasopharynx and the radiosensitivity of NPC. The advent of intensity-modulated radiotherapy has decreased the incidence of side effects, whilst maintaining the same efficacy of traditional techniques.[6,7] Today, a combined therapeutic approach with the addition of chemotherapy (concurrent, neo-adjuvant or adjuvant) to radiotherapy for patients affected by locally advanced disease is preferred. This has led to a drop in treatment failures and improved prognosis.[8–12] The most active and most used chemotherapeutic agents for the treatment of NPC patients are cisplatin, carboplatin, epirubicin, bleomycin, methotrexate and fluorouracil (5-FU).[13]

Life expectancy of these patients and, consequently, post-treatment morbidity, has increased: a higher incidence of oral mucositis, dysphagia, xerostomia, and olfactory and gustatory function deterioration has been registered.[14–16]

Despite the impact on quality of life (QoL), little attention has been given to olfactory impairment. It is known from literature that several chemotherapy drugs used in the treatment of NPC could cause olfactory dysfunction as a side effect.[17] At the same time, radiotherapy for head and neck cancers could have a direct effect on receptors and on the nerve fibres of olfactory pathways.[18–20] Furthermore, although the radiation dose to the olfactory region has decreased significantly with the use of intensity-modulated radiotherapy, some patients still complain of post-treatment olfactory dysfunction.

Olfactory function can be assessed using numerous psychophysical tests and some subjective scales, such as visual analogue scales (VAS) and the six-item Hyposmia Rating Scale.[21] A more objective

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assessment of the integrity of olfactory pathways can be obtained via olfactory event-related potentials, an electrophysiological technique that allows the assessment of changes in olfactory function.

Olfactory event-related potentials are the result of sequential activation of different structures. The transmission of olfactory sensory input travels from the olfactory neuroepithelium located in the nasal cavities towards the olfactory bulbs, through the first cranial nerves, where contact is made with second-order neurons (dendrites of mitral and tufted cells within glomeruli). From here, the post-synaptic fibres that form the olfactory tracts project to the primary olfactory areas, which comprise the anterior olfactory nucleus, tenia tecta, olfactory tubercle, piriform cortex, amygdale, anterior cortical amygdaloid nucleus, and periamygdaloid and entorhinal cortices. The piriform cortex is connected to the thalamus, hypothalamus and orbitofrontal cortex, and the entorhinal cortex is connected to the hippocampus. The thalamus has connections towards secondary olfactory areas, such as the orbitofrontal and insular cortices.[22–25]

Few studies have been conducted to assess the impact of chemotherapy and radiotherapy on the olfactory system. We are not aware of any studies that have assessed olfactory function in patients affected by locoregionally advanced NPC, who were treated with neo-adjuvant chemotherapy followed by radiotherapy and concurrent chemotherapy. For this reason, our team opted for the use of self-rating measurements and olfactory event-related potentials in order to evaluate the impact of chemo-radiotherapy on the olfactory system.

Materials and methods

Study population

Thirty-one patients with histopathologically confirmed non-keratinising carcinoma of the nasopharyngeal region were followed up in the Department of Otorhinolaryngology at the University of Messina from February 2010 to June 2013.

According to the 7th edition of the American Joint Committee on Cancer staging system,[26] the disease distribution was as follows: stage I, 2 patients (6.4 per cent); stage II, 4 patients (12.9 per cent); stage III, 11 patients (35.4 per cent); stage IVa, 5 patients (16.1 per cent); stage IVb, 5 patients (16.1 per cent); and stage IVc, 4 patients (12.9 per cent).

The inclusion criteria were: locoregionally advanced disease, in particular tumour–node–metastasis stages III (T_{3-4},N_{0-1},M_0) and IVa (T_4,N_0,M_0 or T_{1-4}, N_2,M_0); patients who had received chemo-radiotherapy performed with the same protocol; and regular follow up after initial therapy.

The exclusion criteria were: nasal diseases such as persistent allergic rhinitis, and acute or chronic rhinosinusitis; nasal polyps; severe nasal deformity; upper respiratory tract infections; pregnancy; and patients on steroids or other drugs that may affect sense of smell.

Six radiotherapy treated patients with early stage disease (stages I or II), seven chemotherapy treated patients affected by metastatic disease (stages IVb–c), five dead patients (one with stage III, one with stage IVb and three with stage IVc disease), and one patient (with stage IVa disease) with residual lesions after combined therapy, were excluded from the study.

In line with the inclusion and exclusion criteria, 12 patients with a diagnosis of locoregionally advanced (stages III or IVa) nasopharyngeal carcinoma (NPC) were enrolled in our study. Subsequently, three patients were excluded, as they could not be followed up regularly (two with stage III and one with stage IVa disease).

Overall, 9 patients (all males), with a mean age of 55.0 ± 9.96 years, and 9 healthy controls (all males), with a mean age of 52.56 ± 8.56 years, were enrolled in the study. Seven patients (77.77 per cent) had stage III disease and two patients (22.22 per cent) had stage IVa disease.

All patients received neo-adjuvant chemotherapy and concurrent platinum-based chemo-radiotherapy using intensity-modulated radiotherapy. The primary tumour with direct extensions (including metastatic retropharyngeal lymph nodes) was defined as gross tumour volume (gross tumour volume 1), and received a dose of 60–69 Gy, with an average of 225 cGy per day. Metastatic cervical lymph nodes were defined as gross tumour volume 2, and received a dose of 50–54 Gy, with an average of 200 cGy per day. Gross tumour volume 1 included the olfactory region in all patients. All fields were treated once daily, five times a week, with varying treatment plans according to tumour volume and cancer stage.

Three cycles of neo-adjuvant chemotherapy were administered during radiation planning, with the intent to prevent disease progression. All patients underwent the following chemotherapeutical protocol: docetaxel 75 mg/m^2 (1st day of cycle), cisplatin 75 mg/m^2 (1st day of cycle) and fluorouracil 750 mg/m^2 (continuous infusion from 1st to 4th day of cycle) administered for 3 cycles every 21 days. Concurrent chemotherapy with cisplatin 100 mg/m^2 (1st day of cycle) was continued during the period of radiotherapy and limited to 3 cycles, repeated every 21 days.

At enrolment, all patients, who presented with a mean disease-free survival time of 44.77 ± 25.93 months, completed a questionnaire that included questions on: sociodemographic characteristics, cigarette and alcohol use, general diseases (diabetes mellitus, hypertension, heart disease, liver disease and cancer), ongoing medical treatments, and occupational hazards. Furthermore, information on positivity for Epstein–Barr virus and cranial nerve involvement was collected.

Self-rating scales on olfactory function were administered. A VAS was used to measure olfactory

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dysfunction; scores ranged from 0 to 10, where 0 indicated complete olfactory loss and 10 indicated normal function. The impact of olfactory dysfunction on QoL was evaluated using a VAS; scores ranged from 0 to 10, where 0 indicated a significant impact on QoL and 10 indicated no impact on QoL. The six-item Hyposmia Rating Scale was also administered: patients were asked to answer six questions by choosing among five options (with option one giving a score of 1, option two giving a score of 2 and so on) for each question. A final score, ranging from 6 (high sense of smell) to 30 (low sense of smell), was obtained.[21] The presence of parosmia or phantosmia was also recorded.

All subjects also underwent olfactory event-related potential testing. All demographic and clinical data are shown in Table I.

The present study was approved by the local ethics committee and written informed consent was obtained from all patients.

Olfactory event-related potentials

All measurements were performed at the Istituto di Ricovero e Cura a Carattere Scientifico ('IRCCS') Centro Neurolesi 'Bonino Pulejo' of Messina, Italy. A selective, controlled stimulation of the olfactory system, to elicit olfactory event-related potentials, was achieved using a computer-controlled Olfactometer OM2S (Burghart Medical Instruments, Wedel, Germany), linked directly to an electroencephalogram (EEG) recorder (Micromed Brain Quick, 32-channel system; Micromed, Treviso, Italy).

TABLE I
DEMOGRAPHIC AND CLINICAL DATA OF NASOPHARYNGEAL CARCINOMA PATIENTS

Parameter	Value
Patients (*n*)	9
Gender (*n*)	
– Male	9
– Female	0
Age (mean ± SD; years)	55.0 ± 9.96
Months from diagnosis (mean ± SD)	50.66 ± 9.99
Disease-free survival (mean ± SD; months)	44.77 ± 25.93
Olfactory symptom VAS score (mean ± SD)	5.66 ± 3.64
Hyposmia Rating Scale score (mean ± SD)	16.55 ± 10.00
QoL VAS score (mean ± SD)	4.33 ± 3.87
Olfactory ERPs (*n* (%))	
– Absence: anosmic	2 (22)
– Presence (unilateral): hyposmic	2 (22)
– Presence (bilateral): normosmic	5 (56)
NPC stage (*n* (%))	
– III	7 (78)
– IVa	2 (22)
EBV (*n* (%))	
– Presence	9 (100)
– Absence	0 (0)
Cranial nerve involvement (*n* (%))	
– Presence	1 (11)
– Absence	8 (89)
Comorbidity (*n* (%))	
– High BP, DM, dysthyroidism monoclonal gammopathy & hypercholesterolaemia	1 (11)
– Hypertension	2 (22)
– Renal cancer & encephalopathy	1 (11)
– None	5 (56)

SD = standard deviation; VAS = visual analogue scale; QoL = quality of life; ERP = event-related potential; NPC = nasopharyngeal carcinoma; EBV = Epstein–Barr virus; BP = blood pressure; DM = diabetes mellitus

A succession of 40 randomised olfactory stimuli, using phenyl ethyl alcohol (40 per cent v/v; Labochem Science, Sant'Agata li Battiati, Italy) and hydrogen sulfide in nitrogen (4 ppm; Rivoira, Milan, Italy) as odorants, was presented through a Teflon nasal outlet (4 mm lumen tube), which was placed into the nasal vestibule. Subjects were asked to breathe normally through their mouth.[22–25] A constant level of vigilance was maintained by asking subjects to avoid eye blinking. The stimuli were presented whilst the patients were lying down, in a well-ventilated room. During the recording session, subjects were isolated from ambient noise, with a 70 dB constant binaural white noise administered through headphones. The duration of each stimulus was 200 ms and the inter-stimulus interval was 40 seconds.

The EEG was recorded from three scalp electrodes placed along the midline (at Fz, Cz and Pz positions of the international 10–20 system). The reference electrode was placed on the earlobe (A2) and the ground electrode on the forehead. Eye movements and blinks were monitored using an electro-oculogram, obtained by positioning an electrode above the right eyebrow. Other muscle artifacts were monitored and discarded. The data were band-pass filtered at 0.01–30 Hz and a notch filter was used. The EEG activity was averaged from 500 ms in the pre-stimulus period to 2000 ms in the post-stimulus period. Olfactory event-related potentials were obtained by averaging artifact-free EEG epochs.[22–25]

Olfactory event-related potentials consist of a large negative N1 component, followed by a large positive component, P2. The P2 component is often described as a complex consisting of two distinct components, P2 and P3. An initial positive P1 component is not always present. The early olfactory event-related potential components (N1 and P1) reflect the exogenous cortical activity related to sensory input. The later olfactory event-related potential components, such as P2, reflect endogenous cortical activity, related to cognitive processing. Several papers have confirmed that the P2 component occurs between 530 and 800 ms after stimulus onset, with an amplitude of 5–20 μV. Olfactory event-related potential components present maximal amplitudes at the Cz and Pz electrode sites.[22–25] The parameters of olfactory event-related potential components (latency and amplitude) are influenced by several experimental and demographic variables (including age and gender).

The analysis of olfactory event-related potentials was conducted separately for the right and left nostrils (depending on stimulation side), and two recordings (one per side) were obtained for each patient. Latencies were measured at the first negative peak

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(N1) and at the second positive peak (P2). Amplitude was measured from the peak of N1 to the peak of P2. The latencies and amplitudes for NPC patients were compared with those for healthy control subjects, matched in age, sex and smoking habits, recorded in the same conditions.

Olfactory event-related potentials were considered absent when it was not possible to distinguish clear responses from background noise in an artifact-free recording. Patients who showed N1/P2 bilateral responses were considered normosmic. Conversely, the bilateral absence of N1 and P2 waveforms indicated a severe olfactory loss (anosmia). Finally, N1 and P2 waveform presence on one side only was considered a condition of partial olfactory loss (hyposmia).[23–25]

Statistical analysis

Olfactory event-related potential latencies and amplitudes (for each stimulation side), and clinical scale scores, were determined for all patients. Descriptive statistics were used to analyse the patient data and the scores obtained for each clinical scale (VAS for olfactory symptoms and for QoL, and six-item Hyposmia Rating Scale). The Mann–Whitney U test was used to compare patients' and control subjects' olfactory event-related potential latencies and amplitudes according to scalp distribution (Fz, Cz, Pz) (inter-group analysis). The Spearman's rank correlation coefficient was used to assess whether there was a relationship between the olfactory symptoms VAS and six-item Hyposmia Rating Scale and: (1) the latencies and amplitudes of the main olfactory event-related potential components; (2) the absence (score of 0), the unilateral presence (score of 1) and the bilateral presence (score of 2) of olfactory event-related potentials; and (3) the QoL VAS. Correlations were generally considered as of low statistical significance if r was 0.4 or lower, of moderate significance if r was 0.4–0.8, and of strong significance if r was over 0.8.

Statistical analyses were performed using the R3.0 statistical software package (Foundation for Statistical Computing, Vienna, Austria). A 95 per cent confidence level was set, with a 5 per cent alpha error. Statistical significance was set at $p < 0.05$.

Results

Five of the nine nasopharyngeal carcinoma (NPC) patients showed bilateral presence of olfactory event-related potentials. Two NPC patients showed unilateral presence of olfactory event-related potentials. A complete lack of response to odorants (bilateral absence of olfactory event-related potentials) was recorded in the remaining two NPC patients. All of the healthy control subjects had P2 latency and N1–P2 amplitude values within the normal range.[22–25] Examples of patients' olfactory event-related potential waveforms are shown in Figure 1.

The inter-group analysis revealed significant differences in: P2 latency for the right stimulated side (right nostril) at Fz ($p = 0.002$), Cz ($p = 0.002$) and Pz ($p = 0.006$); and in N1–P2 amplitude for the right nostril at Cz ($p = 0.02$) (Tables II and III). In patients with bilateral presence of olfactory event-related potentials, there were significant differences in P2 latency at: Fz, right and left nostrils ($p = 0.004$ and $p = 0.026$); Cz, right nostril ($p = 0.005$); and Pz, right and left nostrils ($p = 0.013$ and $p = 0.026$). In cases of unilateral presence of olfactory event-related potentials, N1–P2 amplitude was significantly lower in the patient group (compared with the healthy controls) (Fz, right and left nostrils ($p = 0.041$ and $p = 0.043$); Cz, right and left nostrils ($p = 0.044$ and $p = 0.043$); and Pz, left nostril ($p = 0.044$)).

Subjective olfactory loss was indicated in 44 per cent of NPC patients based on six-item Hyposmia Rating Scale scores, and in 75 per cent of NPC patients according to olfactory symptom VAS scores (Figure 2).

Spearman's rank correlation analyses (Tables IV and V) highlighted significant negative relationships between the olfactory symptoms VAS and P2 latency for the right stimulated side (right nostril) at Fz (rho = −0.86; $p = 0.03$) and for the right nostril at Cz (rho = −0.85; $p = 0.03$). In addition, significant positive correlations were found between the six-item Hyposmia Rating Scale and P2 latency for the right nostril at Fz (rho = 0.82; $p = 0.04$) and for the right nostril at Cz (rho = 0.84; $p = 0.03$) (Table IV).

The findings also revealed a significant negative correlation between olfactory event-related potentials and the six-item Hyposmia Rating Scale (rho = −0.731; $p = 0.025$), and a significant positive correlation between olfactory event-related potentials and the olfactory symptoms VAS (rho = 0.83; $p = 0.005$). Finally, a highly significant correlation was found between the olfactory symptoms VAS and the QoL VAS (rho = 0.957; $p < 0.001$), and between the six-item Hyposmia Rating Scale and the QoL VAS (rho = −0.973; $p < 0.001$).

Discussion

Chemo-radiotherapy for nasopharyngeal carcinoma (NPC) is associated with several acute and chronic side effects. Because of the close anatomical relations between the nasopharynx and olfactory regions, and given the high radiation dose needed to control NPC, olfactory loss is a possible consequence of treatment. Although the use of intensity-modulated radiotherapy has reduced the dose of rays directed to the olfactory region, several cases of olfactory dysfunction associated with radiotherapy have still come to our attention.

Some previous studies demonstrated a deterioration of olfactory threshold in patients who had undergone radiotherapy for NPC.[19,20] One of these studies[20] was based on an odour identification and discrimination test, the screening Sniffin' Sticks test. This non-invasive method involved the administration of felt-tip pens impregnated with different odours.[27] On the

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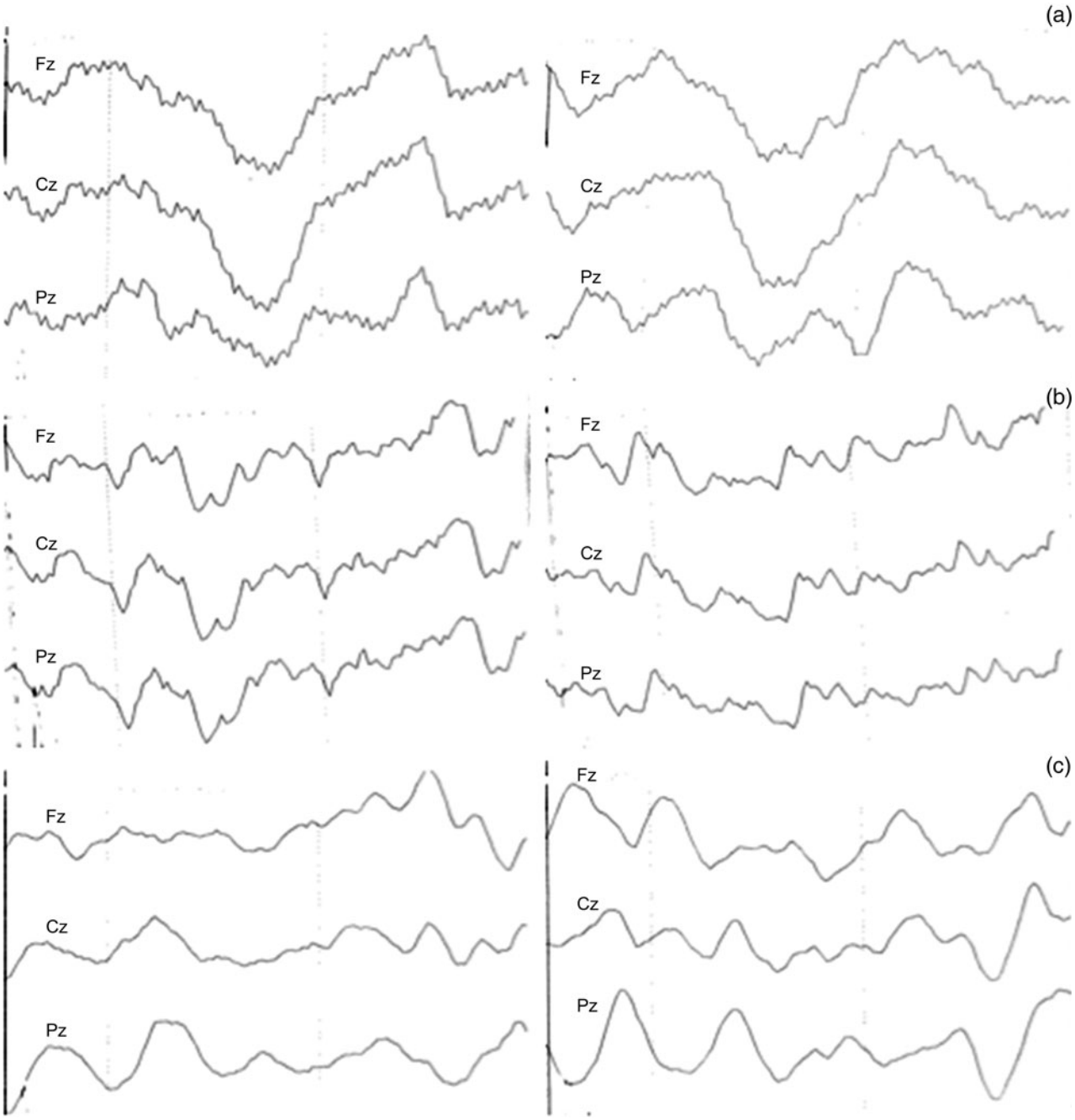

FIG. 1

Averaged olfactory event-related potential waveforms, at Fz, Cz and Pz scalp regions (band-pass filtered at 0.01–30 Hz, from 500 ms pre-stimulus to 2000 ms post-stimulus), of: (a) nasopharyngeal carcinoma (NPC) patient with bilateral olfactory responses, showing normal latencies and amplitudes; (b) NPC patient without olfactory responses; and (c) NPC patient with unilateral olfactory responses.

basis of this approach, Ho *et al.* stated that olfactory change in radiotherapy treated NPC patients was most likely due to sensorineural damage.[20] Bramerson *et al.* evaluated NPC patients by administering odour-detection sensitivity and olfactory identification tests, and highlighted a reduction of function after radiotherapy.[19] Conversely, Hölscher *et al.* reported a non-significant change of olfactory thresholds in patients affected by head and neck cancer, and stated that the olfactory epithelium is relatively resistant against the effects of radiation.[28]

Additional effects on the olfactory bulb and/or orbitofrontal cortex have been hypothesised on the basis of recorded changes of suprathreshold olfactory function. In particular, Hua *et al.* reported that suprathreshold olfactory function defects recorded in their research could not be fully attributed to the absolute olfactory threshold impairment, but had neurological and psychological causes too.[18]

Finally, olfactory toxicity induced by chemotherapy has also been reported. Nakamura *et al.* found decreased olfactory function in patients treated with

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TABLE II
COMPARISON OF OLFACTORY EVENT-RELATED POTENTIAL COMPONENT LATENCIES BETWEEN NPC PATIENTS AND CONTROLS

ERP component	Patients		Controls		p (Mann–Whitney U test)
	Median	Range	Median	Range	
N1 (scalp region)					
– Fz, right	615.00	606.77–682.37	630.00	607.07–650.34	0.86
– Cz, right	626.00	610.00–657.00	630.00	617.25–642.50	0.91
– Pz, right	633.00	622.00–667.00	630.00	618.75–642.00	0.60
– Fz, left	632.50	613.00–648.00	645.00	622.25–654.25	0.26
– Cz, left	639.00	620.00–645.00	648.00	635.50–657.25	0.14
– Pz, left	640.00	630.00–644.00	648.00	632.00–664.75	0.34
P2 (scalp region)					
– Fz, right	754.50	752.00–760.00	712.00	700.00–721.25	0.002*
– Cz, right	761.50	750.00–780.00	710.00	700.00–722.00	0.002*
– Pz, right	775.00	768.00–780.00	720.00	700.00–735.25	0.006*
– Fz, left	742.50	730.00–750.00	720.00	711.50–740.00	0.07
– Cz, left	740.00	730.00–750.00	721.00	710.00–744.75	0.34
– Pz, left	751.00	750.00–757.00	737.00	724.50–747.75	0.09

Data represent latencies (milliseconds), unless indicated otherwise. *$p < 0.05$. NPC = nasopharyngeal carcinoma; ERP = event-related potential

tegafur, a precursor of fluorouracil.[29] Other authors have focused on cisplatin toxicity: subjective olfactory function impairment has been reported by a considerable number of patients.[30,31] However, objective studies have failed to show this cisplatin-induced side effect.[32,33]

Our study evaluated olfactory function using olfactory event-related potentials and self-rating scales in chemo-radiotherapy treated NPC patients. To our knowledge, this is the first study to use olfactory event-related potentials and evaluate interdependence between subjective and electrophysiological methods in these patients. Compared to previous studies, based only on subjective methods, a more objective olfactory dysfunction was found.

It is hypothesised that NPC patients with unilateral or bilateral absence of olfactory responses were affected by damage to the olfactory pathways (peripheral and/or central) of different grades due to varying individual susceptibility to chemo-radiotherapy. In fact, partial or severe olfactory loss was found in four of nine NPC patients who did not demonstrate unilateral or bilateral olfactory event-related potentials. Where olfactory event-related potentials were present in NPC patients, a trend towards increased P2 latency and decreased N1–P2 amplitude compared to control subjects was found. These results highlight the capability of olfactory event-related potentials to identify even slight functionality changes of the olfactory system.[22–25]

There was a high degree of consistency between subjective and objective assessments of smell, in line with other authors' experience.[34] However, the correlation between olfactory event-related potentials and the olfactory symptoms VAS and six-item Hyposmia Rating Scale was only significant for the P2 latencies at Fz and at Cz on the right stimulated side. This finding seems to be related mainly to the small sample size, and, therefore, to the specific olfactory dysfunction of certain patients.

Patients with an absence of olfactory responses presented with very low olfactory symptoms VAS scores and very high six-item Hyposmia Rating Scale scores. Conversely, the presence of olfactory responses was associated with higher olfactory symptoms VAS scores and lower six-item Hyposmia Rating Scale scores. Moreover, a highly significant correlation between clinical scales and QoL VAS was found,

TABLE III
COMPARISON OF OLFACTORY EVENT-RELATED POTENTIAL COMPONENT AMPLITUDES BETWEEN NPC PATIENTS AND CONTROLS

P2 (scalp region)	Patients		Controls		p (Mann–Whitney U test)
	Median	Range	Median	Range	
Fz, right	3.75	1.50–7.50	7.00	6.00–7.32	0.12
Cz, right	5.25	2.50–7.70	9.20	8.17–10.05	0.02*
Pz, right	3.50	2.00–6.00	5.80	5.00–7.20	0.09
Fz, left	4.25	2.50–7.70	6.00	5.72–7.00	0.34
Cz, left	4.25	3.00–8.00	8.30	6.75–8.52	0.06
Pz, left	4.00	4.00–5.00	5.80	4.82–6.20	0.05

Data represent amplitudes (μV), unless indicated otherwise. *$p < 0.05$. NPC = nasopharyngeal carcinoma

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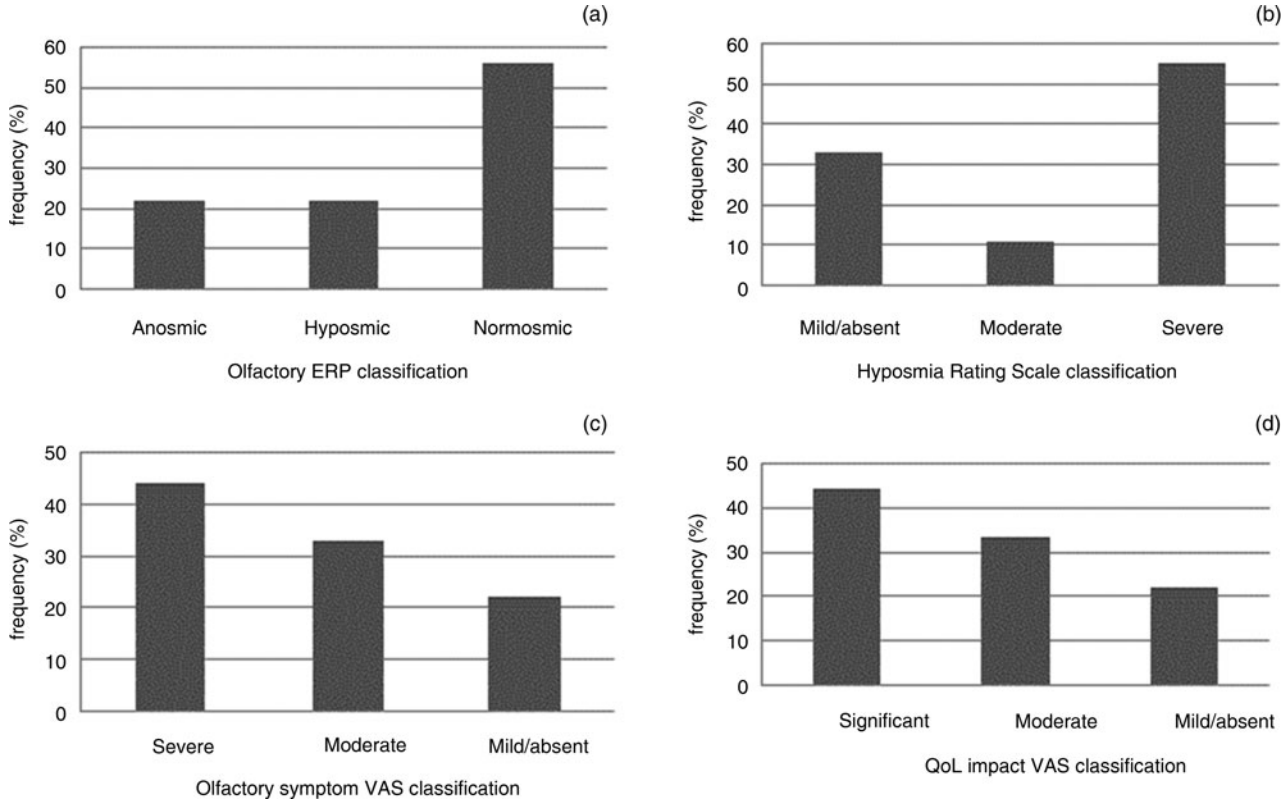

FIG. 2

Frequencies of anosmic, hyposmic and normosmic patients, according to: (a) olfactory event-related potentials (ERPs) (anosmic = N1 and P2 bilaterally absent, hyposmic = N1 and P2 only in one nostril, and normosmic = N1/P2 bilateral responses); (b) Hyposmia Rating Scale scores (score of 23–30 = severe hyposmia (insufficient olfaction), 14–22 = moderate hyposmia, and 6–13 = mild or absent hyposmia (satisfactory olfaction)); (c) olfactory symptom visual analogue scale (VAS) scores (score of 0–3 = severe olfactory dysfunction (insufficient olfaction), 4–6 = moderate, and 7–10 = mild/absent (satisfactory olfaction)); and (d) quality of life (QoL) VAS scores (score of 0–3 = significant impact on QoL, 4–7 = moderate, and 8–10 = mild or absent (minimal impact on QoL)).

showing that olfactory dysfunction negatively affected QoL.

The main limitations of this study are the small sample size and the absence of pre-treatment evaluations. Furthermore, psychophysical evaluations were not performed in our patients. Nevertheless, the homogeneity of the clinical and therapeutic features of the sample, and the use of olfactory event-related potentials, make this research original. In particular, the results indicate that olfactory event-related potentials are a reliable tool that may be used in addition to the Sniffin' Sticks test within a diagnostic protocol.

TABLE IV
SPEARMAN'S RANK CORRELATION BETWEEN SELF-RATING SCALES AND OLFACTORY EVENT-RELATED POTENTIAL COMPONENT LATENCIES

ERP component	Latency (mean ± SD; ms)	Olfactory symptom VAS		Hyposmia Rating Scale	
		Rho	*P*	Rho	*P*
N1 (scalp region)					
– Fz, right	632.17 ± 33.62	−0.554	0.253	0.497	0.315
– Cz, right	634.17 ± 33.12	−0.661	0.153	0.699	0.122
– Pz, right	648.00 ± 41.60	−0.704	0.119	0.690	0.129
– Fz, left	629.33 ± 21.14	0.006	0.991	−0.208	0.693
– Cz, left	632.17 ± 18.77	−0.166	0.753	0.088	0.868
– Pz, left	634.00 ± 17.88	−0.099	0.853	0.059	0.911
P2 (scalp region)					
– Fz, right	760.17 ± 20.61	−0.859	0.028*	0.823	0.044*
– Cz, right	765.50 ± 27.38	−0.845	0.034*	0.842	0.035*
– Pz, right	776.00 ± 31.47	−0.704	0.118	0.700	0.121
– Fz, left	738.17 ± 14.00	0.211	0.688	0.194	0.712
– Cz, left	738.00 ± 16.73	0.550	0.258	−0.190	0.718
– Pz, left	749.83 ± 22.59	0.017	0.975	0.385	0.450

*$p < 0.05$. ERP = event-related potentials; SD = standard deviation; VAS = visual analogue scale

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TABLE V
SPEARMAN'S RANK CORRELATION BETWEEN SELF-RATING SCALES AND OLFACTORY EVENT-RELATED POTENTIAL COMPONENT AMPLITUDES

P2 (scalp region)	Amplitude (mean ± SD; μV)	Olfactory symptom VAS		Hyposmia Rating Scale	
		Rho	*p*	Rho	*P*
– Fz, right	4.33 ± 2.94	0.628	0.182	−0.716	0.109
– Cz, right	5.37 ± 2.29	0.623	0.186	−0.665	0.149
– Pz, right	3.97 ± 2.29	0.513	0.298	−0.535	0.273
– Fz, left	4.87 ± 2.72	0.680	0.137	−0.698	0.123
– Cz, left	5.25 ± 2.64	0.639	0.171	−0.618	0.191
– Pz, left	4.47 ± 0.86	0.552	0.256	−0.460	0.358

SD = standard deviation; VAS = visual analogue scale

An increased sample size and the recruitment of patients who have received only chemotherapy or radiotherapy could provide more details on the aetiopathogenesis of olfactory dysfunction. Moreover, localisation of the affected site of the olfactory pathway may be possible by analysing the olfactory event-related potential waveforms from each electrode. In addition, comparative analysis with psychophysical measures could further validate the use of olfactory event-related potentials.

- **Olfactory loss is a possible consequence of chemo-radiotherapy**
- **This is due to the anatomical closeness of nasopharynx and olfactory regions, and the high radiation dose needed to control nasopharyngeal carcinoma (NPC)**
- **Olfactory function can be assessed using numerous psychophysical tests and some subjective scales**
- **Olfactory pathway integrity can also be evaluated using olfactory event-related potentials**
- **Olfactory event-related potentials highlighted an olfactory impairment in NPC patients**
- **Olfactory event-related potentials and subjective scales results were concordant**

In our opinion, olfactory event-related potentials could be a useful tool to monitor changes in the olfactory system, supporting the physician in finding solutions to minimise the effects of olfactory dysfunction on patients' QoL.

References

1 Wenig BM. Nasopharyngeal carcinoma. *Ann Diagn Pathol* 1999;**3**:374–85
2 Black RJ, Bray F, Ferlay J, Parkin DM. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. *Eur J Cancer* 1997;**33**: 1075–107
3 Yu MC, Yuan JM. Epidemiology of nasopharyngeal carcinoma. *Semin Cancer Biol* 2002;**12**:421–9
4 Ren JS, Chen WQ, Shin HR, Ferlay J, Saika K, Zhang SW *et al*. A comparison of two methods to estimate the cancer incidence and mortality burden in China in 2005. *Asian Pac J Cancer Prev* 2010;**11**:1587–94
5 Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev* 2006; **15**:1765–77
6 Kam MK, Chau RM, Suen J. Intensity-modulated radiotherapy in nasopharyngeal carcinoma: dosimetric advantage over conventional plans and feasibility of dose escalation. *Int J Radiat Oncol Biol Phys* 2003;**56**:145–57
7 Lee N, Xia P, Quivey JM, Sultanem K, Poon I, Akazawa C *et al*. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. *Int J Radiat Oncol Biol Phys* 2002;**53**:12–22
8 Geara FB, Glisson BS, Sanguineti G, Tucker SL, Garden AS, Ang KK *et al*. Induction chemotherapy followed by radiotherapy versus radiotherapy alone in patients with advanced nasopharyngeal carcinoma: results of a matched cohort study. *Cancer* 1997;**79**:1279–86
9 Chua DT, Sham JS, Choy D, Lorvidhaya V, Sumitsawan Y, Thongprasert S *et al*. Preliminary report of the Asian–Oceanian Clinical Oncology Association randomized trial comparing cisplatin and epirubicin followed by radiotherapy versus radiotherapy alone in the treatment of patients with locoregionally advanced nasopharyngeal carcinoma. *Cancer* 1998;**83**: 2270–83
10 Al-Sarraf M, Pajak TF, Cooper JS, Mohiuddin M, Herskovic A, Ager PJ. Chemo-radiotherapy in patients with locally advanced nasopharyngeal carcinoma: a radiation therapy oncology group study. *J Clin Oncol* 1990;**8**:1342–51
11 Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T *et al*. Chemotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol* 1998;**16**:1310–17
12 Dimery IW, Legha SS, Peters LJ, Goepfert H, Oswald MJ. Adjuvant chemotherapy for advanced nasopharyngeal carcinoma. *Cancer* 1987;**60**:943–9
13 Decker DA, Drelichman A, Al-Sarraf M. Chemotherapy for nasopharyngeal carcinoma: a ten-year experience. *Cancer* 1983;**52**:602–5
14 Maes A, Huygh I, Weltens C, Vandevelde G, Delaere P, Evers G *et al*. De Gustibus: time scale of loss and recovery of tastes caused by radiotherapy. *Radiother Oncol* 2002;**63**:195–201
15 Mossman KL, Shatzman A, Chencharick J. Long-term effects of radiotherapy on taste and salivary function in man. *Int J Radiat Oncol Biol Phys* 1982;**8**:991–7
16 Temmel AF, Quint C, Schickinger-Fischer B, Klimek L, Stoller E, Hummel T. Characteristics of olfactory disorders in relation to major causes of olfactory loss. *Arch Otolaryngol Head Neck Surg* 2002;**128**:635–41
17 Ravasco P. Aspects of taste and compliance in patients with cancer. *Eur J Oncol Nurs* 2005;**9**:S84–91
18 Hua MS, Chen ST, Tang LM, Leung WM. Olfactory function in patients with nasopharyngeal carcinoma following radiotherapy. *Brain Inj* 1999;**13**:905–15
19 Bramerson A, Nyman J, Nordin S, Bende M. Olfactory loss after head and neck cancer radiation therapy. *Rhinology* 2013;**51**: 206–9
20 Ho W-K, Kwong DL, Wei WI, Sham JS. Change in olfaction after radiotherapy for nasopharyngeal cancer – a prospective study. *Am J Otolaryngol* 2002;**23**:209–14

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21 Millar Vernetti P, Perez Lloret S, Rossi M, Cerquetti D, Merello M. Validation of new scale to assess olfactory dysfunction in patients with Parkinson's disease. *Parkinsonism Relat Disord* 2012;**18**:358–61
22 Rombaux P, Mouraux A, Bertrand B, Guerit JM, Hummel T. Assessment of olfactory and trigeminal function using chemosensory event-related potentials. *Clin Neurophysiol* 2006;**36**: 53–62
23 Barresi M, Ciurleo R, Giacoppo S, Foti Cuzzola V, Celi D, Pramanti P *et al*. Evaluation of olfactory dysfunction in neurodegenerative diseases. *J Neurol Sci* 2012;**323**:16–24
24 Caminiti F, Ciurleo R, Bramanti P, Marino S. Persistent anosmia in a traumatic brain injury patient: role of orbitofrontal cortex. *Brain Inj* 2013;**27**:1715–18
25 Caminiti F, De Salvo S, De Cola MC, Russo M, Bramanti P, Marino S *et al*. Detection of olfactory dysfunction using olfactory event related potentials in young patients with multiple sclerosis. *PLoS One* 2014;**9**:e103151
26 Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG *et al*. *AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual*, 6th edn. New York: Springer-Verlag, 2002;50–2
27 Hummel T, Konnerth CG, Rosenheim K, Kobal G. Screening of olfactory function with a four-minute odor identification test: reliability, normative data, and investigations in patients with olfactory loss. *Ann Otol Rhinol Laryngol* 2001;**110**:976–81
28 Hölscher T, Seibt A, Appold S, Dorr W, Herrmann T, Huttenbrink KB *et al*. Effects of radiotherapy on olfactory function. *Radiother Oncol* 2005;**77**:157–63
29 Nakamura H, Nonomura N, Fujiwara M, Nakano Y. Olfactory disturbances caused by the anti-cancer drug tegafur. *Eur Arch Otorhinolaryngol* 1995;**252**:48–52
30 Rhodes VA, McDaniel RW, Hanson B, Markway E, Johnson M. Sensory perception of patients on selected antineoplastic chemotherapy protocols. *Cancer Nurs* 1994;**17**:45–51
31 de Graeff A, de Leeuw JR, Ros WJ, Blijham GH, Hordijk GJ, Winnubst JA. Long-term quality of life of patients with head and neck cancer. *Laryngoscope* 2000;**110**:98–106
32 Ovesen L, Sorensen M, Hannibal J, Allingstrup L. Electrical taste detection and chemical smell detection thresholds in patients with cancer. *Cancer* 1991;**68**:2260–5
33 Yakirevitch A, Talmi YP, Baram Y, Weitzen R, Pfeffer MR. Effects of cisplatin on olfactory function in cancer patients. *Br J Cancer* 2005;**92**:1611–13
34 Nguyen DT, Nguyen-Thi PL, Jankowski R. How does measured olfactory function correlate with self-ratings of the sense of smell in patients with nasal polyposis? *Laryngoscope* 2012; **122**:947–52

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