Olfactory function in patients with nasopharyngeal carcinoma following radiotherapy

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The aim of this study was to examine the impact of radiation treatment on olfactory function in patients with nasopharyngeal carcinoma (NPC). An olfactory function test battery was administered to 25 adult NPC patients having received radiotherapy, 24 adult nasopharyngeal carcinoma patients awaiting to receive radiation treatment, and 36 adult normal control subjects. Members of the three groups were matched in terms of age, educational level, and full-scaled IQ score. Comparing the test results revealed that the NPC patients with radiotherapy had olfactory information processing impairments including absolute threshold, odour-tactile cross-modality matching, verbal identification of odours, and recall and recognition of identity of odours. The deficits of suprathreshold olfactory functioning in these patients did not seem to arise from impaired absolute threshold sensitivity. Provided that the results are reproducible, an evaluation of olfactory functioning in NPC patients during the period of radiotherapy may be useful for detecting or even avoiding side effects of radiation.

Introduction

Nasopharyngeal carcinoma (NPC) is the most familiar tumour found in the head and neck among inhabitants of southern mainland China and Taiwan. Official surveys recently estimated that the incidence of NPC in Taiwan in 1984 was 7.37 men and 3.15 women/100 000 population [1].

Radiation therapy is the principal method of treating NPC. Since the tumour's location is in close proximity to the central nervous system, some of the brain structures are in the track of the radiation beams when the patients receive radiation treatment. These brain structures, primarily involving the basal frontal and the temporal areas, the olfactory bulbs, the hypothalamus, the brain stem, and the spinal cord, are often inevitably exposed to considerable dosages of radiation [2, 3]. Evidence concerning radioneurosis of neural tissue in the central nervous system, due to damage to both nerve fibres and vasculature, has been well documented [4-6]. More specifically, the principal sites of lesion consist of inferomedial temporal areas, cervical spinal cord, pituitary gland, and cranial nerves [7-9].

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Olfactory information is transmitted from the mitral and tufted cells of the olfactory bulb via the medial and lateral olfactory tract to the ipsilateral olfactory tubercle, the temporal prepiriform located on the medial aspect of the temporal lobe, and the orbitofrontal cortex which is seated on the base of the frontal lobe [10–12]. The olfactory pathways and cortex, thus, are also inescapably exposed to a considerable dosage of radiation in NPC patients with radiotherapy.

Abundant evidence verifies the perilous effects of radiation treatment on life expectancy, and genetic structures [13]. Nevertheless, whether radiation therapy has an adverse effect on olfactory information processing received only limited attention. Clinically, understanding how NPC patients' olfactory functioning might be affected by radiotherapy can be useful for encouraging radiation oncologists to proceed with radiotherapy while imposing as few adverse effects as possible on the patients.

Olfactory function covers a group of complex components. The NPC patients' olfactory functions were therefore examined, including olfactory threshold, odour quality discrimination, odour recognition memory, odour–visual matching, odour–tactile, verbal identification of odours, and odour function on the basis of the Eskenazi *et al.* [14] conceptual framework. The specific objective of this study was to address the following issues: (1) Is there any impairment of olfactory function in NPC patients following radiotherapy? and (2) If so, does the impairment involve all or only some of the function components tested?

Materials and methods

Subjects

All subjects were adult volunteers. Group 1 (Gp1) included 36 normal controls who were normal healthy adults recruited from the community. Group 2 (Gp2) contained 28 patients who had histologically proven NPC and were awaiting radiotherapy. Group 3 (Gp3) contained 25 patients who had received a course of radiotherapy for their histologically proven NPC. Participants in both groups 1 and 2 were used as controls. Based on UICC NPC staging criterion [15], only those patients whose tumour proximity did not invade skull and cranial nerve (i.e. T1, T2, or T3) were included in the present study (table 1). The location of the tumour was clearly demonstrated by computed tomographic scans and/or magnetic resonance imaging. Each patient had also received neurological examination and evoked potential studies which were all normal [16].

For the patients in Gp3, their tumours were treated with a 6MV photon beam for 4680 cGy/26 fractions/5.5 weeks through bilateral parallel opposing fields, including the entire pharynx, base of the skull and the neck lymphatics. The fields were then reduced to include the nasopharynx and base of the skull, excluding the spinal cord. By using 10MV photon from a linear accelerator, all patients, with the exception of one who was treated up to 8400 cGy/46 fractions for 9 weeks, were treated up to 6840–7280 cGy/38–42 fractions/8–9 weeks. The estimated dose to the temporal lobe was 6780–8400 cGy (Mean = 7101 cGy). In 23 patients (92%), the basal frontal lobe was definitely included in the radiation field (Mean = 5174 cGy). The neck lymph nodes were boosted with shrinking fields of 9–12 MeV electron beams, up to 2000–3000 cGy.

Table 1. Demographic characteristics of subject groups

		Group 1 (n = 36)	Group 2 (n = 24)	Group 3 (n = 25)	F(2, 82)	p value
Age (years)	M	43.64	40.96	45.20	1.29	>0.05
	SD	10.11	9.60	7.86		
	Range	28–67	27–59	28–60		
Education (years)	M	10.92	10.75	9.76	0.73	>0.05
	SD	3.52	4.25	3.82		
	Range	6–16	6–18	6–16		
Sex	Male	26	16	23		
	Female	10	8	2		
NPC staging*	T1	—	4	1		
	T2	—	14	14		
	T3	—	6	10		

Group 1: Normal subjects; Group 2: NPC patients without radiotherapy; and Group 3: NPC patients with radiotherapy.
*UICC (1988) NPC staging criterion.

Demographic data for the subjects are shown in table 1. The mean differences in age and years of education were not statistically significant. None of the subjects had a psychiatric history or emotional problems apparent during the evaluation. All subjects were free of dementia, aphasia, confusional problems, anosmia, sinusitis, or other significant medical illnesses. All subjects, with the exception of two patients in Gp 2, were right-handed; hand dominance was ascertained according to which hand the subject always preferred to use for writing, holding chopsticks, and performing skillful activities.

Tests and procedure

Each subject received a series of non-olfactory and olfactory function tests at a well-ventilated neuropsychological examination room at the Department of Neurology of Chang Gung Memorial Hospital, Taiwan. The non-olfactory function tests (table 2) included the WAIS-R [17], the Temporal Orientation Test [18], the Orientation to Personal Information and Place [19], the Token Test [20], the Paced Auditory Serial Addition Task-Revise (PASAT-R) [21], and the Vigilance subtest of Gordon Diagnostic System [22].

The olfactory function test battery included the followings: (1) Olfactory Threshold test [23]; (2) Odour Quality Discrimination test [14]; (3) Odour Recognition Memory Test [14]; (4) Odour–Visual Matching Test [14]; (5) Odour–Tactile Matching Test [14]; (6) Verbal Identification of Odours [14]; and (7) Odour Function Test [14].

On each trial of the Olfactory Threshold Test, every subject sniffed a pair of glass vessels in which one contained a weak solution of *n*-butyl alcohol and the other distilled water. The subject had to decide which vessel contained the odourant. The concentration of the alcohol was increased by successive factors of three, beginning at 10⁻⁵ m until the patient correctly selected three consecutive concentrations. Each nostril was tested twice. The test of this alcohol detection was the only test invol-

Table 2. Comparisons of non-olfactory test performance by groups

	Group 1 (n = 36)		Group 2 (n = 24)		Group 3 (n = 25)		F(2, 82)
	M	SD	M	SD	M	SD	
Vigilance task correct	28.14	2.09	27.92	2.21	27.00	3.30	1.58
PASAT-R							
Total correct	73.03	16.95	82.00	17.21	66.76	18.70	0.87
Temporal orientation	0.08	0.28	0	0	0.28	1.13	1.21
Orientation to personal information and place	12.0	0	12.0	0	11.93	0.37	0.38
FSIQ(WAIS-R)	97.28	14.06	94.67	15.16	90.12	13.89	1.85
Verbal IQ(WAIS-R)	100.83	15.28	100.29	17.44	92.59	14.49	2.34
Token test	42.08	2.35	42.11	1.97	41.48	3.01	0.55

Group 1: Normal subjects; Group 2: NPC patients without radiotherapy; and Group 3: NPC patients with radiotherapy.

ving monorhnic presentation, while the rest of the olfactory tests involved birhnic presentation.

On each trial of the Odour Quality Discrimination Test, the subject received three vials in a random sequence. Two vials contained the same and one a different odourant. The subject had to point out which two smelled the same. Odourants could be sniffed as many times as the subject wanted. All compoundings of five different odourants were given. These five odourants included a 1.6% solution of 1-carvone, 0.5% di-isopropylase (replaced ethyl-n-butylamine, used in Eskenazi *et al.*'s [14] study), 0.01% acetophenon (again, this replaced 2,3-pentanedione used by Eskenazi *et al.* [14]), 1% benzaldehyde, and 1% pyridine. These odourants were diluted with odourless diethyl phthalate to about equal intensity of moderate level. The test consisted of 20 trials. During testing, the subject was instructed to recollect the odourants for a succeeding test of odour recognition.

On each trial of the Odour Recognition Test, the subject sniffed from two vials in which one contained an odourant from the discrimination test and another a distractor odourant. The subject was required to recognize the odour that had been shown in the antecedent test. The subject could sniff an odourant only once per trial. There were 20 trials, in which 10 trials occurred about 5 minutes after the discrimination test and another 10 trials about 30 minutes following the discrimination test, during which the odour-visual matching test and a short break were given.

In the Odour-Visual Matching Test, 15 odourants, which were ecologically relevant, were presented randomly to each subject. Because some of the objects were not available in Taiwan, and the odour of other odourants was hard to recognize manifested in the pilot study, some objects originally used in Eskenazi *et al.* [14] were modified. These odourants contained the following objects: salon-pas, which was a special band-aid for sore muscle relief (replaced band-aid), garlic, toothpaste (replaced bubble gum), zanthoxyli fructus (replaced popcorn), pineapple (replaced coconut), angelicae sinensis radix (replaced mustard), naphthalene ball (replaced crayon), cigarette, black pepper, brush ink (replaced pencil), milk (replaced orange), glue (replaced pipe), guava (replaced apple), grape (replaced cherry), and preserved fish (replaced olive). The odourants, masked by gauze,

were sniffed from an opaque glass jar. The subject was seated in front of an array of the 15 real objects and was asked to indicate the object that matched the smell. The examiner showed the correct object without telling its name, when the subject made an incorrect response. Each object was presented three times. At the end of the test, the subject stated the name of objects in the display in order to indicate that he/she knew their identity.

On the Odour-Tactile Matching Test, the subject was seated before a box, which had a slanted top and an open side through which he/she might place his/her hand. The examiner sat across a table from the subject. The examiner guided the subject's hand to each of 10 objects in an array. The subject was asked to explore each one tactually. The objects consisted of soap, wood, onion, eucalyptus leaf (replaced newspaper), peanut shells (replaced peanuts), tea, banana, Chinese spicy seasoning, ginger (replaced egg), and lemon. The subject could use either right or left hand to explore the objects, but most subjects used the right hand. Each object was presented as an odourant three times. The subject was asked to match the odour to the feel of the adequate object. The examiner guided the subject's hand to the correct object if he/she did not get the right response. The subject was also required to state the name of the objects, but his/her naming errors were rare.

On the Verbal Identification of Odours, the subject had a list of 20 names of odourant during testing. The list of names included 10 objects (rice wine, sandalwood, chocolate, cinnamon, coffee, sulphur lotum, peanut butter, tangerine, ketchup, and seal ink), and 10 distractors (burnt paper, garlic, grape jam, black pepper, rubber, sardines, spoiled meat, tobacco, turpentine, and wood shaving). On each trial, the subject sniffed the odourant and matched it with a name from the list. The examiner accepted correct response and also responded to incorrect answers by giving the answer. The 10 odourants were presented randomly and each presented three times.

On the Odour Function test, there were 20 relatively difficult-to-identify items including perfume, orange, crackers, shoe polish, preserved soil bean, almond powder, Tiger balm, preserved bombooo shoots, turpentine, vinegar, Chinese spicy barbecue sauce, ginseng, green oil, honey, soy sauce, medical herb pills, sesame oil, mentholatum, prunes, and dried turnip. Each of the items was presented once. The subject was asked to sniff an odourant and then responded to the following questions in a sequence as follows: (a) Was this odour the smell of something edible or inedible?; (b) What was the function of something smelling like this? (the subject was provided with a list of functions, such as You ate it; You put it on; You played with it.); (c) What was the identity of the odourant? (identity recall); and (d) What was the identity of the odourant given a choice of the following four possibilities (i.e. identity recognition)? (possibilities stated).

To maximize the ability of the olfactory tests for differentiation between NPC patients with and without radiation exposure, the non-olfactory functioning tests were used to rule out subjects' possibly being demented, aphasic, or confused, conditions that might confound the olfactory test performance. Because of the sensitivity of the Temporal Orientation Test for screening the early stage of dementia [24], an error score of 2 or more was used to exclude those subjects suspected for dementia. A Verbal IQ score of 83 or less on the WAIS-R, and a score of 38 or less on the Token Test was adopted to eliminate subjects suspectable for aphasia, and a score of 11 or less on the Orientation to Personal Information and

Place and of 38 or less on the Token Test, as well as an error score of 2 or greater on the Temporal Orientation, were used to screen subjects susceptible for confusion.

The testing procedure began by recording each subject's demographic data and medical history, followed by tests in the following order: Temporal Orientation, Orientation to Personal Information and Place, Token Test, WAIS-R, Olfactory Threshold Test, Odour Quality Discrimination Test, Odour Recognition Memory, Odour-Visual Matching Test, Odour-Tactile Matching, Verbal Identification of Odours, and Odour Function Test. A total of about 4 hours was needed for each subject to complete the testing. In order to minimize the effects of fatigue on the subject's performance, all subjects completed the testing in two sessions.

Results

Univariate statistical procedures, one-way analysis of variance (ANOVA) and covariance (ANCOVA), and Scheffe's *post hoc* pairwise comparisons were used to analyse the data. The one-way ANOVA was used to examine whether a performance difference arose, among the three subject groups on each of the olfactory function tests. If the difference did arise, a Scheffe's *post hoc* pairwise contrast was then used to inspect the performance difference between the two subject groups. When the subjects' performance on the olfactory threshold test was suspected for confounding the otherwise olfactory function tests, the one-way ANCOVA in which the olfactory threshold score was used as a covariate to examine whether there was a performance difference among the three subject groups on each olfactory test. Again, if the difference did exist, a Scheffe's *post hoc* pairwise comparison was then used to inspect the performance difference between the two subject groups. The results are shown in tables 3 and 4.

On the olfactory threshold test, the right nostril performance of the NPC patients was significantly inferior to that of normal subjects, while there was no remarkable difference between the two patient groups. The left nostril performance of the NPC patients having received radiotherapy was significantly inferior to that of normal subjects and NPC patients who had not yet received radiation treatment; the performance of normal subjects was also significantly superior to that of NPC

Table 3. Comparisons of olfactory threshold test performance by groups

Olfactory test	Group 1 (n = 36)		Group 2 (n = 24)		Group 3 (n = 25)		ANOVA F(2, 82)
	M	SD	M	SD	M	SD	
Threshold (M)							
Right nostril	0.002	0.003	0.221	0.234	0.274	0.242	19.92*
Left nostril	0.002	0.004	0.193	0.229	0.365	0.263	28.36*
Average score	0.002	0.003	0.207	0.203	0.318	0.211	31.24*

Group 1: Normal subjects; Group 2: NPC patients without radiotherapy; and Group 3: NPC patients with radiotherapy.
**p* < 0.001.

Note: For the right nostril score of the Olfactory Absolute Threshold Test, group 1 significantly differed from groups 2 and 3 (*p* < 0.01); for the left nostril, groups 1 and 2 significantly differed from group 3 (*p* < 0.01), and group 1 also significantly differed from group 2 (*p* < 0.05); for the average score, group 1 significantly differed from groups 2 and 3 (*p* < 0.01), and group 2 significantly differed from group 3 (*p* < 0.05).

Table 4. Comparisons of suprathreshold olfactory functioning test performance by groups

Olfactory test	Group 1 (n = 36)		Group 2 (n = 24)		Group 3 (n = 25)		ANOVA F(2, 82)	ANCOVA F(2, 81)
	M	SD	M	SD	M	SD		
Discrimination correct	16.50	2.91	15.79	3.24	13.56	3.57	6.39**	2.53
Recognition memory								
5 minutes delay	9.14	0.99	7.29	1.57	7.36	1.66	17.81***	9.63***
30 minutes delay	8.64	1.13	5.88	2.44	6.48	1.94	19.59***	14.91***
Visual matching	13.0	1.48	10.48	2.67	7.47	1.92	56.27***	23.87***
Tactile matching	7.59	2.17	6.58	2.12	4.10	1.61	22.66***	10.92***
Verbal identification	8.20	1.49	6.23	2.57	3.94	1.83	35.74***	14.06***
Odour function								
edible/inedible	17.83	2.78	16.13	2.89	15.76	1.99	5.59***	1.79
function	17.81	2.83	15.58	3.01	14.96	1.95	9.83***	4.38*
identity recall	6.72	3.89	5.04	2.71	3.28	2.01	9.06***	3.49*
identity recognition	17.53	2.27	15.88	3.13	14.12	2.32	13.24***	5.14*

Group 1: Normal subjects; Group 2: NPC patients without radiotherapy; and Group 3: NPC patients with radiotherapy.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Note: For 5- and 30-minutes delay of the Recognition-Memory and Visual Matching Test, group 1 significantly differed from groups 2 and 3 ($p < 0.01$); for Tactile Matching Test, groups 1 and 2 significantly differed from group 3 ($p < 0.01$); for Verbal Identification of Odours, group 1 significantly differed from groups 2 and 3 ($p < 0.05$ and 0.01 , respectively), and group 2 significantly differed from group 3 ($p < 0.01$); for the Function subtest of Odour Function, group 1 significantly differed from groups 2 ($p < 0.05$) and 3 ($p < 0.01$) while for Identity Recall and Recognition, group 1 significantly differed from group 3 ($p < 0.01$).

patients without radiotherapy (table 3). In order to examine whether, for each subject group, there was a performance difference between two nostrils on this test, a matched-pair t procedure was used. The results revealed no significant difference between the two nostrils in each subject group (normal controls: $t(34) = 0.000$, $p > 0.05$; NPC patients without radiotherapy: $t(22) = 0.028$, $p > 0.05$; NPC patients with radiotherapy: $t(23) = 0.094$, $p > 0.05$). Therefore, an average threshold score over the two nostrils was calculated for each subject and used for further analysis.

On the Odour Quality Discrimination Test, the NPC patients who had received radiotherapy performed poorer than the NPC patients without radiotherapy and the control subjects. The score differences among the three subject groups reached a significant level with ANOVA. However, further data analysis with ANCOVA, in which the average of the olfactory threshold test score over the two nostrils was used as a covariate, did not reveal any performance difference among these three subject groups (table 4).

On the Odour Recognition Memory Test, normal control subjects performed better than the NPC patients with and without radiotherapy on both 5- and 30-minute delay recognition. One-way ANOVA revealed a significant difference between the normal subjects and the NPC patients. The difference remained significant in the one-way ANCOVA, with the mean of absolute olfactory threshold over the two nostrils as a covariate. The Scheffe's *post-hoc* pairwise contrasts indicated a significant difference between the normal subjects and the NPC patients, while no significant difference arose between the two NPC patient groups (table 4).

On the Odour–Visual and Odour–Tactile Matching Tests, and the Verbal Identification of Odours, the performance of normal control subjects was superior to that of the NPC patients, and the performance of NPC patients without radiotherapy was better than that of NPC patients with radiotherapy. The one-way ANOVA indicated a significant difference among the three subject groups. The differences remained significant in the one-way ANCOVA, with the mean of absolute olfactory threshold over the two nostrils as a covariate. The Scheffe's *post-hoc* pairwise contrasts showed that the differences between the normal control group and the NPC patient group with radiotherapy, and between the NPC patient groups without and with radiation treatment were significant (table 4).

On the Odour Function Test, normal control subjects performed better than the NPC patients, and the NPC patients without radiotherapy performed better than the NPC patients with radiotherapy. The one-way ANOVA showed a significant difference among the three subject groups. This difference remained, with the exception of the edible/inedible subtest with the one-way ANCOVA (table 4), with the average of absolute threshold over the two nostrils as a covariate. The *post-hoc* pairwise comparisons with Scheffe's procedure revealed that the differences arose between the normal control subjects and the NPC patients without radiotherapy, and between the normal controls and the NPC patients with radiotherapy for the function subtest, while for the other two subtests (identity recall, and identity recognition) the difference only arose between normal control subjects and the NPC patients with radiotherapy (table 4).

Discussion

As mentioned earlier, this study attempts to determine whether NPC patients, having been exposed to considerable dosages of irradiation, had an impairment of olfactory function. If they did, an item of additional interest was the specificity of the defects.

The NPC patients having received radiation treatment exhibited some changes of olfactory function, in comparison with their normal counterparts. The impairments consisted of absolute olfactory sensitivity of both nostrils, and suprathreshold olfactory functions including immediate and delayed recognition, cross-modality matching (i.e. visual and tactile matching), verbal identification of odours, and odour function. These defects of suprathreshold olfactory functions in patients with radiotherapy were not primarily owing to the impairment of absolute olfactory threshold sensitivity. The results further corroborate Eskenazi *et al.*'s [14], and Martinez *et al.*'s [25] earlier observations, showing that suprathreshold olfactory defects arose in the context of normal absolute olfactory sensitivity in patients with temporal lobectomy.

Compared with NPC patients awaiting radiotherapy, NPC patients with radiation treatment also revealed impairments in both absolute olfactory sensitivity, and suprathreshold olfactory function. These defects of suprathreshold olfactory function, however, only included odour–tactile cross-modality matching, verbal identification of odours, and identity recall and recognition of odours. Apparently, the defect of absolute olfactory sensitivity again was unable to account fully for these higher-order olfactory function difficulties.

Poor attention might often stem from the effects of medication that the patients take, or the patients' fatigue or emotional disturbances, such as anxiety

and depression during the testing. Could these olfactory function deficits in NPC patients with radiotherapy be attributed to their attentional problem? The answer might not be true because these patients did not have any remarkable attention defect reflected by their performance on the non-olfactory function test, such as PASAT and Token Test.

Furthermore, suprathreshold olfactory function tasks require more complicated cognitive skills than absolute odour detection. For instance, the tasks of identity recall and recognition of odours demand the subjects' abilities of language comprehension to understand the test instructions, search and retrieval strategies to recollect the odour from long-term memory, semantic memory to storage to specify the odour, and working memory to keep a trace of the odour while retrieval manoeuvres are carrying on [26]. Could non-olfactory neuropsychological deficits, such as dementia, confusional state, or aphasia, therefore, account for these suprathreshold olfactory function impairments? Again, this is not the case, because patients possibly having those neurobehavioural syndromes were excluded from the study.

The NPC patients awaiting radiotherapy unexpectedly displayed impairments in absolute olfactory sensitivity in both nostrils, immediate and delayed odour recognition, odour-visual cross-modality matching, verbal identification of odours, and function statement of odours compared with normal control subjects. These results are quite unexpected and confusing. Because the patients had not been exposed to radiation, brain dysfunction owing to radiation treatment was not responsible for these deficits. Also remaining unclear is whether those patients were sustaining psychological distress concerning their recently discovered physical illness, as Lee *et al.* [27] suggested, which subsequently, adversely affected their performance on these tasks.

Generally, the NPC patients with radiotherapy manifested impairments in absolute olfactory threshold sensitivity, odour-tactile cross-modality matching, verbal identification of odours, and recall and recognition of odour identity. Based on these findings, a conjecture of the adverse effects of radiation therapy on some of the olfactory functions seems appropriate. In terms of neuroanatomical correlations, the deficit of absolute olfactory threshold manifested in the NPC patients with radiotherapy indicated the dysfunction of both orbitofrontal and temporal prepiriform areas, and peripheral olfactory neural substrates [10]. The impairments of verbal identification of odours, and recall and recognition of identity of odours seemed to reflect the dysfunction of the orbitofrontal cortex, and the mesial temporal structures including the temporal prepiriform. However, the neuroanatomical correlations for the specific manifestation of odour-tactile cross-modality matching impairment, rather than the general cross-modality matching one, in NPC patients with radiotherapy were hard to specify. Lee *et al.* [27] claimed that radiation damage might not be confined to the boundaries of the irradiation beams. If this is the case, vascular changes might affect normal functioning of distant regions, such as the parietal lobes and their connection pathways. The dysfunction of parietal areas and their neural pathways subsequently disrupts tactile information processing in NPC patients with radiotherapy. However, thus far, no evidence indicates that olfactory efferents terminate either the left or the right parietal areas [28]. Further investigation on this issue seems necessary.

In this study, certain aspects need clarification. A single ascending procedure was used to measure the absolute olfactory threshold. However, Doty *et al.* [29] recently reported that olfactory detection values derived from the measure based on a single

ascending procedure might be less reliable than that based upon a staircase method. If this is the case, the findings that the deficits of absolute olfactory sensitivity in the NPC patients could be attributed to such a psychometric drawback. The other is that the construct validity of the olfactory function tests used in the present study has not yet been well established. Subsequently, paradoxical findings might be found in the study, because these different tests might measure the same sources of variance rather than the various roots of variance. In order to clarify this issue, a composite measure of olfactory function, derived either from principal component analysis or factor analysis, as Doty *et al.* [30] suggested, is merited.

Summary and conclusions

The study revealed that the NPC patients with radiotherapy definitely had olfactory information processing deficits including absolute threshold sensitivity, odour-tactile cross-modality matching, verbal identification of odours, and recall and recognition of identity of odours. The suprathreshold olfactory function defects could not be fully attributed to the absolute olfactory threshold impairment. On the condition that these results are replicable, adequate tests to examine the NPC patients' olfactory functioning may be useful in detecting potential side effects of radiation treatments. Such an avenue would make radiation oncologists possible to detect radiation side-effects as soon as possible and, thus, to minimize the side-effects as much as possible during radiotherapy on NPC patients.

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