EUROMEDITERRANEAN BIOMEDICAL JOURNAL
2019,14 (20) 085–089
(FORMERLY: CAPSULA EBURNEA)

Original article

RADIOTHERAPY-RELATED NASAL AND OLFACTORY DYSFUNCTION AMONG HEAD AND NECK CANCER PATIENTS: A COHORT STUDY

Francesco Gigante [1], Pasquale Gianluca Albanese [2], Daniele Spada [2], Alessandra Li Voti [2], Veronica Castro [3], Claudio Andaloro [2]

1. Radiotherapy Unit, Belcolle Hospital, Viterbo, Italy.
2. Department of Medical Sciences, Surgical and Advanced Technologies, GF Ingrassia, University of Catania, - ENT Unit, Policlinico "G. Rodolico" University Hospital, Catania, Italy.
3. Ear Nose and Throat Unit, Institute for Maternal and Child Health - IRCCS Burlo Garofolo, Trieste, Italy

ARTICLE INFO

Article history:
Received 13 March 2019
Revised 30 April 2019
Accepted 06 June 2019

Keywords:
Radiotherapy, Head and Neck Neoplasms, Olfaction Disorders, Quality of Life.

ABSTRACT

There is contradicting literature on radiotherapy associated with olfactory dysfunction among head and neck cancer (HNC) patients, especially concerning the recovery and its impact on the quality of life. The aim of this study was to evaluate the olfactory function, mucociliary clearance and quality of life (QoL) at several time points after the initiation of RT. An HNC RT-treated cohort study was tested for the olfactory function using the Connecticut Chemosensory Clinical Research Center (CCCRC) test, the nasal mucociliary clearance by the Saccharin Transit test (STT) and QoL through the Appetite, Hunger and Sensory Perception (AHSP) questionnaire. Both the CCCRC score and saccharin perception time show a significantly deteriorating trend at each time period (all p values <0.05). Overall QoL scores at the mid- and end of RT were significantly reduced (p=0.019 and 0.003; respectively). RT following HNC resulted in diminished olfactory and nasal functions. Although a partial recovery may be seen, these dysfunctions persisted over 3 months after treatment and could impact the quality of life.

1. Introduction

Worldwide, head and neck cancer (HNC) is the sixth most common type of cancer, with high incidence in Southeast Asian countries and representing 1-4% of all cancers in North America and 4% in Europe[1,2].
Radiotherapy (RT) is a common treatment modality for patients with head and neck malignancies as a potentially curable primary modality or as adjuvant RT which has been used over the last two decades to improve tumor control and survival among HNC patients; however, this treatment approach significantly impacts quality of life for the patients' relative treatment-related symptoms both in the acute stage and with a later onset [3,4].
Reduced and/or altered taste and smell are amongst the common symptoms reported by HNC patients who appear early and may continue over the long term. Moreover, these factors may contribute to a significant impact on quality of life [5]. While recent reviews have explored taste alterations in HNC [6,7], only a few prospective studies have been done on the effect of radiation on olfactory function [8].
Olfactory dysfunction can appear secondary to tumor growth onto or near the olfactory bulb, nerve or epithelium, or after surgery for tumors affecting the olfactory epithelium [9] and RT can further impair smell perception. Deterioration of olfaction following RT can be either due to the neurosensory effect of the radiation to olfactory nerve fibers and receptors at the cribriform plate or conductive effectwhen related to the obstruction of airflow as a secondary effect on the nasal mucosa[10].
There is contradicting data as to the regeneration of the olfactory system following RT. A gradual improvement is believed to occur due to the regeneration of olfactory nerve fibers, anyway, in some patients, the recovery is delayed and the olfactory deficit seems to persist [11-13].
So, the aim of our work was to evaluate the effects of radiation on olfaction in patients with HNC treated with RT, also evaluating the nasal mucociliary clearance function and the impact on the patients' quality of life during the course of RT treatment.

Corresponding author: Pasquale Gianluca Albanese, *gianlucaalba15@hotmail.com*
DOI: 10.3269/1970-5492.2019.14.20

2. Material and Methods

This is a hospital-based, prospective, observational, bicenter, cohort study involving two medical centers: The Radiotherapy Unit of the Belcolle Hospital in Viterbo and the Ear Nose and Throat Unit of the University of Catania. HNC patients treated by RT +/− surgery, with curative intent were prospectively and consecutively recruited from the two centers. Patients were included if over 18 years of age and diagnosed with a malignancy of head and neck planned for conformal RT; RT treatment field includes olfactory cleft region; normal baseline olfactory function; no previous RT or surgery of the olfactory region. We excluded patients with malignancy involving the olfactory cleft and/or anterior skull base and those diagnosed with nasal cavity tumors. All patients in the study were treated with intensity modulated RT.

After determining the exact site, dose and tumor volume to be irradiated, 200 cGy (2 Gy) of irradiation per day was given for 5 days a week in all the cases over a period of 6 – 7 weeks in 33 to 35 fractions. Total dose ranged from 60 – 70 Gy (mean total dose – 65.75 Gy). The mean olfactory region dose volume varied from 0.00 – 2.36 cm^3 (mean – 1.47 cm^3).

The study design was approved by the local ethics committee of both hospitals. All patients gave written consent. Investigations were performed according to the Declaration of Helsinki on Biomedical Studies Involving Human Subjects.

Olfactory function was evaluated using the Connecticut Chemosensory Clinical Research Center (CCCRC) test consisting of n-butanol odor threshold test and odor identification test and it was performed elsewhere according to a procedure previously described [14].

Olfactory tests were administered to both the right and left sides of the nose separately, then they were scored on a scale of 0 (worst) to 7 (best olfaction) and a mean score was calculated as the total CCCRC test score. Test scores were categorized as previously defined [14] and the patients were evaluated as anosmic, severely hyposmic, moderately hyposmic, mildly hyposmic or normosmic.

Nasal mucociliary clearance was assessed with the saccharin transit test (STT) by using a technique previously described [15]. A normal value for a healthy adult is <12 minutes [16].

Quality of life assessment was done using the Appetite, Hunger and Sensory Perception (AHSP) questionnaire which is a validated, 29-item, multi-domain appetite assessment tool that is scored with a 5-point (A to E) Likert-type scale with verbally labeled categories. Items on the AHSP are grouped into 3 domains: taste (14 items), smell (6 items), and hunger (9 items). The score for each domain is the sum of scores on the individual items, with lower scores indicating deterioration. The total AHSP score is the sum of scores in the 3 domains. Possible scores range from 29 (worst) to 145 (best) [17].

All patients were evaluated at four time-points: pre-treatment, mid-RT, immediate post-RT and at 3 months after RT.

Descriptive and inferential statistics were used for analysis. Continuous variables were presented as mean ± SD, while categorical variables were expressed as frequencies and percentages. Pre-post

testing was performed using paired samples of a t-test. All statistical tests were performed using a commercially available statistical software package, SPSS 17.0 forWindows (SPSS, Inc, Chicago, IL), and P values of less than 0.05 were regarded as statistically significant.

PASS 2008 (NCSS LLC lnc, Utah) was used to compute the minimum sample size of the study.

Parameters used for the computation of the mean differences in total CCCRC olfactory scores were obtained from previously published literature [18].

To detect a mean difference of 1.2, the minimal, clinically important difference in total CCCRC olfactory scores, with at least 80% power at the 5% significance level, based on a pooled standard equal to 0.4, a total of 14 subjects, the minimum sample size, were required for this study. The sample size was increased to 20 to account for 25% potential dropouts and those lost after follow-ups.

3. Results

A total of 20 patients who fulfilled the inclusion and exclusion criteria, as per the study protocol, were recruited in the study. Three patients were lost after a follow-up as one patient had disease progression at follow-up and dropped out and two other patients were unwilling to continue in the study. Thus, the remaining 17 patients were included in the final analysis in the present study. The patient characteristics are shown in Table 1.

Characteristics	Data
Age, in years	
Mean ± SD	49.4±14.12
Median	50
Range	20-83
Gender, N. (%)	
Male	14 (82.4%)
Female	3 (17.6%)
Presence of comorbidities, N. (%)	
No comorbidities	15 (88.2%)
Diabetes	1 (5.9%)
Hypertension	1 (5.9%)
Tumor site, N. (%)	
Nasopharynx	12 (70.6%)
oropharynx	3 (17.6%)
oral cavity	1 (5.9%)
sinonasal region	1 (5.9%)
Treatment modality, N. (%)	
Radiotherapy alone	8 (47.1%)
Radiotherapy + surgery	9 (52.9%)
Tumor histology, N. (%)	
Poorly differentiated ca	9 (52.9%)
Undifferentiated nasopharyngeal ca	4 (23.5%)
Moderately differentiated SCC	2 (11.8%)
Well-differentiated SCC	1 (5.9%)
Haemangiopericytoma	1 (5.9%)

Table 1. **Demographic, disease and treatment characteristics of the patients included in the study (n=17)**

The mean age at the start of the study was 49.4 years (range, 20-83 years). The gender most represented was male (82.4%). The majority of the patients (88.2%) did not have any comorbidities. One patient was diabetic and another was hypertensive on regular medication. 70.6% of all patients had malignancies involving nasopharynx, followed by oropharynx (17.6%), oral cavity (5.9%) and sinonasal region (5.9%). Considering the different primary sites, treatment modality of these patients varied from surgery followed by adjuvant RT in 9 patients (52.9%) and RT alone in 8 patients (47.1%). The study group showed a wide range of histological variants with poorly differentiated carcinoma being the most common (52.9%).

The mean total CCCRC score achieved before treatment yielded a score of 6.09±2.50 for the right nasal side and 6.16±2.26 for the left. Subsequently, in regard to the radiation treatment, the score shows a deteriorating trend both for the right and left sides as the radiation exposure increases over time. The decrease in the total CCCRC score was significant at each time period, including the 3-month follow-up as compared to the baseline (all p values <0.05) as shown in Table 2. Detailed n-butanol odor threshold and odor identification scores are also presented in Table 2.

Olfactory tests	Pre RT	Mid RT	End of RT	3 months post-RT	P values		
N-butanol odor threshold score, mean±SD					**Pre RT vs. Mid RT**	**Pre RT vs. End of RT**	**Pre RT vs. 3-month follow up**
Right	6.15±3.14	4.48±2.23	3.96±2.45	5.13±2.54	**0.006**	**0.002**	**0.044**
Left	6.05±2.47	4.37±2.48	4.05±2.16	5.43±2.27	**0.007**	**0.003**	**0.037**
Odor identification score, mean±SD							
Right	6.03±1.86	4.79±1.57	3.98±1.36	5.01±1.97	**0.010**	**0.005**	**0.042**
Left	6.26±2.04	4.30±1.84	3.72±1.43	4.98±1.55	**0.004**	**0.002**	**0.035**
Total CCCRC test score, mean±SD							
Right	6.09±2.50	4.64±1.90	3.97±1.91	5.07±2.26	**0.008**	**0.002**	**0.041**
Left	6.16±2.26	4.34±2.16	3.89±1.79	5.21±1.91	**0.005**	**<0.001**	**0.036**

RT: radiotherapy; CCCRC: Connecticut Chemosensory Clinical Research Center.

Table 2. Olfactory threshold, odor identification and composite scores of right and left nasal sides at each time period in the study.

According to the CCCRC scores at the end of RT, 1 (5.9%) patient was classified as normal, 1 (5.9%) as mildly hyposmic, 5 (29.4%) as moderately hyposmic, 7 (41.2%) as severely hyposmic and 3 (17.6%) as anosmic. The distribution of severity of olfactory dysfunction based on olfactory scores at 3 months post RT saw instead, 3 (17.6%) patients classified as normal, 5 (29.4%) as mildly hyposmic, 3 (17.6%) as moderately hyposmic, 4 (23.5%) as severely hyposmic and 2 (11.8%) as anosmic (Table 3).

The study cohort showed a significant increase in STT at each time period when compared to the baseline. Patients developed prolonged mucociliary clearance time at mid-RT (19.85 ± 3.11; p=0.011) and at the end of RT (26.15 ± 2.68; p=0.003). At the 3-month post-RT follow up, there was a slight improvement in STT, however, patients continued to have a significantly prolonged mucociliary clearance time compared to the baseline (21.56±2.15; p=0.010).

Level of olfactory function	End of RT	3-month follow-up
Normosmic, N. (%)	1 (5.9%)	3 (17.6%)
Mildly hyposmic, N. (%)	1 (5.9%)	5 (29.4%)
Moderately hyposmic, N. (%)	5 (29.4%)	3 (17.6%)
Severely hyposmic, N. (%)	7 (41.2%)	4 (23.5%)
Anosmic, N. (%)	3 (17.6%)	2 (11.8%)

RT: radiotherapy

Table 3. Evaluation of CCCRC olfactory test scores, patient distribution (percentage). Normosmic: 6.00–7.00, mildly hyposmic: 5.00–5.75, moderately hyposmic: 4.00–4.75, severely hyposmic: 2.00–3.75, anosmic: 0–1.75.

Although there were only a few AHSP domains significantly affected by treatment (appetite and hunger domains), when the total QoL scores were compared before and after therapy, there appeared to be a significant fall in the overall total QoL score post-therapy, both at mid RT (84.81±13.32; p=0.019) and at the end of RT (83.82±9.36; p=0.003). No significant differences were observed for overall QoL at the 3-month point post RT compared to pre-RT scores (p=0.125) (Table 4).

	Pre RT	Mid RT	End of RT	3 months post-RT	P values: Pre RT vs. Mid RT	P values: Pre RT vs. End of RT	P values: Pre RT vs. 3-month follow-up
Saccharine Transit Test (minutes)	11.25±2.58	19.85±3.11	26.15±2.68	21.56±2.15	**0.011**	**0.003**	**0.010**
AHSP questionnaire domains scores							
Appetite, mean ± SD	20.15±3.47	16.79±4.13	17.55±3.53	17.42±3.21	**0.045**	**0.048**	0.089
Present smell perception, mean ± SD	9.02±2.08	9.04±3.32	8.37±2.87	7.62±1.98	0.708	0.311	0.212
Present smell perception as compared to past, mean ± SD	8.10±2.31	8.05±2.47	8.50±2.07	8.38±1.55	0.742	0.298	0.442
Taste, mean ± SD	24.60±4.95	21.76±3.59	22.12±3.10	23.37±3.77	**0.026**	0.095	0.195
Hunger, mean ± SD	32.50±4.61	29.17±7.12	27.28±6.46	33.54±6.61	**0.047**	**0.013**	0.577
Total QoL score, mean ± SD	94.37±10.63	84.81±13.32	83.82±9.36	90.33±10.46	**0.019**	**0.003**	0.125

RT: radiotherapy; AHSP: Appetite, Hunger and Sensory perception; QoL: Quality of Life

Table 4. STT and AHSP questionnaire domain scores at each time period in the study.

4. Discussion

RT is an important nonsurgical component of HNC treatment and although olfactory fibers and olfactory receptors lie within the field of irradiation, the impairment of olfactory function has rarely been reported [19]. Notably, when such patients complain of decreased olfactory function during the radiation treatment course, there seems to be a low level of interest in the disorder even though it may be life-threatening[20]. In order to look at this aspect, the aim of this study was to evaluate changes in nasal and olfactory function in patients with head and neck malignancies who have received radiation to the head and neck.

Olfactory function, nasal mucociliary clearance, and quality of life assessment were evaluated at four time-points: pre-treatment, mid-RT, immediate post-RT and at 3 months after RT.

This study shows a gradual and significant decline in both olfactory threshold and odor identification in our patients following 2 weeks of RT (mid-RT period) which progressed until the end of RT. When olfactory function was assessed at the 3-month point follow-up, there was a recovery of olfaction to a normal level in a very few while olfactory loss still persisted in others. In a similar study, Ophir et al followed 12 patients with nasopharyngeal carcinoma or pituitary adenoma for up to 6 months after RT. The olfactory function significantly decreased during the course of treatment and varying degrees of recovery was noted in most patients 3–6 months after treatment [21]. This is in agreement with our study where a significant reduction was noted at mid-RT assessment and even though there was an improvement in olfaction at the 3-month point post RT evaluation, it continued to be significantly reduced compared to the pre-RT baseline. In another study, Ho et al measured olfactory threshold, odor identification, and odor discrimination in 48 patients. They used the 'Sniffin–Sticks' test within the first 6 months after treatment for nasopharyngeal carcinoma. Contrary to our findings, a mostly negative result was found in this prospective study. Only 12 months after RT there was a significant deterioration in olfactory thresholds. However, olfactory discrimination and identification did not show any significant change [11]. Several hypotheses were proposed about the role of RT on olfactory dysfunction. These included a reduced turnover of olfactory neurons due to halted mitosis in the basal cell layer [18],damage to the Bowman's glands in the olfactory mucosa [12,22],damage to the olfactory bulb [18],temporary demylinization of olfactory fibres [12]and development of mucosal edema that blocks access to odorants [23]. Overall, findings from these studies are controversial and there is no consensus as to which mechanism is predominant.

Many patients undergoing radiation therapy for HNC complain of a mild increase in subjective nasal symptoms such as nasal congestion, facial pain and foul smell during treatment. This was attributed to the prolonged mucociliary clearance time and inadequate drainage of secretions [24]. Damage to the respiratory mucosa and the cilia due to direct effects of irradiation have been reported in several studies following physiological changes such as vacuolation of the ciliary cells, goblet cell secretions, nuclear pyknosis, decreased ciliary cells and sloughing [25].

In the present study, nasal mucociliary clearance was assessed by performing the STT following the method described in previous studies [15,26]. The difference between the post-irradiation saccharin perception time and the pre-irradiation saccharin perception time was found to be statistically significant at all of the study's time points including at the 3-month point follow-up. Our findings confirm previous observations [24,27] that showed significantly prolonged saccharin perception time in HNC patients after RT when compared to their pre-irradiation values.

Several studies have investigated the effect of RT on taste and smell alterations and how these have a negative impact on the quality of life in HNC patients [28,29]. HNC-RT treated patients usually experience decreased food intake that could be due to decreased appetite induced by nausea and altered taste or smell, oral ulcers and oropharyngeal mucositis, hyposalivation, and xerostomia and decreased interest in food associated with feelings of depression that consequently lead to low quality of life in these patients [29]. We used the AHSP questionnaire to assess QoL and present status of the patients' appetite, smell, frequency of meals and alterations in taste.

We observed that the total overall QoL score at the end of RT was significantly reduced as compared to the total score prior to RT. However, individual components such as appetite and hunger were also significantly reduced even though olfaction did not show a significant reduction. Our findings confirm Baharvand and colleagues' observations of a significant deterioration in QoL associated with clinically evaluated RT-induced taste loss [30].

There are some limitations to the study. Factors such as nasogastric tubes and nasal packing were confounding. Hence, prolonged effects of mucociliary clearance time could not be effectively assessed. Furthermore, the few numbers of studies in this area of interest along with different tests used in the literature did not help comparison of data.

5. Conclusions

Olfactory threshold and identification, as well as mucociliary clearance, are functions impaired after RT for HNC. Although a partial recovery at the 3-month point follow-up was seen, these dysfunctions persisted even after 3 months following radiation therapy. The patients did not notice olfactory dysfunction subjectively so we highlight the importance of screening all HNC patients treated with RT to verify the occurrence of taste and smell alterations. Moreover, our findings suggest that the impairment of the quality of life can be attributed as an indirect impact of olfactory loss. All of these alterations should be considered when selecting a therapy for HNCs. Future studies should adopt more useful and validated tools to capture alterations that cannot be measured by conventional instruments to help healthcare professionals identify the nature and severity of the taste and smell alterations and choose the best strategy for reducing their impact on QoL.

References

1. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 2018; 391:1023-1075.
2. Grillo C, Saita V, Grillo CM, Andaloro C, Oliveri S, Trovato L, La Mantia I. Candida colonization of silicone voice prostheses: Evaluation of device lifespan in laryngectomized patients. Otorinolaringol 2017; 67:75-80.
3. Fischer DJ, Epstein JB. Management of patients who have undergone head and neck cancer therapy. Dent Clin North Am 2008; 52:39-60.
4. La Mantia I, Rossitto F, Andaloro C. Quality of life in head and neck cancer: Patients' and family caregivers' perceptions. Egypt J Ear Nose Throat Allied 2017; 18:247-250.
5. Epstein JB, Phillips N, Epstein MS, Nevill T, Stevenson-Moore P. Quality of life, taste olfactory and oral function following highdose chemotherapy and allogeneic cell transplantation. Bone Marrow Transplant 2002; 30:785-792.
6. Porter SR, Fedele S, Habbab KM. Taste dysfunction in head and neck malignancy. Oral Oncol 2010; 46:457-459.
7. Irune E, Dwivedi RC, Nutting CM, Harrington KJ. Treatment-related dysgeusia in head and neck cancer patients. Cancer Treat Rev 2014; 40:1106-1117.

8. McLaughlin L, Mahon S. A meta-analysis of the relationship among impaired taste and treatment, treatment type, and tumor site in head and neck cancer treatment survivors. Oncol Nurs Forum 2014; 41:E194-E202.
9. Henkin RI, Hoye RC. Hyposmia secondary to excision of the olfactory epithelium. The definition of primary and accessory areas of olfaction. Life Sci 1966; 5:331-341.
10. Hovan AJ, Williams PM, Stevenson-Moore P, Wahlin YB, Ohrn KE, Elting LS, Spijkervet FK, Brennan MT; Dysgeusia Section, Oral Care Study Group, Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO). A systematic review of dysgeusia induced by cancer therapies. Support Care Cancer 2010; 18:1081-1087.
11. Ho W-, Kwong DLW, Wei WI, Sham JST. Change in olfaction after radiotherapy for nasopharyngeal cancer - A prospective study. Am J Otolaryngol 2002; 23:209-214.
12. Hölscher T, Seibt A, Appold S, Dörr W, Herrmann T, Hüttenbrink KB, Hummel T. Effects of radiotherapy on olfactory function. Radiother Oncol 2005; 77:157-163.
13. Michelazzo MB, Pastorino R, Mazzucco W, Boccia S. Distance learning training in genetics and genomics testing for Italian health professionals: results of a pre and post-test evaluation. Epidemiol Biostat Public Health 2015; 12:1-6
14. Cain WS, Gent JF, Goodspeed RB, Leonard G. Evaluation of olfactory dysfunction in the Connecticut Chemosensory Clinical Research Center. Laryngoscope 1988; 98:83-88.
15. La Mantia I, Andaloro C. Effectiveness of intranasal sodium hyaluronate in mitigating adverse effects of nasal continuous positive airway pressure therapy. Am J Rhinol Allergy 2017; 31:364-369.
16. Ciprandi G, Natoli V, Puccinelli P, Incorvaia C. Allergic rhinitis: the eligible candidate to mite immunotherapy in the real world. Allergy Asthma Clin. Immunol 2017; 13:1.
17. Savina C, Donini LM, Anzivino R, De Felice MR, De Bernardini L, Cannella C. Administering the “AHSP Questionnaire” (appetite, hunger, sensory perception) in a geriatric rehabilitation care. J Nutr Health Aging 2003; 7:385-389.
18. Veyseller B, Ozucer B, Degirmenci N, Gurbuz D, Tambas M, Altun M, Aksoy F, Ozturan O. Olfactory bulb volume and olfactory function after radiotherapy in patients with nasopharyngeal cancer. Auris Nasus Larynx 2014; 41:436-440.
19. Jalali MM, Gerami H, Rahimi A, Jafari M. Assessment of olfactory threshold in patients undergoing radiotherapy for head and neck malignancies. Iran J Otorhinolaryngol 2014; 26:211-217.
20. Santos DV, Reiter ER, DiNardo LJ, Costanzo RM. Hazardous Events Associated with Impaired Olfactory Function. Arch Otolaryngol Head Neck Surg 2004; 130:317-319.
21. Ophir D, Guterman A, Gross-Isseroff R. Changes in Smell Acuity Induced by Radiation Exposure of the Olfactory Mucosa. Arch Otolaryngol Head Neck Surg 1988; 114:853-855.
22. Landis BN, Hummel T, Hugentobler M, Giger R, Lacroix JS. Ratings of overall olfactory function. Chem Senses 2003; 28:691-694.
23. Brämerson A, Nyman J, Nordin S, Bende M. Olfactory loss after head and neck cancer radiation therapy. Rhinology 2013; 51:206-209.
24. Kilic C, Tuncel U, Comert E, Kaya BV. The effect of radiotherapy on mucociliary clearance in patients with laryngeal and nasopharyngeal cancer. Eur Arch Otorhinolaryngol 2015; 272:1517-1520.
25. Lou PJ, Chen WP, Tai CC. Delayed irradiation effects on nasal epithelium in patients with nasopharyngeal carcinoma - an ultrastructural study. Annal Otol Rhinol Laryngol 1999; 108:474-480.
26. La Mantia I, Andaloro C. Demographics and clinical features predictive of allergic versus non-allergic rhinitis in children aged 6–18 years: A single-center experience of 1535 patients. Int J Pediatr Otorhinolaryngol 2017; 98:103-109.
27. Gupta SC, Chandra S, Singh M. Effects of irradiation on nasal mucociliary clearance in head and neck cancer patients. Indian J Otolaryngol Head Neck Surg 2006; 58:46-50.
28. Rose-Ped AM, Bellm LA, Epstein JB, Trotti A, Gwede C, Fuchs HJ. Complications of radiation therapy for head and neck cancers: The patient's perspective. Cancer Nurs 2002; 25:461-469.
29. Alvarez-Camacho M, Gonella S, Ghosh S, Kubrak C, Scrimger RA, Chu KP, Wismer WV. The impact of taste and smell alterations on quality of life in head and neck cancer patients. Qual Life Res 2016; 25:1495-1504.
30. Baharvand M, Shoalehsaadi N, Barakian R, Jalali Moghaddam E. Taste alteration and impact on quality of life after head and neck radiotherapy. J Oral Pathol Med 2013; 42:106-112.