



## Olfaction in chemotherapy for head and neck malignancies



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### ABSTRACT

**Objective:** Systemic chemotherapy for different malignancies occurs alongside various side effects, including reduced sensory function. To date, little is known about the effect of chemotherapeutic agents on olfaction. The aim of this study was to provide new data about changes in sense of smell during chemotherapy among patients with advanced squamous cell carcinomas of the head and neck region.

**Methods:** In a prospective, controlled cohort study of patients undergoing up to three courses of chemotherapy (cis- or carboplatin, 5-fluorouracil and docetaxel), olfaction was evaluated prior to and directly following completing a cycle, as well as 3 weeks later with the beginning of the next cycle. For evaluation of sense of smell, the established Sniffin' Sticks test with a determination of threshold, discrimination and identification (TDI) was used. Thirty-three patients (44–85 years old, 25 men and 8 women) were included in the study. Most malignancies were located in the oropharynx.

**Results:** Among the 28 patients who scored normosmic or hyposmic at the beginning of the study, the mean decrease in TDI-score was 0.72 points (24.0–23.2) in the first cycle, 2.1 points (24.5–22.4) in the second cycle and 0.77 points (24.2–23.4) in the third cycle. The decrease during the second cycle was significant. Age (>55 years) had a significant (negative) influence in the first and the second cycles. Smoking only showed a tendency to decreased TDI-scores in chemotherapy. In-between consecutive cycles an increase in TDI-score was obvious (+1.0 points after the first and +1.5 points after the second cycle).

**Conclusion:** Chemotherapy with cisplatin, 5-fluorouracil and docetaxel significantly affected sense of smell to a small extent. This effect was more pronounced in elderly patients and smokers. This fact must be taken into account as a possible additional negative effect in usually prevailing malnutrition in these patients. Furthermore, no cumulative effect of the administered therapeutic agents on olfaction could be proven during this study and recovery occurred within a 3-week period.

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### 1. Introduction

Chemotherapy is a common therapeutic option among patients with malignant tumors. For head and neck malignancies, platinum-based chemotherapy with 5-fluorouracil and docetaxel (TPF) is used as inductive chemotherapy for organ preservation among patients with locally advanced or metastasized tumors, followed by a radiotherapy regimen [1–3].

During chemotherapy, multiple known side effects may occur. Besides gastro-enteric complaints, bone marrow depression and renal complications, and sensory functions such as hearing can be impaired; therefore, audiograms are recommended prior to each

cycle [4–8]. To date, little is known about the effect of chemotherapeutic agents on olfaction. A reduced sense of smell can cause an additional decrease in quality of life in these patients and a reduced oral intake of food, which could cause additional reduction in nutrition [9].

In addition to some notifications in the literature indicating a decrease of olfactory and taste function in cancer patients treated with chemotherapy via self-reports [10–14], there have only been a few studies that have used validated smell tests. Two of these were conducted among patients with gynecologic malignancies [15,16]. In another study, the influence of chemotherapy on olfaction in heterogeneous tumor entities was described [17]. In particular, possible gender differences, the effects of smoking and the time interval for a possible recovery are unclear.

The aim of this study was to investigate the short-term effects of chemotherapeutic agents on olfaction in sequential courses of chemotherapy among patients with locally advanced or metastasized head and neck malignancies. The validated Sniffin' Sticks test

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as a standardized testing method, including olfactory threshold, discrimination and identification, was used. Additionally, the influence of different parameters such as the patient's age, gender and smoking habits was investigated.

## 2. Patients and methods

### 2.1. Patients

The study was conducted at the Department of Otorhinolaryngology, Head and Neck Surgery of the University Medical Center Mainz in Germany. In a prospective, controlled study, olfaction was investigated among 40 in-patients undergoing chemotherapy (cisplatin or carboplatin, 5-fluorouracil and docetaxel) for locally advanced or metastasized squamous cell carcinomas of the head and neck region.

Exclusion criteria were rhinitic symptoms or signs of chronic rhinosinusitis, neurodegenerative disorders, other oncologic diagnoses or treatment prior the actual disease, or medications that may influence the sense of smell or taste. All subjects underwent a complete ear, nose and throat-examination, including nasal endoscopy. Additionally, they underwent a detailed psychophysical olfactometry of threshold, discrimination and identification testing (Sniffin' Sticks test). All participants signed an informed consent form and the study was approved by the local ethics committee.

From the 40 initially recruited patients, in 33 patients, the analysis of at least one complete cycle of chemotherapy could be included. In four cases, the patients refused further participation in the trial; one patient suffered from severe side effects during the first cycle and two patients refused further treatment. The 33 analyzed patients showed an age range from 44 to 85 years and the mean age was 61.6. Eight patients were under 55 years of age and 25 were 55 years or older. The gender distribution was 25 male and 8 female patients; 7 patients were non-smokers and 26 were smokers. The localization of the tumor site was as follows: oropharynx (20), hypopharynx (5) and larynx (8). For demographics, see [Table 1](#).

### 2.2. Ethics statement

The study was approved by the local ethics committee (Landesärztekammer Rheinland-Pfalz) and all participants signed an informed consent prior to participating in the study.

**Table 1**  
Demographic data of included patients.

	Patient group
Total number	33
Female	8 = 24.2%
Male	25 = 75.8%
Age range	44–85
Mean age ( $\pm$ SD)	61.6 $\pm$ 9.14
Smokers	26 = 78.8%
Non-smokers	7 = 21.2%
Tumor site	
Oropharynx	20
Larynx	8
Hypopharynx	5
Olfaction at beginning of the study	
Normosmia	66.7%
Hyposmia	18.2%
Anosmia	15.1%
Number of completed cycles (normosmic and hyposmic patients)	
1	28
2	23
3	16

### 2.3. Chemotherapeutical regimen

All patients received at least one cycle of chemotherapy with cisplatin (100 mg/m<sup>2</sup>) or adapted carboplatin in the case of renal dysfunction at day 1, docetaxel (75 mg/m<sup>2</sup>) at day 1 and 5-fluorouracil (1000 mg/m<sup>2</sup>) at days 1–4 (TPF) [18] in the ward of our department. After each cycle, a recovery period of 3 weeks followed before the start of the next cycle. Patients who underwent at least one and up to three cycles of chemotherapy were included in the analysis.

### 2.4. Sniffin' Sticks test

To evaluate sense of smell, the Sniffin' Sticks test battery (Burghart, Wedel, Germany) was used [19]. It includes a threshold test, a discrimination test and an odor identification test. Using felt-tip pens, odorants were presented approximately 2 cm in front of both nostrils for 2 s. During the threshold (T) testing, three pens were presented to the patient in a randomized order: two contained odorless solvent (propylene glycol) and the other n-butanol in a certain dilution. The pen with the odorant had to be identified. The higher concentration was presented if one of the blanks was chosen and a lower concentration if the correct pen was identified twice in a row single-staircase, three alternative forced choice procedure. The mean of the final four out of a total of seven reversal points was used as a detection threshold (ranging from 1 to 16). The second subtest, an odor discrimination (D) test, was performed with 16 triplets of pens, with two containing the same and one a different odorant. Subjects had to determine which one of the three presented pens smelled differently. The score was the sum of correct responses ranging from 0 to 16. Odor identification (I) was assessed for 16 common odors. The patient had to identify each of the odorants in a forced-choice task from a list of four descriptors. Again, the scores ranged from 0 to 16.

The summation of these three subtests yielded the TDI-score that allows for a classification of olfactory function as normosmic, hyposmic or anosmic [20]. In this study, the differentiation between normosmia and hyposmia referred to the 10% percentile of gender- and age-specific limits of recently published data [21]. Functional anosmia was defined as a TDI-score lower than 15.5. In this study, olfaction was evaluated prior to and directly following completing a chemotherapy cycle, as well as 3 weeks later with the beginning of the next cycle.

### 2.5. Statistical analysis

For statistical analysis, SPSS 16.0 for Windows (Chicago, IL) was employed. Histograms and skewness were used to evaluate normal distribution. Mean values were computed  $\pm$  standard deviations. For verifying initial differences, independent *t*-tests were performed. For the detection of differences in single chemotherapy cycles, the paired samples *t*-test was used. A linear mixed model was used for analysis of longitudinal data with continuous target variables and repeated measures. The level of significance was set at 0.05. Box plots were used for graphical illustrations.

## 3. Results

### 3.1. Classification of olfaction

The category of the subject's olfactory performance at initial presentation was determined. The classification of normosmia, hyposmia and functional anosmia refers to gender- and age-adapted normative data yielded by the Sniffin' Sticks TDI-score [21]; 22 patients showed normosmic scores, six patients were

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