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Olfactory bulb volume and olfactory function after radiotherapy in patients with nasopharyngeal cancer

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ABSTRACT

Objective: Radiotherapy is the primary method of treatment for nasopharyngeal cancer (NPC) and many side effects were reported in patients receiving radiation to this area. This study was conducted to evaluate the long-term effects of radiotherapy following NPC on olfactory bulb (OB) volume and olfactory function.

Methods: Twenty-four patients with NPC who received radiotherapy at least 12 months ago were recruited. Fourteen healthy subjects with similar demographical characteristics were recruited as the healthy control group. All volunteers were subjected to a nasoendoscopical examination, and abnormalities that could potentially cause olfactory dysfunction were the exclusion criteria from the study. An experienced radiologist segmented the MRI coronal, axial and sagittal slices manually for three-dimensional OB volume measurement in a blinded manner. Olfactory function was assessed using the Connecticut Chemosensory Clinical Research Center (CCCRC) test, and average score (0: worst, 7: best) was calculated as the total CCCRC olfactory score.

Results: The mean CCCRC score was 5.5 ± 1.1 for the nasopharyngeal cancer patients, whereas the mean score of healthy control group was 6.4 ± 0.4. There was a significant difference in the olfactory scores ($p = 0.003$). The mean OB volume in the NPC group was 46.7 ± 12.1 mm^3. Among the patients with NPC, the cisplatin receiving group had a mean OB volume of 47.2 mm^3, whereas the cisplatin + docetaxel receiving group had a mean OB volume of 46.5 mm^3, and they were similar. The MRI measurement of the healthy control group was 58.6 ± 13.8 mm^3. The OB volumes of the healthy control group were significantly higher ($p < 0.05$).

Conclusion: Radiotherapy following nasopharyngeal cancer results in a diminished OB volume and deteriorated olfactory function. Chemosensory olfactory dysfunction might be a contributing factor to lack of appetite, cancer cachexia and consequent lowered quality of life in NPC patients.

1. Introduction

Radiotherapy (RT) is the primary method of treatment for all types of nasopharyngeal cancer (NPC). RT to the head and neck region can result in serious consequences because important tissues are often included in the field of irradiation [1–4]. Dental problems, xerostomia, gustatory dysfunction and mucositis eventually contribute to poor nutritional status and cancer cachexia and consequently lead to low quality of life in patients [5–8].

The olfactory nerve is purely sensory and is specialized for the sense of smell. The olfactory system is connected to the cortical olfactory area, also known as the rhinencephalon, via olfactory nerve endings and the olfactory bulb and tract. Afferent nerve endings are situated in the olfactory epithelium and olfactory bulb (OB) and are primarily responsible for the plasticity of the olfactory system [5–9].

RT used in the treatment of NPC, apart from other head and neck tumors, is directed and focused especially to the region of nasal mucosa, receptor cells and nerve endings in the olfactory bulb. This study was conducted to evaluate the long-term side effects of radiotherapy on the olfactory bulb and olfactory function in NPC patients.

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2. Materials and methods

This study was performed with the approval of the local ethics committee following the National Health and Medical Research guidelines and in accordance with the Declaration of Helsinki. All volunteers were provided information about the procedures, and written informed consents were obtained from them before participating in the study.

2.1. Patient characteristics

Twenty-four patients with histologically proven NPC who received radiotherapy at least 12 months earlier were recruited in the study. All of the patients received additional chemotherapy with either cisplatin or cisplatin and docetaxel. Fourteen healthy subjects with similar demographical characteristics were recruited as the control group. The participants underwent a detailed nasoendoscopical examination, and any patient with a condition that could cause olfactory dysfunction, such as septum deviation, nasal polyposis, congenital olfactory dysfunction, septum surgery, head trauma, chronic rhinosinusitis, allergic rhinitis, or psychiatric or neurological disorders, such as Parkinson's and Alzheimer's disease, was excluded from the study.

2.2. Oncological evaluation

The TNM classification system of the American Joint Committee for Cancer Staging (AJCC) was used and accordingly the disease extent was T_1: 8, T_2: 10, T_3: 1, and T_4: 4 for T classification and N_0: 3, N_1: 2, N_2: 17, and N_3: 1 for N classification. None of the patients had distant metastatic disease at presentation.

All except two patients received 2D conventional RT with shrinking fields with a ^{60}Co treatment unit. In most cases, a beam of 6–13 meV electrons was applied for supplemental doses after spinal cord tolerance. The primary tumor in the nasopharynx and all its direct extensions defined by CT or MRI were treated with two opposed lateral fields, using ^{60}Co. The margins included the base of the skull, the nasopharynx, the oropharynx, and the upper neck. After 50 Gy the fields were reduced to include the nasopharynx and paranasopharyngeal area and the base of the skull. A total dose of 70 Gy was administered in daily fractions of 2 Gy, 5 days a week in all of the patients except two of the 24 patients who received 6880 and 7230 cGy total dose with 180 cGy/fraction. The spinal cord was shielded after 46 Gy and the posterior lymphatic chains were treated with electron beams. The lower cervical and supraclavicular regions were treated using ^{60}Co with a single anterior portal and a median shield to protect the larynx and the spinal cord, with doses of 46–50 Gy. Clinically involved neck areas were boosted with direct oppositional fields with doses of 66–70 Gy using 6–13 MeV electrons. The dose to the uninvolved neck area was 50 Gy in 5 weeks with conventional fractionation. The other two patients received IMRT with 6 MV photons, using simultaneous integrated boost technique in 33 fractions of 69.96 Gy. Target volume definition and treatment planning were performed according to the recommendations of the International Commission on Radiation Units and Measurements Reports 50 and 62 [10,11].

All patients received chemotherapy in addition to radiotherapy; eight patients received three doses of 100 mg/m^2 concomitant cisplatin, whereas 16 patients received 3 doses of 100 mg/m^2 docetaxel in addition to cisplatin. Olfactory tests and OB volume measurements were conducted individually.

2.3. Evaluation of olfactory function

The Connecticut Chemosensory Clinical Research Center (CCCRC) test was conducted as described previously elsewhere [12,13]. The CCCRC test is composed of n-butanol odor threshold test and odor identification test. Olfactory tests were conducted individually and were scored out of 7 (0: worst, 7: best olfaction) and mean score was calculated as the total CCCRC test score. Test scores were categorized as previously defined [12] and the patients were evaluated as anosmic, severely hyposmic, moderately hyposmic, mildly hyposmic or normosmic.

2.4. Evaluation of olfactory bulb volume

OB volumes were measured with a 1.5-Tesla General Electric Signa Excite MRI scanner. Each consecutive cross-section was taken with 2-mm slice thickness (gap = 0) and 8-channel head coil was used. Coronal, axial and sagittal slices were manually segmented and measured by an experienced radiologist (DG) on T2W TSE cross-sections for three-dimensional evaluation of olfactory bulb volume (Fig. 1). Measurements were carried out individually on the right and left olfactory bulbs in a single-blinded fashion, and the mean olfactory bulb volume was calculated in cubic millimeters. Posttraumatic parenchymal or meningeal hemosiderin accumulation in MRI T2W GRE cross-sections was a criteria for exclusion from the study. T2W TSE images were scrutinized for other organic disorders, and detection of any pathological finding was a criterion for exclusion from the study.

2.5. Statistical analysis

Data were analyzed using Medcalc Software v. 12.3 (Mariakerke, Belgium). All values were calculated as mean ± standard deviation. Mann Whitney *U* test was used for *statistical analysis* for independent groups; a *p*-value of less than 0.05 was accepted as statistically significant.

3. Results

The mean age of the NPC group was 48.7 ± 11.4 years; 10 were women (43.5%) and 14 were men (56.5%). Mean age of the healthy control group was 48.8 ± 7.0 years; nine were women (64.3%) and five were men (35.7%). There was no statistical significance in terms of age between the two groups. Olfactory tests and MRI scans were carried out 66.0 ± 48.6 (range, 14–218) months (mean ± SD) following the conclusion of radiotherapy and chemotherapy in the NPC group.

3.1. Olfactory function tests

The mean CCCRC score was 5.5 ± 1.1 (range, 3.5–7) for the NPC group, whereas the CCCRC score of the control group was 6.4 ± 0.4 (range, 5.5–7). There was a significant difference in the olfactory scores ($p = 0.003$, $Z = 2.984$) (Fig. 2). Detailed n-butanol odor threshold and odor identification scores are presented in Table 1.

According to the CCCRC scores, 11 (45.8%) patients were classified as normal, 7 (29.2%) as mildly hyposmic, 3 (12.5%) as moderately hyposmic, and 3 (12.5%) as severely hyposmic. The healthy control group consisted of 13/14 (92.9%) normosmic patients; only one patient (7.1%) was mildly hyposmic (Fig. 3).

3.2. OB volume analyses

The mean of right and left OB volume in the NPC group was 46.7 ± 12.1 (range, 24–65.5) mm^3. The MRI measurement of the healthy control group was 58.6 ± 13.8 (range, 42–91). A comparison of the olfactory bulb volumes revealed a significant difference in olfactory volumes ($p < 0.05$) (Fig. 4). OB volumes of the cisplatin receiving and cisplatin + docetaxel receiving group were 47.2 and 46.5 mm^3, respectively, and the difference was insignificant.

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