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Radiation-Induced Rhinitis: Cytological and Olfactory Changes

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Abstract

Background: Oral mucositis is a well-known adverse event of radiotherapy (RT) for head and neck cancer (HNC). Its nasal counterpart, the radiation-induced rhinitis, is poorly studied and considered in clinical practice.

Objective: The aim of this observational study was to evaluate acute cytological and olfactory alterations during RT and their correlation with RT doses.

Methods: Ten patients who underwent RT for HNC, excluding tumors of the nasal cavities, were evaluated with nasal scraping for cytological examination, Sniffin' Sticks test for olfactory assessment, and Nasal Obstruction Symptom Evaluation scale. The examinations were performed before (T0), at mid-course (T1), and at the end (T2) of RT. They were repeated 1 and 3 months after RT (T3 and T4). Mean dose (D_{mean}) and near maximum dose ($D_{2\%}$) to nasal cavities and inferior turbinates were used for correlation analyses.

Results: Radiation-induced rhinitis was present in 70% of patients at T2, and it was still observed in 40% of cases after 3 months. Although olfactory function remained within the normal range at the evaluated times, a significant decrease in odor threshold and discrimination was observed during RT, which returned to baseline levels after RT. Nasal cytology showed a radiation-induced rhinitis with neutrophils and sometimes bacteria. Mucous and squamous cell metaplasia appeared in 10% of patients. D_{mean} and $D_{2\%}$ to inferior turbinates were associated to neutrophilic rhinitis at T2, and $D_{2\%}$ to inferior turbinates was correlated to mucous cell metaplasia at T2.

Conclusions: RT for HNC induces acute rhinitis that may persist after the completion of treatment and can affect patient's quality of life. Nasal cytology can help to choose the best treatment on an individual basis.

Keywords

radiation, rhinitis, radiotherapy, smell, nasal cytology, Sniffin's stick, mucositis, head and neck cancer, nasal cavities, adverse events

Introduction

Radiation therapy (RT) is a mainstay option in the multimodality approach of head and neck cancer (HNC) patients.[1] It is frequently combined with concurrent chemotherapy to enhance radiation sensitivity and provide spatial cooperation.[2] New technologies consistently improved the therapeutic ratio in this setting, but acute and long-term side effects still occur.[3,4]

Treatment volumes for HNC patients also include mucous membranes and submucosa, which potentially expose normal tissues to develop acute mucositis and late submucosal fibrosis.[5] Among the acute alterations

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induced by RT, some characteristically involve the mucosa of the head and neck region.[6] Erythema and ulceration are the most frequent mucosal adverse effects. Cytological changes of the mucosa also occur on a long-term basis. As an example, neutrophilic inflammation, squamous cell metaplasia, and mucous cell metaplasia were found in patients after RT for nasopharyngeal carcinoma.[7] Moreover, RT may lead to chronic rhinosinusitis with squamous metaplasia and subepithelial oedema.[8,9]

Another side effect may be olfactory impairment.[6] Smell disorders could be conductive, when related to mechanical obstruction of airflow to the upper nasal cavity, or sensorineural, due to defects in the receptors, olfactory nerve fibers, or central structures. Mean olfactory threshold scores by the Sniffin' Sticks test were shown to deteriorate significantly at 12 months when compared with the scores before irradiation.[10] At a mean follow-up of 59 months after RT for nasopharyngeal cancer, Sniffin' Sticks tests demonstrated a statistically significant difference between healthy subjects and irradiated patients.[11]

Few studies evaluated nasal toxicities after RT in HNC patients,[7–9] and hence there is a lack of data regarding acute adverse effects on nasal cavities. In particular, the cytological alterations of the nasal mucosa have not yet been studied, although rhinitis is a common adverse event of RT and could affect patient's quality of life.

The aim of this observational study was to evaluate acute cytological and olfactory alterations during radiation-induced rhinitis. Moreover, we performed correlation analysis with nasal radiation doses.

Materials and Methods

Ten consecutive patients who underwent RT for HNC at the same center in 2017 were included in the present observational study. The patients were treated by the same physician. We included patients whose treatment volumes involved or were in close proximity to the nasal cavities. Exclusion criteria were nasal cavity cancer, neurological diseases or drugs that could interfere with olfactory function, and chronic rhinosinusitis with or without nasal polyps before RT. Written informed consent was obtained for all patients. This study was performed in agreement with the University of Turin institutional review board.

Symptoms reported by the patients were recorded (olfactory and gustatory alterations). All patients underwent an objective evaluation of nasal and oral signs (rhinorrhea, turbinate hypertrophy, nasal crusting, oral and nasal mucositis) by the same examiner. Nasal cavities were evaluated with an endoscopic fiber optic examination. Endoscopic videos were validated by a second assessor. The grading of oral mucositis was based on the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE, grade 0 = none, grade 1 = erythema of the mucosa, grade 2 = patchy pseudomembranous reaction, grade 3 = confluent pseudomembranous reaction, and grade 4 = necrosis or deep ulceration).[12] For the others symptoms and endoscopic rhinitis characteristics, we reported their presence or absence. The presence of hyperaemia of nasal mucosa indicated nasal mucositis. No intranasal therapies were administered to the patients, except for nasal washing. Nasal washes did not contain any additives other than saline.

Nasal symptoms were assessed by means of the Italian version of the Nasal Obstruction Symptom Evaluation (NOSE) scale.[13] It is a self-administered questionnaire consisting of 5 well-constructed questions with 5 possible responses: not a problem (score = 0), very mild (score = 1), moderate (score = 2), fairly bad (score-= 3), and severe problem (score = 4). The evaluated nasal symptoms are nasal obstruction during rest and exercise, nasal stuffiness, trouble breathing through my nose, and trouble sleeping. A total score is calculated.

Smell was investigated with Sniffin' Sticks test (Burghart Messtechnik, Wedel, Germany). It was based on pen-like odor dispensing devices and consisted of 3 tests for odor threshold, odor discrimination, and odor identification. Nonlateralized measures were used in our analysis. Olfactory tests were performed as previously described.[11,14] Results of the 3 subtests were summed to obtain a "TDI (Threshold Discrimination Identification) score". A TDI score inferior to 19.6 was considered consistent with hyposmia for patients aged >55 years.[15]

Nasal scraping for cytological examination was performed to analyze the inflammation of the nasal mucosa. Cytological samples were collected from the medial portion of the inferior turbinate, by scraping with a Rhinopro® Curette (ASI Arlington Scientific Inc, Springville, UT). The material was laid on a microscope slide, fixed in 95° alcohol for 4 s and stained by the May-Grünwald-Giemsa method. Observation was performed by a common optical microscope, able of a 1000× magnification, analyzing at least 50 microscopic fields. The presence of inflammatory or abnormal epithelial cells was evaluated. Cytology for infectious rhinitis included neutrophils and bacteria.

The objective examination and the tests for smell and nasal cytology were performed before (T0), at midcourse (T1), and at the end (T2) of RT. They were repeated also 1 and 3 months after the end of the RT (T3 and T4). Mean dose (D_{mean}) and near maximum dose ($D_{2\%}$) to the nasal cavities and to the inferior turbinates were used for correlation analyses. Doses to nasal cavities were analyzed in relationship to olfactory changes, while doses to the inferior turbinates were

correlated to nasal cytology because nasal scraping was performed in that region.

All statistical analyses were carried out using Statistical Package for Social Sciences, version 20.0. A descriptive analysis of all data was performed, and they were reported as means or percentages and standard deviations. Since the Kolmogorov–Smirnov test demonstrated a non-Gaussian distribution of variables, except for age and radiation doses, nonparametric tests were used. The Kruskal–Wallis test was used to assess differences between groups in the mean of continuous variables (evolution over time). Furthermore, multiple comparison analyses between 2 time points were always performed by adopting Mann–Whitney U test and χ^2 test. The Spearman's correlation coefficient was used to measure linear association between variables. A P value $<.05$ was considered statistically significant.

Results

Patient-Reported Outcomes and Objective Evaluation

The mean age was 56.90 ± 9.97 years (range: 39–72 years). Table 1 reports clinical characteristics. Two out of 5 smokers stopped smoking during RT. Surgical treatments and chemoradiotherapy regimens are reported in Table 2.

All nasal and oral symptoms and endoscopic rhinitis characteristics peaked at the end of RT (T2), except for cacosmia and dysgeusia that reached the pick in the middle of RT (T1) (Figure 1). Significant changes over time were observed for hyposmia and hypogeusia (P values .001 and .006, respectively). There was a reported decrease in hyposmia (80% vs 40%) and hypogeusia (80% vs 50%) between T2 and T4. Dysgeusia had significant changes over time (P value .006), while cacosmia had not (P value .065). Cacosmia and dysgeusia were not seen to decrease from T2 to T3. Rhinorrhea was observed in 70% of cases at T2 (P value .187 for changes over time), but only 20% had thick secretions. Rhinitis with crusting was present in 40% of the patients at T2 (P value .051 for changes over time). P values for the evolution over time of turbinate hypertrophy and thick nasal secretions were .486 and .644, respectively. The analysis of the evolution over time of these symptoms and signs showed a statistically significant difference only for hyposmia, hypogeusia, and dysgeusia.

Oral mucositis, based on CTCAE scale, was observed in 90% of cases at T1 and T2, while it was near absent at T4 (10% of cases) (P value .016 for changes over time). Nasal mucositis was present in 70% of patients at T2, and it was still observed in 40% of cases at T4 (Figure 2) (P value .032 for changes over time). NOSE total score showed a nonsignificant increase at T2 (P value .064 for

Table 1. Clinical Characteristics.

Characteristic	Number of Subjects (%)
Sex	
Male	10 (100)
Female	0 (0)
Alcohol consumption	
Yes	2 (20)
No	8 (80)
Smoker	
Yes	5 (50)
No	5 (50)
Allergies	
Yes	1 (10)
No	9 (90)
Gastroesophageal reflux disease	
Yes	2 (20)
No	8 (80)
Tumor site	
Nasopharynx	3 (30)
Oral cavity	3 (30)
Parotid gland	3 (30)
Primary unknown	1 (10)
Histological type	
Keratinizing squamous cell carcinoma	3 (30)
Nonkeratinizing carcinoma	2 (20)
Adenocarcinoma	2 (20)
Undifferentiated carcinoma	2 (20)
Myoepithelial carcinoma	1 (10)
Tumor stage	
I	1 (10)
II	4 (40)
III	4 (40)
IV	1 (10)

Table 2. Treatments.

Surgery (number of patients, %)	
Partial glossectomy with cervical node dissection	2 (20)
Removal of floor of the mouth with cervical node dissection	1 (10)
Total parotidectomy	2 (20)
Total parotidectomy with cervical node dissection	1 (10)
Cervical node dissection	2 (20)
No surgery	2 (20)
Chemotherapy (number of patients, %)	
Concurrent chemoradiotherapy	5 (50)
Neoadjuvant chemotherapy + Concurrent chemoradiotherapy	1 (10)
Total fractionated dose to T (number of patients, %)	
66/70 Gy in 33/35 fractions	7 (70)

(continued)

Table 2. Continued

54/60 Gy in 30 fractions	3 (30)
Total fractionated dose to high risk nodes (number of patients, %)	
60/63 Gy in 35 fractions	3 (30)
59.4 Gy in 33 fractions	2 (20)
54.25 Gy in 35 fractions	1 (10)
Total fractionated dose to low risk nodes (number of patients, %)	
54.45 Gy in 33 fractions	2 (20)
54.25 Gy in 35 fractions	3 (30)
Radiation doses (Gy)	
Mean dose (D_{mean}) to nasal cavities	13.59 ± 17.74
Near maximum dose ($D_{2\%}$) to nasal cavities	26.73 ± 31.80
Mean dose (D_{mean}) to inferior turbinates	18.90 ± 24.08
Near maximum dose ($D_{2\%}$) to inferior turbinates	26.46 ± 31.43

changes over time). No clinical and endoscopic findings of rhinosinusitis were found in the patients.

Olfactory Outcomes

A mean TDI score <19.6, which indicated hyposmia, was not observed at any time points. Odor threshold, discrimination, and identification decreased during RT and recovered thereafter (Figure 3). Only odor identification did not show a statistically significant evolution over time (*P* values .001, .046, and .434 for odor threshold, discrimination, and identification, respectively). The decrease during RT and the increase after was particularly evident for TDI score (*P* value .002).

Nasal Cytology

Nasal cytology showed that a radiation-induced rhinitis with neutrophils and sometimes bacteria occurred in 70% of cases and persisted after 1 month. Mucous cell metaplasia appeared in 10% of patients during RT and disappeared after 3 months. On the contrary, squamous cell metaplasia was observed in 10% of cases only after the completion of RT (Figures 3 and 4).

Correlations

Analyzing the correlations among clinical results and radiation doses, we found the following statistically significant correlations: (1) D_{mean} and $D_{2\%}$ to inferior turbinates were associated to neutrophilic rhinitis at T2 (rho = 0.653, $P = .041$ and rho = 0.697, $P = .025$, respectively, for D_{mean} and $D_{2\%}$); (2) $D_{2\%}$ to inferior turbinates was correlated to mucous cell metaplasia at T2 (rho = 0.696, $P = .025$). A borderline significant correlation was observed: (1) between $D_{2\%}$ to inferior turbinates and squamous cell metaplasia at 1 month after RT (rho = 0.609, $P = .062$); (2) between D_{mean} to nasal cavities and subjective hyposmia at T2 (rho = 0.570, $P = .086$); (3) between $D_{2\%}$ to nasal cavities and cacosmia at T2 (rho = 0.610, $P = .061$). There was not a statistically significant correlation of radiation doses with NOSE total score and Sniffin' Sticks results.

Discussion

Acute mucositis represents one of the most debilitating side effects for HNC patients during and soon after RT.[5,6] It does not necessarily involve only oral but also the nasal cavity. Radiation-induced rhinitis is a frequent disorder that has been poorly studied. Our previous study on long-term cytological changes of nasal mucosa after RT for nasopharyngeal cancer showed the presence of inflammatory cells, squamous cell metaplasia and/or prevalence of goblet cells.[7] Moreover, we found a high rate of late olfactory alterations in irradiated patients.[11]

Since the mucosal layer consists of rapidly renewing, proliferating cells, while vasculoconnective components are slowly renewing structures, acute RT toxicity mainly affects the former. Indeed, actively cycling tissues tend to be more susceptible to radiation-induced mitotic deaths. Decrease in oral epithelial cell density, cytological atypia, inflammatory infiltrate and viral cytopathic effects are reported during chemotherapy and/or radiotherapy.[16,17] Clinically important late alterations rarely occur until doses higher than 50 Gy, given with conventional fractionation, and mucosal ulceration remains rare for doses <65 Gy.[6] Late RT effects are usually characterized by paleness and thinning of the epithelium, submucosal induration and, occasionally, chronic ulceration and necrosis with exposure of underlying bone and/or soft tissue.[6]

Using ultrastructural studies, Lou et al. found ciliary loss and disturbed mucociliary function at the infundibular epithelium at a median time of 5.9 years after RT in patients with rhinosinusitis.[18] In our study, we used a safe, not invasive method for evaluating mucosal changes in irradiated patients. Nasal cytology is a low-cost method, and it is already a currently used tool for the diagnosis of allergic and nonallergic rhinitis and other pathological alterations of nasal mucosa. It proved to be adequate for the assessment of oncologic patients.[7,19]

Olfactory function is often altered after RT for nasopharyngeal cancer.[13,14,20] Some studies have been conducted on acute and late taste disorders during RT to the head and neck region.[21] However, acute olfactory impairments have not been well investigated, although they are frequently encountered in daily clinical practice.

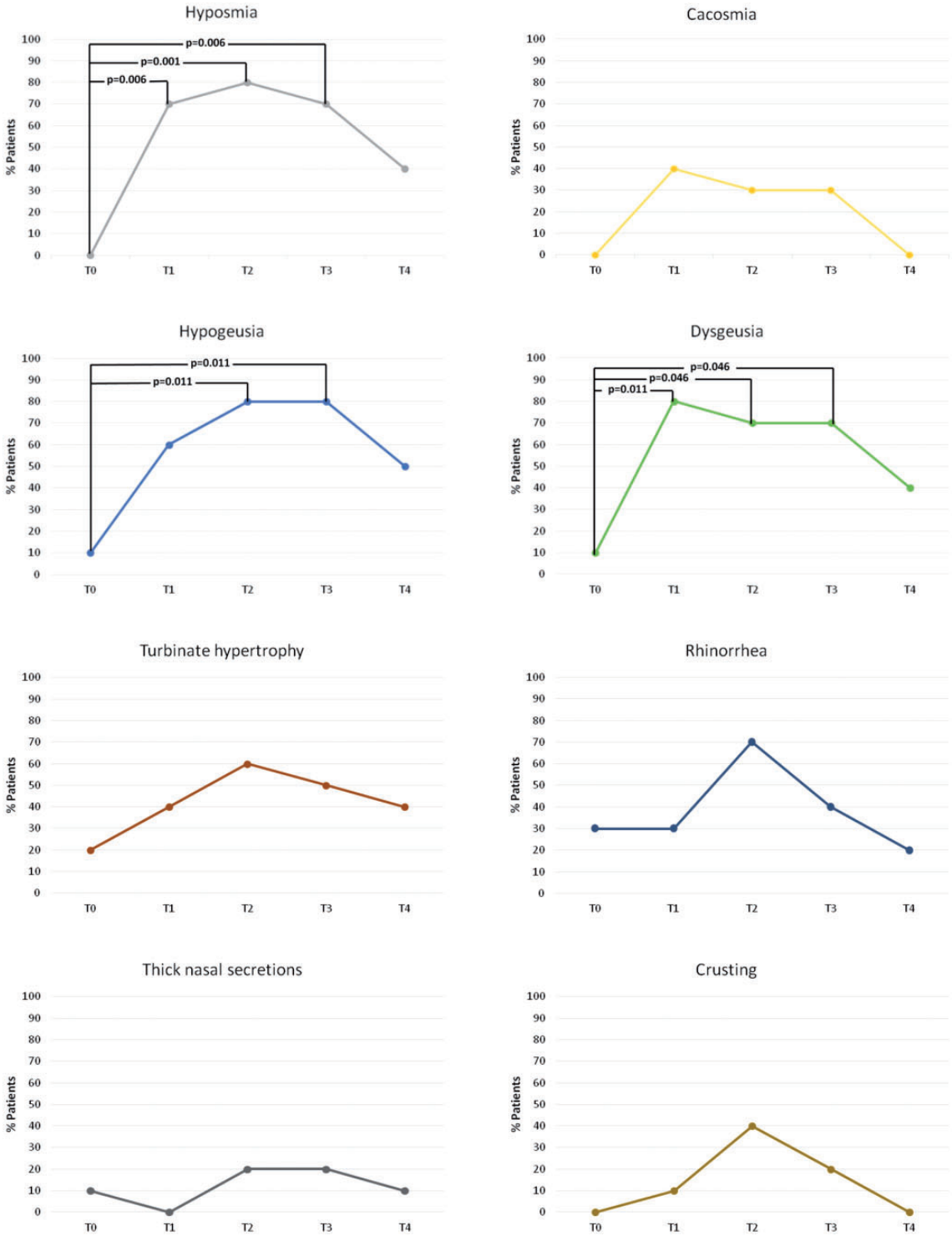

Figure 1. Oral symptoms and signs, and endoscopic features of rhinitis. The graphs represent the impact of RT over time. T0, before RT; T1, at mid-course; T2, at the end of RT; T3, 1 month after the end of the RT; T4, 3 months after the end of the RT.

Irradiated patients for nasopharyngeal cancer show a prominent alteration in olfactory threshold score, compared to odor discrimination and identification.[10,11] This suggests that suprathreshold functioning is not altered since it involves higher brain centers, which are spared from RT delivered to the nasopharynx.[10,11] Moreover, adaptation to sensorial impairment could explain the discrepancy between reported subjective symptoms

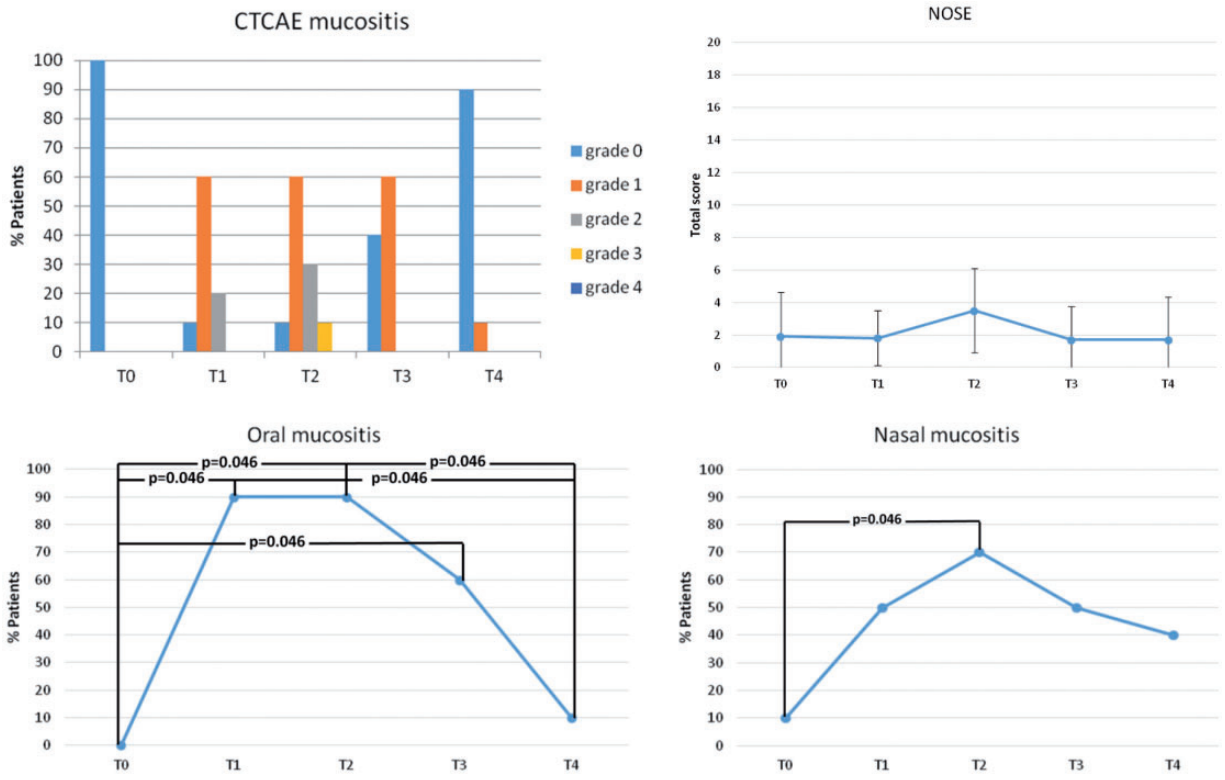

Figure 2. Oral and nasal mucositis, and NOSE total score. The graphs represent the impact of RT over time. Error bars refer to interquartile range. CTCAE, Common Terminology Criteria for Adverse Events version 4.0 (grade 0 = none, grade 1 = erythema of the mucosa, grade 2 = patchy pseudomembranous reaction, grade 3 = confluent pseudomembranous reaction, and grade 4 = necrosis or deep ulceration). NOSE, Nasal Obstruction Symptom Evaluation. T0, before RT; T1, at mid-course; T2, at the end of RT; T3, 1 month after the end of the RT; T4, 3 months after the end of the RT.

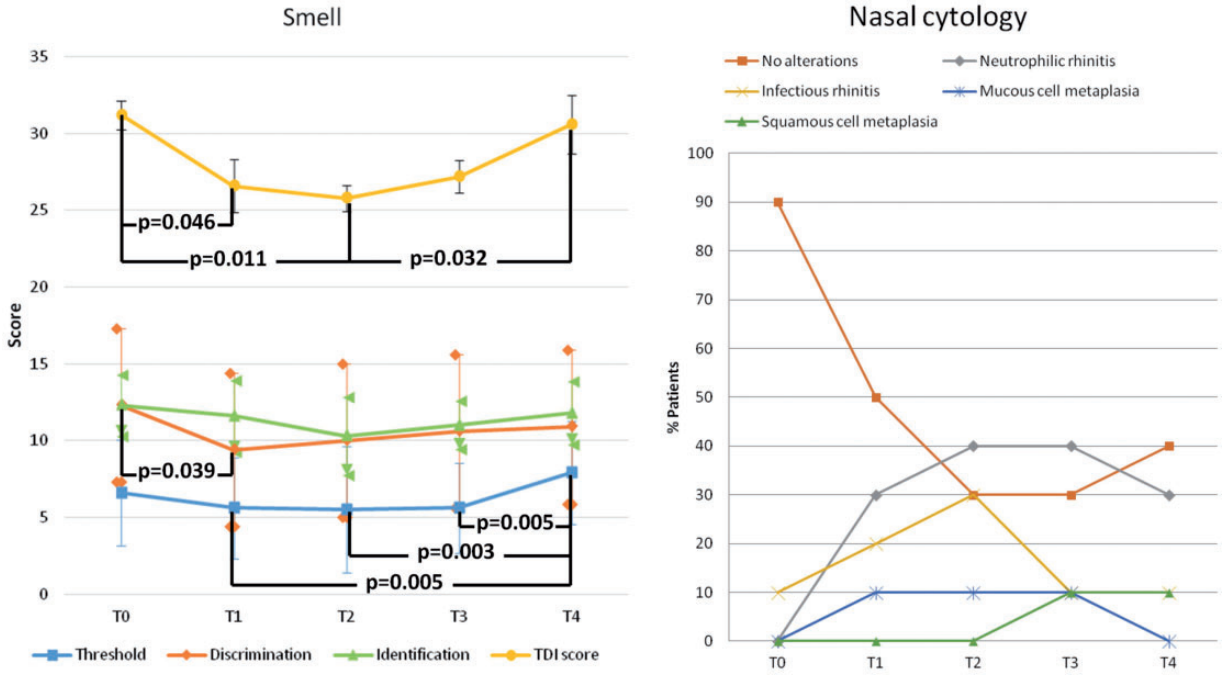

Figure 3. Smell and nasal cytology. The graphs represent the impact of RT over time. Error bars refer to interquartile range. TDI, threshold discrimination identification. T0, before RT; T1, at mid-course; T2, at the end of RT; T3, 1 month after the end of the RT; T4, 3 months after the end of the RT.

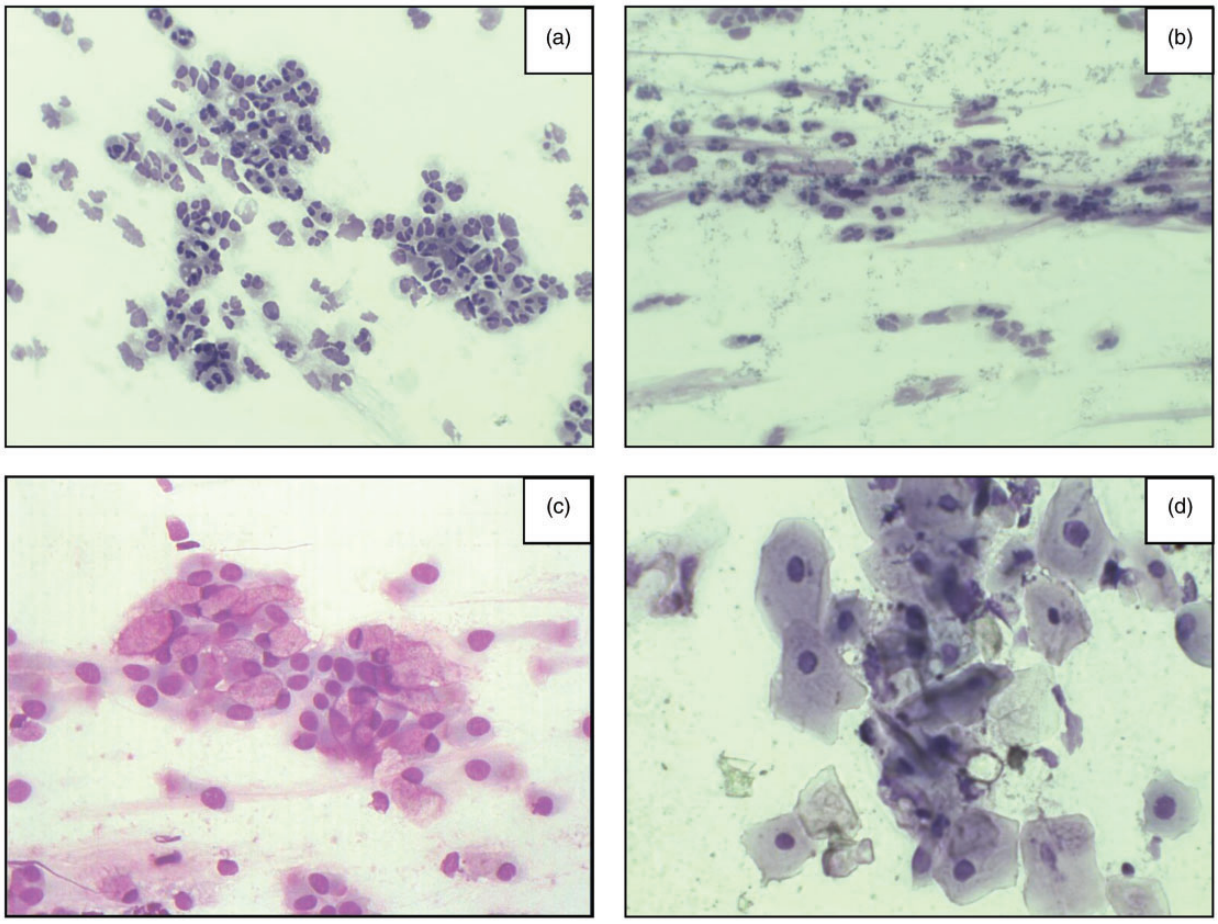

Figure 4. Nasal cytology (May-Grünwald-Giemsa staining, magnification ×400): (a) neutrophilic rhinitis, (b) infectious rhinitis with neutrophils and bacteria, (c) mucous cell metaplasia, and (d) squamous cell metaplasia.

(hyposmia 30%) and objective measurements (hyposmia 86%).[11] The absence of correlation between clinical findings (inferior turbinate hypertrophy, nasal mucositis) and late olfactory impairment suggests that threshold score alterations may be related to a sensorineural deficit of olfactory mucosa or nerve fibers, rather than conductive problems.[13,14] Odor identification and detection threshold impairments occur upon RT completion, especially among patients receiving >10 Gy to olfactory epithelium.[20,22] Impaired odor discrimination function occurs 2 weeks after RT initiation in patients receiving >20 Gy to the olfactory epithelium and returns to normal beyond 12 months posttreatment.[10,11,23]

Our study showed that nasal complaints are frequent in patients undergoing RT. Symptoms usually reached a peak at the end of RT and then decreased. Nevertheless, they persisted in a high percentage of cases at 1 and 3 months after RT completion. This is true also for objective nasal findings. Rhinorrhea, crusting, and nasal obstruction were the main issues. The worsening of nasal obstruction at the end of RT is confirmed by the NOSE questionnaire. Similar to oral mucositis, its nasal counterpart peaked at the end of RT. Conversely, it seemed to persist longer than oral inflammation.

Nasal scraping allowed to show the cytological basis of radiation-induced rhinitis, responsible for nasal complaints. In particular, we investigated the presence of inflammatory cells, squamous cell metaplasia and/or prevalence of goblet cells. A high rate of neutrophilic inflammation (70%) was observed at the end of RT. Some of these cases (almost 50%) were associated to the presence of bacteria, without endoscopic findings of rhinosinusitis. It may be related to an impairment of mucociliary clearance, which is an effect of RT. The presence of bacteria rapidly decreased after the completion of RT, whereas the neutrophilic inflammation persisted in the majority of the patients also 3 months later. Mucous cell metaplasia occurred in 10% of cases during RT and disappeared at 3 months. On the contrary, squamous cell metaplasia appeared 1 month after RT and then persisted. These results are in agreement with our previous study on late effects of RT for nasopharyngeal

cancer that showed 40% of neutrophilic rhinitis, 20% squamous cell metaplasia, and 13% mucous cell metaplasia, after a median follow-up of 59 months.[7] The higher percentages in our previous study were likely to be due to higher radiation doses received by the nasal cavities, given the clinical setting.

A subjective and objective decrease of smell were observed in this study. In particular, odor threshold and TDI score had a nadir at the end of RT and almost recovered after 3 months. It is not in contrast with the previous observation of slightly decreased TDI score as late effect of RT for nasopharyngeal cancer.[11] Concerning odor discrimination, it reached its lower values in the middle of RT, similarly to subjective cacosmia and dysgeusia. Globally, we can say that altered smell and taste perceptions occurred before the peak of reduced perceptions. Finally, odor identification decreased during RT with a lower variation compared to odor threshold and discrimination. The reason is probably related to the sparing of higher brain centers that are involved in suprathreshold functioning. Further studies with larger samples are mandatory to better assess the evolution of smell over time.

The etiologic role of RT in the development of the radiation-induced rhinitis is confirmed by the statistically significant association between cytological changes and radiation doses to the inferior turbinates. Since a near significant association was present between subjective smell complaints and radiation doses, the absence of a significant correlation between objective olfactory impairments and radiation doses is probably due to the small sampling number.

Future studies with larger samples are necessary for a detailed knowledge of the various types of radiation-induced rhinitis (with neutrophils, infectious, mucous and squamous cell metaplasia). On this basis, the best treatment for each patient could be found. Nasal irrigation, topical antibiotics, corticosteroids, and hyaluronic acid are the main available therapies for rhinitis. Nasal cytology would help the physician to choose the treatment that best suits to each patient. Longer studies evaluating acute and late radiation-induced rhinitis will allow to identify subjects prone to develop late toxicities and to intervene promptly. Moreover, since gender may have an impact on smell, the absence of females in our study represents a limit. Larger studies should analyze the impact of sex, age, and smoke on irradiated patients.

Furthermore, it is important to consider that chemotherapy may induce sensorial and cytological side effects. Although smell alterations are generally transient after chemotherapy,[24] there are no data about the role of chemotherapy in the development of nasal mucositis. Further studies are mandatory to assess its role with respect to nasal side effects in HNC patients. Given that most of the patients in our study underwent chemotherapy and the sampling number was low, we did not consider chemotherapy as a variable in the analyses. It represents a possible bias that should be addressed in future studies.

To our knowledge, this is the first study evaluating cytological changes during acute radiation-induced rhinitis and their relationship with radiation doses. Hence, it can be considered as a pilot study and a starting point for future insights.

In conclusion, RT for HNC induces acute rhinitis that may persist after the completion of treatment and can affect patient's quality of life. A better understanding of this clinical entity is mandatory to correctly manage these patients. Nasal cytology can help to choose the best treatment on an individual basis.

Declaration of Conflicting Interests

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References

1. Franco P, Potenza I, Schena M, et al. Induction chemotherapy and sequential concomitant chemo-radiation in locally advanced head and neck cancers: how induction-phase intensity and treatment breaks may impact on clinical outcomes. *Anticancer Res*. 2015;35:6247–6254.
2. Rampino M, Ricardi U, Munoz F, et al. Concomitant adjuvant chemoradiotherapy with weekly low-dose cisplatin for high-risk squamous cell carcinoma of the head and neck: a phase II prospective trial. *Clin Oncol*. 2011;23:134–140.
3. Merlotti A, Alterio D, Vigna-Taglianti R, et al. Technical guidelines for head and neck cancer IMRT on behalf of the Italian association of radiation oncology – head and neck working group. *Radiat Oncol*. 2014;9:264.
4. Franco P, Potenza I, Moretto F, et al. Hypericum perforatum and neem oil for the management of acute skin toxicity in head and neck cancer patients undergoing radiation of chemo-radiation: a single-arm prospective observational study. *Radiat Oncol*. 2014;9:297.
5. Franco P, Martini S, Di Muzio J, et al. Prospective assessment of oral mucositis and its impact on quality of life and patient-reported outcomes during radiotherapy for head and neck. *Med Oncol*. 2017;34:81.
6. Cooper JS, Fu K, Marks J, Silverman S. Late effects of radiation therapy in the head and neck region. *Int J Radiation Oncology Biol Phys*. 1995;31(5):1141–1164.
7. Riva G, Boita M, Ravera M, et al. Nasal cytological changes as late effects of radiotherapy for nasopharyngeal cancer. *Am J Rhinol Allergy*. 2015;29(2):41–45.

8. Kamel R, Al-Badawi S, Khairy A, Kandil T, Sabry A. Nasal and paranasal sinus changes after radiotherapy for nasopharyngeal carcinoma. *Acta Otolaryngol*. 2004;124:532–535.
9. Kuhar HN, Tajudeen BA, Heilingoetter A, et al. Distinct histopathologic features of radiation-induced chronic sinusitis. *Int Forum Allergy Rhinol*. 2017;7(10):990–998.
10. Ho WK, Kwong DL, Wei WI, Sham JS. Change in olfaction after radiotherapy for nasopharyngeal cancer—a prospective study. *Am J Otolaryngol*. 2002;23(4):209–214.
11. Riva G, Raimondo L, Ravera M, et al. Late sensorial alterations in different radiotherapy techniques for nasopharyngeal cancer. *Chem Senses*. 2015;40(4):285–292.
12. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Published 2010.
13. Mozzanica F, Urbani E, Atac M, et al. Reliability and validity of the Italian nose obstruction symptom evaluation (I-NOSE) scale. *Eur Arch Otorhinolaryngol*. 2013;270:3087–3094.
14. Riva G, Sensini M, Corvino A, Pecorari G, Garzaro M. Smell and taste impairment after total laryngectomy. *Ann Otol Rhinol Laryngol*. 2017;126(7):548–554.
15. Hummel T, Kobal G, Gudziol H, Mackay-Sim A. Normative data for the "Sniffin' Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. *Eur Arch Otorhinolaryngol*. 2007;264(3):237–343.
16. Dörr W, Hamilton CS, Boyd T, Reed B, Denham JW. Radiation-induced changes in cellularity and proliferation in human oral mucosa. *Int J Radiation Oncology Biol Phys*. 2002;52(4):911–917.
17. Ahmed GH, Al Elemirri D. Assessment of oral cytological changes associated with exposure to chemotherapy and/or radiotherapy. *Cytojournal*. 2009;6:8.
18. Lou PJ, Chen WP, Tai CC. Delayed irradiation effects on nasal epithelium in patients with nasopharyngeal carcinoma. An ultrastructural study. *Ann Otol Rhinol Laryngol*. 1999;108:474–480.
19. Riva G, Boita M, Corvino A, et al. Nasal and tracheal cytological changes after total laryngectomy in long term survivors. *Ann Otol Rhinol Laryngol*. 2017;126(2):124–131.
20. Hua MS, Chen ST, Tang LM, Leung WM. Olfactory function in patients with nasopharyngeal carcinoma following radiotherapy. *Brain Inj*. 1999;13(11):905–915.
21. Wismer WV. Assessing alterations in taste and their impact on cancer care. *Curr Opin Support Palliat Care*. 2008;2(4):282–287.
22. Álvarez-Camacho M, Gonella S, Campbell S, Scrimger RA, Wismer WV. A systematic review of smell alterations after radiotherapy for head and neck cancer. *Cancer Treat Rev*. 2017;54:110–121.
23. Holscher T, Seibt A, Appold S, et al. Effects of radiotherapy on olfactory function. *Radiother Oncol*. 2005;77:157–163.
24. Fischer DJ, Epstein JB. Management of patients who have undergone head and neck cancer therapy. *Dent Clin North Am*. 2008;52(1):39–60.