

Olfactory loss after head and neck cancer radiation therapy*

Annika Brämerson¹, Jan Nyman², Steven Nordin³, Mats Bende¹

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¹ Department of Otorhinolaryngology, Central Hospital, Skövde, Sweden

² Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden

³ Department of Psychology, Umeå University, Umeå, Sweden

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Summary

Background: A reduced sense of smell may be one explanation for why patients with cancer in the ear, nose and throat (ENT) region who are treated with radiation therapy lose weight. The purpose of this study was to investigate whether radiation therapy has a negative effect on olfactory function and, if so, whether this effect is dose-related.

Methodology: Seventy-one patients were tested using odour-detection sensitivity and olfactory identification tests before radiation therapy and 20 months after it.

Results: Patients who received radiation close to the olfactory organ showed a reduced sense of smell, in both tests. A multiple regression analysis showed that the radiation dose was related to decline in the olfactory function, while age, sex, chemotherapy and interactions between these variables were not.

Conclusion: Radiation therapy can damage olfactory cells.

Key words: smell/radiation effects, radiotherapy/adverse effects, head and neck neoplasms, humans, adults

Introduction

Cancer of the head and neck is related to significant weight loss because of reduced food intake, reduced nutrient absorption and increased metabolic demand. An explanation for this may be that cancer or the cancer treatment is often associated with nausea, pain, dysphagia, hyposalivation, poor oral hygiene, infection in the oral/nasal cavity, and anxiety and depression. The patients may also experience reduced and/or altered taste and smell, and these factors may contribute to a significant impact on quality of life⁽¹⁻³⁾.

Taste disorders can be an immediate effect of chemotherapy, but most often the aetiology of taste disorders is multi-factorial^(1,2). Naturally, an impaired sense of taste is associated with extensive surgery of the tongue, and patients frequently complain of a poor sense of taste when, in fact, the olfactory function

is disturbed⁽⁴⁾. Radiation for head and neck cancer has been shown to induce impaired taste function for a few months⁽⁵⁻⁷⁾. However, only a few prospective studies have been done on the effect of radiation on smell function.

Reduced olfactory function after radiation can be due either to a sensorineural effect of the radiation on the olfactory nerves and receptors or to a secondary effect on the nasal mucosa, with impaired air flow as a conductive effect. An impaired sense of smell is often clinically recognized as a problem of olfactory detection and/or identification. In one study of 48 patients treated with radiation for nasopharyngeal cancer, no effect on the sense of smell was found until 12 months after termination of the therapy. There was a significant deterioration of the detection sensitivity, but no effect on identification or discrimination⁽⁸⁾. In a study of 44 patients with head and neck cancer,

the patients' sense of smell was assessed every second week up to 6 weeks after the start of radiotherapy. Some of them also received chemotherapy. Odour discrimination was significantly decreased 2–6 weeks after onset of the therapy in those who had received more than 20 Gy. In a subgroup of 10 patients, the effect remained more than 6 months after therapy⁽⁹⁾. Therefore, effects of radiation therapy in patients treated for head and neck cancer on the sense of smell are not obvious and data on long-term outcomes are needed.

The aim of this study was to evaluate the effects of radiation on odour detection sensitivity and identification in patients treated for head and neck cancer. We hypothesized that radiation therapy would have a negative effect on olfactory function and that the effect would be greater for high doses than for low doses of radiation.

Materials and methods

Study population

Between 1996 and 2006, all the patients with head and neck tumours at our ENT department were recruited; if they were to have radiotherapy (some had it in combination with chemotherapy and/or surgery). A few patients were excluded for medical or social reasons. A total of 141 agreed to participate. Of that number, 70 patients performed the first olfactory test, but did not the second one. Finally, 71 patients, 20 women and 51 men, aged 35–86 (mean 60.9) years completed the study. The sense of smell was evaluated prior to the radiotherapy as well as between 12 and 35 (mean = 20) months after the therapy. On both occasions the patients were asked about their experience of their sense of smell, and their weight was registered. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Gothenburg Regional Ethics Board.

Tests of olfaction

Olfactory identification was assessed using the Scandinavian Odor Identification Test (SOIT), which consists of 16 odorants (pine needle, peppermint, juniper, violet, anise, clove, vanilla, bitter almond, orange, cinnamon, lemon, lilac, vinegar, tar, ammonia, and apple) and 4 response alternatives for each odorant. SOIT was developed for the Scandinavian population and has satisfactory test–retest and split-half reliability^(11,12). As a test of smell identification, it requires olfactory functions that are important for daily human routines (detection, quality discrimination, and recognition). It has been validated⁽¹¹⁾ by comparison with the University of Pennsylvania Smell Identification Test⁽¹³⁾ and the CCCRC threshold test⁽¹⁰⁾.

Statistical analysis

Differences in olfactory function between those who received

a high and a low radiation dose, respectively, were analysed using t-test. The differences between the first and the second assessment were analysed using paired t-test. A stepwise multiple regression model was used in the statistical analyses of the data. The following explanatory variables were selected in this model: age, sex, radiation dose to the olfactory epithelium, any chemotherapy, time interval between the measurements, and interactions between these variables. To keep this model as parsimonious and plausible as possible, we used stepwise selection (forward and backward) procedures. The alpha level for entry and removal of a variable was set at 5%.

Results

The pre-radiation olfactory tests showed a mean value of the SOIT scores for women of 13.2 (95% confidence interval (CI) = 12.5–13.9) and for men of 12.2 (95% CI = 11.4–13.0). The corresponding values for the butanol threshold test for women was 6.3 (95% CI = 5.1–7.4) and for men was 5.8 (95% CI = 5.1–6.6). The results of the SOIT was in accordance with normative data at corresponding ages from a population-based study with a SOIT value of 13.4 for women and 12.8 for men⁽¹⁴⁾.

The tumours were located on different sites, so patients received different radiation doses (Table 1) in the olfactory epithelium. None of the patients underwent nasosinus surgery. The patients were divided into two groups according to the dose of radiation they received to the olfactory epithelium. The dosages were reconstructed based on the patients' computerized dose plan (Cadplan and Eclipse, Varian Medical Systems, Palo Alto, CA, USA). The uncertainty of the reconstructed doses was $\pm 20\%$ or at least 3 Gy. The uncertainty exists because the dose-calculating system used, a pencil beam in this case, has unreliable dose calculation close to air cavities because of density changes in the tissue.

The patients were divided into two groups: those who were not or were minimally exposed to radiation (<10 Gy) and those who had received some or up to the maximum radiation dose (>10 Gy). A high radiation dose of mean 36.1 (95% confidence interval (CI) 21.7–50.4) Gy was given to 15 patients, six women and nine men, mean age 65.9 (95% CI 61.1–70.6) years. A low radiation dose of mean 2.2 (95% CI 1.5–2.8) Gy was given to 14 women and 42 men, mean age 59.6 (95% CI 56.0–63.3) years.

The assessment of detection sensitivity before treatment showed a mean threshold of dilution step 6.1 (95% CI 4.8–7.4) in the high-dose group and of 5.9 (95% CI 5.2–6.6) in the low-dose group. The corresponding dilution steps after treatment were 4.5 (95% CI 2.9–6.1) and 6.5 (95% CI 5.7–7.3), respectively. Before treatment there was no significant difference between the groups, but after treatment a significant inter-group difference

Table 1. Location sites of 71 ear, nose and throat (ENT) tumours and of the radiation dose to the olfactory epithelium.

Tumour location	Number of patients	Mean radiation dose (Gy)	95% confidence interval of the radiation dose (Gy)
Nose/sinuses	10	48.0	35.0 - 65.0
Parotid gland/ ear/ facial skin	8	6.9	3.8 - 10.1
Oral cavity	12	5.4	2.8 - 8.0
Oropharynx	26	2.2	1.0 - 3.3
Nasopharynx/larynx	15	0.5	0.1 - 0.9

was seen ($p < 0.05$). The difference between the first and the second assessment was larger for the high-dose group ($p < 0.05$).

The identification test given before treatment yielded a mean score of 12.4 (95% CI 11.0–13.8) in the high-dose group and 12.5 (95% CI 11.8–13.2) in the low-dose group. The corresponding scores after treatment were 10.2 (95% CI 8.6–11.8) and 12.4 (95% CI 11.5–13.2), respectively. Before treatment there was no significant difference between groups, but after treatment there was ($p < 0.05$). The difference between the first and the second assessment was larger for the high-dose group ($p < 0.001$).

Thirty-two patients also received two to three cures of chemotherapy, usually before radiation therapy (Table 2). Of these, 26% received a high dose of radiation and 74%, a low dose. Among the 39 patients who were not treated with chemotherapy, 18% received a high dose of radiation and 82%, a low dose (not significant, chi-square analysis).

Regarding the patients' subjective experience of olfactory capability after therapy, in the high-radiation group one patient (7%) reported improvement and six (40%) reported a decline, while in the low-radiation group, four (7%) reported improvement and four (7%) reported a decline in olfactory capacity.

The mean weight for all patients was 80.5 (95% CI 77.3–83.7) kg before treatment and 75.2 (95% CI 71.9–78.5) kg after treatment. The difference was statistically significant ($p < 0.0001$). There was no significant difference in weight change between those who received a high and those who received a low dose of radiation.

A multiple regression analysis showed that the radiation dose was significantly related to olfactory function, while age, sex,

Table 2. Additional chemotherapy given to 32 patients: platinum compounds (cisplatin, carboplatin), pyrimidine compounds (fluorouracil, tegafur) and taxanes (docetaxel, paclitaxel).

Number of patients	Mean age (yrs)	Female/ male (n)	Chemotherapy (type of drug)		
			platinum	pyrimidine	taxanes
29	64	4/25	X	X	
2	55	0/2	X	X	X
1	50	0/1		X	

any chemotherapy, time interval between the measurements, and interactions between these variables were not.

Discussion

The findings from this longitudinal study demonstrate that patients with tumours of the head and neck who received radiation to the olfactory epithelium showed a decline in both detection sensitivity and odour identification. This was in accordance with the hypothesis. As expected, the effect of radiation on olfactory performance was greater for the high-dose than for the low-dose radiation group. It should be noted that there is no clinical definition of "high" and "low" radiation dose. Although the study group were heterogeneous we could not find any factor other than the radiation dose as being an important in the difference in olfactory function between the two assessments. The factors we considered included age, sex and treatment with different chemotherapeutic drugs. Other factors such as ageing may have influenced the results and likely there are genetic variations in the sensitivity to radiation. Because of variations in factors such as age, gender, and in the initial value of the smell tests, it was not possible to further divide material, for instance, based on diagnosis.

A previous study in an Asian population reports deterioration in detection sensitivity but not in smell discrimination or identification 12 months after radiotherapy, and no effects on olfaction 6 months after radiotherapy. The authors suggest that the radiation had a sensorineural effect on the receptor cells and nerve endings in the olfactory region of the upper nasal vault⁽⁸⁾. The lack of effects on identification, and possibly also on discrimination, may be due, to some extent, to the test odorants being culturally valid for a European population rather than for an Asian population. Another study reports impairment in olfactory discrimination during radiation therapy and

impairment in odour identification 6 months after therapy, but no effect on olfactory sensitivity⁽⁹⁾. Because there were no changes in olfactory sensitivity, that study discussed whether radiotherapy affects the olfactory bulb/orbito-frontal cortex and whether the olfactory epithelium is relatively resistant to the effects of radiation therapy. No previously published study assessing olfaction before and after radiation therapy has shown impairment in both odour detection and identification. Because we found impairment in both odour sensitivity and identification, we propose that radiation may have an effect both on the olfactory epithelium in the nasal cavity and on more central pathways. Our results could also reflect an entirely peripheral effect such as damage to the olfactory receptors or neurons or blockage of the nasal mucosa (keeping the odour from reaching the olfactory region). Biopsies of the olfactory mucosa and nasal endoscopy, before and after radiation therapy, are suggested for further studies. The peripheral olfactory system has a significant ability to regenerate, so it would be useful to study the long-term effects of radiation therapy on the olfactory epithelium in the nasal cavity.

The results from the psychophysical and perceptual assessment of olfaction were to some extent supported by self-reports on olfactory capability. Seven per cent of the patients in the low-radiation group and 40% of the patients in the high-radiation group reported a decline in olfactory capability after radiation therapy. However, a large proportion of the patients in both dose groups reported no change in olfactory capability. This

may be, in part, the result of the relatively high unawareness of olfactory decline in the general population; this lack of awareness is manifested when comparing self-reports⁽¹⁵⁾ with outcome on psychophysical and perceptual assessment⁽¹⁴⁾.

Conclusion

In conclusion, the results from the present study suggest that radiation therapy is deleterious to the sense of smell, possibly because of a direct effect of the radiation on the olfactory epithelium. In addition, an impaired sense of smell may be burdensome for a patient with a head and neck tumour.

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Authorship contribution

AB: Planning, performing all measurements, and writing.
SN: Planning, writing, and responsible for olfactory tests. JN: Responsible for calculations of the radiation dose, and writing.
MB: Planning, writing, and supervision

Conflict of interest

None to declare.

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Prof. Mats Bende
Department of Otorhinolaryngology
Hospital of Skaraborg
SE 54185 Skövde
Sweden

Tel +46-76-945 4353
Fax +46-50-043 1628
E-mail mats.bende@vgregion.se