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Effect of platinum-containing chemotherapy on olfactory, gustatory, and hearing function in ovarian cancer patients

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Abstract
Purpose Most patients with epithelial ovarian cancer have a poor overall prognosis. Therefore, one of the main therapeutic aims after cytoreductive surgery for these patients is to identify, delay and relieve chemotherapy-induced side effects and optimise the quality of life, especially after first-line therapy.
Methods Twelve ovarian cancer patients undergoing carboplatinum-containing chemotherapy were assessed using validated tests for olfactory, gustatory, and hearing functions before, during, immediately after, and 3 months after chemotherapy.
Results All chemosensory functions decreased during and after carboplatinum-containing chemotherapy, but recovered 3 months after treatment ended. For olfaction, this decrease was significant, affecting odour identification minimally, and odour threshold the most. For taste, the decrease was not significant, but could be observed in total scores and in each quality (sweet, sour, salty, and bitter). For hearing, the decrease was not significant, but a recovery of the deep and middle frequencies was clearly evident 3 months after chemotherapy.
Conclusions Patients must be informed about transient declines in chemosensory functions during chemotherapy. Symptomatic relief provided by the use of more spices, a small amount of glutamate, or additional flavouring might help to compensate for decreased functions during chemotherapy and increase patient quality of life.

Keywords Smell · Taste · Hearing · Ovarian cancer · Side effects of chemotherapy

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Introduction

Epithelial ovarian cancer has the highest mortality rate of all gynaecological malignancies [1] and is seldom diagnosed before the tumour has disseminated throughout the entire abdominal cavity. Standard guideline-directed therapy consists of radical, debulking surgery with the aim of complete tumour resection, followed by cytotoxic chemotherapy. Most ovarian cancer patients receive a chemotherapy regimen that includes a platinum drug (carboplatin) and a taxane (paclitaxel) which induce tumour response in the range 60–80 % [2]. The median overall survival for ovarian cancer patients with FIGO II–IV lesions treated with platinum/paclitaxel chemotherapy ranges from 36 to 39 months. This survival time is 6–7 times longer than the median survival time after surgery only [3]. Unfortunately, recurrence rates after initial chemotherapy are quite high. Patients

sensitive to first-line platinum-based chemotherapy can be re-challenged with the same drugs; others require alternative single agents that induce tumour responses in the range 10–30 % [3]. Until now, the main therapeutic aims for ovarian cancer patients, in particular those undergoing chemotherapy beyond first-line treatment, also included reducing the severity of the symptoms, delaying symptom occurrence, and optimising the quality of life.

Buckingham et al. [4] estimated the incidence and severity of carboplatinum side effects in the treatment of ovarian cancer. Eleven ovarian cancer patients completed a self-report questionnaire for each course of treatment. Seventy-two side effects were reported. The most frequently named side effects were tiredness (95 %), difficulty sleeping (82 %), nausea (69 %), constipation (69 %), change in taste (57 %), and weight gain (50 %). According to subjective assessment of severity, the patients were mostly troubled by weight gain, followed by constipation, taste changes, tiredness, sleeping difficulty, and nausea. Thus, taste and smell changes during chemotherapy are among the major complaints; however, they have not received much attention. Dysfunction of the olfactory system can lead to weight gain. Patients suffering from olfactory dysfunction like to eat more sweet food to compensate for loss of smell [5].

Only a few objective studies have focused on olfactory changes during chemotherapy [6–8], particularly ovarian cancer patients as a separate group [6]. In the study of Ovesen et al. [6], olfactory thresholds did not change in 6 ovarian cancer patients at re-evaluation after 2–3 months' chemotherapy. To the best of our knowledge, four studies have investigated electrical taste thresholds in patients undergoing chemotherapy [6, 9–11]. Ovesen et al. [6] showed that taste thresholds in six ovarian cancer patients decreased nonsignificantly at re-evaluation after 2–3 months' chemotherapy. Berteretche et al. [11] investigated cancer patients without specifying diagnoses. These authors found a significantly higher taste threshold during chemotherapy but no significant increase 3 weeks after treatment, or later.

The present study investigated odour identification, odour discrimination, and odour threshold in 12 ovarian cancer patients before, during, immediately after, and 3 months after chemotherapy. Our aim was to investigate the discrepancy between self-reported olfactory changes in ovarian cancer patients and the results of the study of Ovesen et al. [6]. In addition, gustation of 12 ovarian cancer patients was assessed quantitatively and qualitatively using taste strips. Hearing thresholds were measured at the same time, because carboplatinum administration can lead to ototoxicity [12, 13].

This study compared the olfactory and gustatory functions of ovarian cancer patients prior to chemotherapy with the normative data of healthy persons published by Hummel et al. [14] and Mueller et al. [15]. The aim was to investigate whether ovarian cancer patients suffer from distorted functions of smell and taste prior to chemotherapy, which may explain weight loss, reduced appetite, or reduced quality of life in these patients.

Table 1 Tumour stages of 12 ovarian cancer patients included in the present study

	n		*n*		*n*		*n*		*n*		*n*
FIGO 1a	1	pT1c	2	N0	6	M0	6	R0	5	G1	1
FIGO 1c	1	pT2a	1	N1	5	M1	6	R1	5	G2	2
FIGO 2a	1	pT3a	1	N2	0			R2	2	G3	9
FIGO 3c	8	pT3c	8	N3	1						
FIGO 4	1										

Materials and patients

Patients

Twelve ovarian cancer patients undergoing chemotherapy (carboplatinum plus taxol) were prospectively included, and written informed consent was obtained. The study protocol was approved by the Ethics Committee of the Faculty of Medicine at the Technical University of Munich (number: 1677/06). The mean age was 56.5 ± 9.8 years (range 40.5–69 years); mean weight, 60.9 ± 8.8 kg (range 50–75 kg); and mean height, 165 ± 4.4 cm (range 159–173 cm). The tumour stage for each patient is shown in Table 1. All patients had radical surgery (unilateral or bilateral oophorectomy, salpingectomy, hysterectomy, pelvic and paraaortic lymphadenectomy, and omentectomy; two patients had hemicolectomy). The interval between surgery and the first smell/taste/hearing test was 28.9 ± 6.7 days. At this time point, mean haemoglobin was 11.5 ± 1.2 g/dl. Two patients suffered from recurrence and had previously received carboplatinum-containing chemotherapy. None of them had co-morbidities such as liver or renal problems, hyperactivity or hypoactivity of the thyroid gland, diabetes, rhinosinusitis, or neurological disorders. None were smokers or alcohol drinkers. None reported any prior decrease in smell or taste functions, or had undergone nasal surgery.

Study protocol

Olfactory, gustatory, and otological functions were tested four times: before (0 weeks), during (9 weeks), immediately after (18 weeks), and 3 months after (30 weeks) chemotherapy. In addition, the patients completed a questionnaire assessing their symptoms before and after chemotherapy. The purpose of the questionnaire was to provide data on quality of life, negative effects of disease,

smelling and tasting irritations, and existing co-morbidities. Most questions were answered using a scale bar (0–100).

Smell test

The "Sniffin' Stick" test battery was introduced more than 10 years ago [16] and comprises tests for odour identification, odour discrimination, and odour threshold. This test is recommended by the "Working Group on Olfaction and Gustation" of the German Society for Otorhinolaryngology, Head and Neck Surgery and is well-validated [14].

Odours were presented in felt-tip pens. The cap of the pen was removed, and the pen's tip was held approximately 2 cm in front of the patient's nostrils for 3 s.

For odour identification, 16 pens with different odours were presented. The patient had to choose one of four items that best fit the presented odour in a forced-choice procedure (four alternative forced choices). For odour discrimination, 16 groups of three pens were presented. A triplet consisted of two pens with the same odour and one pen with a different odour. The patient had to choose the pen with a different odour (three alternative forced choices). For odour threshold tests, 16 dilutions were prepared in a series, starting with a solution of 4 % *n*-butanol. Three pens were presented in randomised order, with two containing solvent alone and one containing the odorant. Patients were asked to identify the pen containing the odorant. Triplets were presented in increasing *n*-butanol concentrations ("staircase fashion"), starting with the lowest odour concentration. After recognising the pen containing the odour twice in a presented triplet, a reversal of the staircase was started until the patient could no longer identify the pen containing the odour. The odour threshold was the mean of the last four of seven staircase reversals. The score for odour identification and odour discrimination ranged from 0 to 16; for odour threshold, it ranged from 1 to 16. The sum of the scores of odour identification, discrimination, and threshold was called the total score (TDI; range 1–48). Odour discrimination and threshold testing were performed blindfolded to eliminate visual identification of the pens containing the odorant.

Taste test

Taste was assessed using taste strips which were first introduced by Mueller et al. [15]. The taste strips were prepared from filter paper and impregnated with a taste solution at one end, with four concentrations of either sweet (0.05, 0.1, 0.2, and 0.4 g/ml sucrose), sour (0.05, 0.09, 0.165, and 0.3 g/ml citric acid), salty (0.016, 0.04, 0.1, and 0.25 g/ml sodium chloride), or bitter (0.0004, 0.0009, 0.0024, and 0.006 g/ml quinine-hydrochloride). Taste strips were placed separately on the left and right side of the patient's tongue, approximately 1.5 cm from the tip. Flavours were presented in increasing concentrations in a randomised order, with an interstimulus interval of approximately 30 s. After placing one of the taste strips on the tongue, the patients had to identify the taste stimuli and answer in a forced-choice procedure. The identification of all taste stimuli was scored from 0 to 16, and identification of taste stimuli of each quality from 0 to 4.

Audiometry

Audiometric evaluations (threshold) were obtained for each ear at frequencies of between 250 and 8,000 Hz. Measurements were obtained using a tone-screening audiometer ST 3 (Audio-Med, Braunschweig, Germany).

Statistical analysis

The Friedman test, Mann–Whitney test, or Kruskal–Wallis test was used where appropriate. Statistical analysis was performed using SPSS (15.0, Chicago, USA). p values of <0.05 were considered to indicate significance.

Table 2 Mean scores of olfactory function in ovarian cancer patients and in healthy women

	Mean value of normative data [14]	Mean value of patients	p value
36–55 years			
Identification	13.49 ± 1.56	13.83 ± 1.60	0.630
Discrimination	12.46 ± 1.96	13.5 ± 2.95	0.433
Threshold	9.08 ± 3.09	8.63 ± 0.77	0.270
Total score	35.16 ± 4.52	35.95 ± 4.66	0.703
>55 years			
Identification	12.06 ± 2.31	14.17 ± 0.75	<0.001
Discrimination	10.66 ± 2.50	13.17 ± 0.75	<0.001
Threshold	7.44 ± 3.51	7.46 ± 0.90	0.966
Total score	29.83 ± 6.77	34.79 ± 1.01	<0.001

Table 3 Mean scores of gustatory function in ovarian cancer patients and in healthy women

	Mean value of normative data [15]	Mean value of patients' left tongue	Mean value of patients' right tongue
Sweet	3.3 ± 0.8	3.25 ± 0.9	3.17 ± 0.7
Sour	3.0 ± 0.8	2.41 ± 0.8*	2.92 ± 0.9
Salty	3.1 ± 0.9	3.0 ± 0.8	3.33 ± 0.8
Bitter	3.0 ± 1.1	3.0 ± 0.7	3.0 ± 0.8

* $p = 0.008$

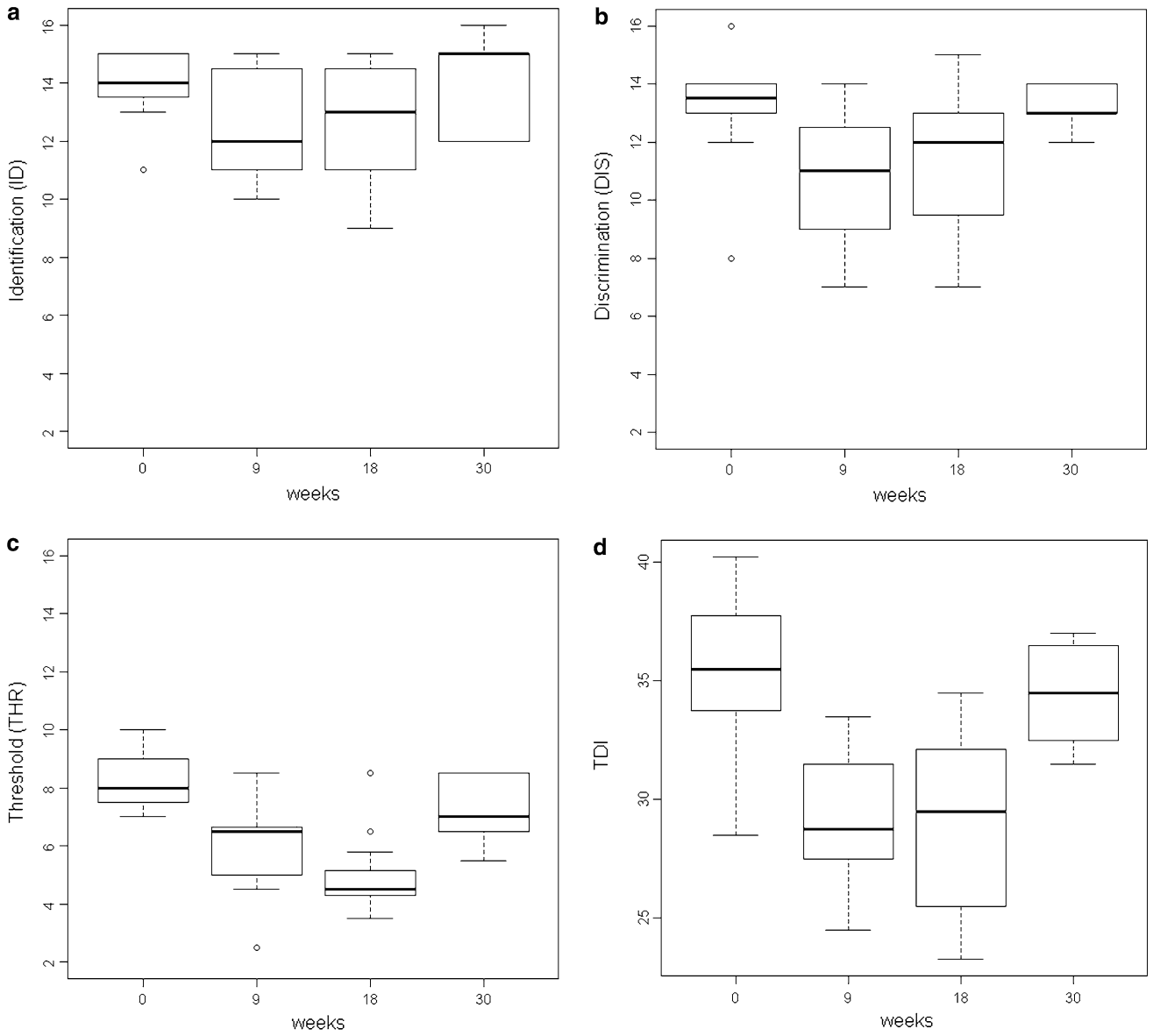

Fig. 1 Odour identification (**a**), odour discrimination (**b**), odour threshold (**c**), and total scores (TDI) (**d**) of ovarian cancer patients before (0 weeks), during (9 weeks), immediately after (18 weeks), and 3 months after (30 weeks) carboplatinum-containing chemotherapy

Results

Subjective assessment

On a scale of 0–100, patients rated their subjective olfactory, gustatory, and hearing function. Average scores were 89.1 ± 11.3, 85.5 ± 14.3, and 84.5 ± 15.1 before chemotherapy and 86.7 ± 16.7, 85.7 ± 17.3, and 85.5 ± 14.1 at 3 months after chemotherapy. Immediately after chemotherapy, the patients rated a decrease in subjective olfactory, gustatory, and hearing function. The scale for this test was 0–100 (no complaints = 0; severe complaints = 100). Total scores were 20.0 ± 28.2, 27.3 ± 25.3, and 25.5 ± 33.8. Reduced appetite scores were 26.4 ± 36.9; less pleasure eating, 27.3 ± 31.9; weight loss, 2 cases (1 and 3 kg); aversions to fatty meals, 27.3 ± 39.3; things that smell differently (parosmia), 9.1 ± 19.2; false perception of odour (phantosmia), 0; the wish to sweeten and salt food more, 18.2 ± 40.4 and 1.8 ± 4.0; and tinnitus complaints, 20.9 ± 38.5.

Smell and taste tests

Comparison between the normative data of the "Sniffin' Sticks" battery [14] and the scores of ovarian cancer patients before chemotherapy showed better mean values for odour identification and discrimination in ovarian cancer patients, but no significant difference in odour threshold (Table 2). For

taste, there was a significant decrease in the quality of sour taste on the left side of the patient's tongue as compared to the normative data [15]; however, no significant difference was observed for sweet, salty, and bitter tastes (Table 3).

Comparison of the total score (TDI) of all 12 ovarian cancer patients before (mean 35.4 ± 3.2), during (mean 29.3 ± 3.0), and immediately after (mean 28.3 ± 3.9) chemotherapy showed significant decreases in olfactory function during chemotherapy ($p = 0.019$). 3 months after chemotherapy, olfactory function had recovered almost completely (mean 34.4 ± 2.4). Odour threshold was affected most ($p = 0.047$), whereas odour identification was hardly affected ($p = 0.39$; Fig. 1).

No significant decreases in taste function, i.e. total taste values, were observed on the left and right sides of the tongue before (mean: left, 11.7 ± 2.2; right, 12.4 ± 2.4), during (mean: left, 9.8 ± 3.4; right, 9.2 ± 3.0), immediately after (mean: left, 8.2 ± 3.8; right, 7.75 ± 3.7), or 3 months after (mean: left, 11.8 ± 1.3; right, 10.8 ± 3.0) chemotherapy. Nevertheless, the tendencies toward decreased taste function during and after chemotherapy and toward recovery of function 3 months after chemotherapy was clearly present in total values (Fig. 2) and for each quality (sweet, sour, salty, and bitter).

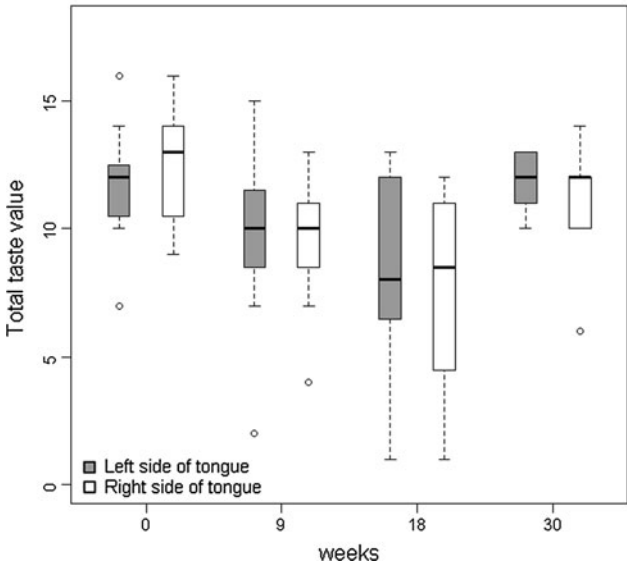

Fig. 2 Total taste values of ovarian cancer patients on left and right side of tongue before (0 weeks), during (9 weeks), immediately after (18 weeks), and 3 months after (30 weeks) carboplatinum-containing chemotherapy

Results of pure tone audiometry

Figure 3 shows the average pure tone audiometry results for all ovarian cancer patients before, during, immediately after, and 3 months after platinum-containing chemotherapy for both ears. There were no significant changes in hearing thresholds during or after chemotherapy. Nevertheless, hearing thresholds tended to decrease in all frequencies during chemotherapy and recovered in the deep and middle frequencies 3 months afterwards. This recovery was not observed in high frequencies 3 months after chemotherapy.

Discussion

It is unclear if nutrient deficiencies caused by distorted taste and smell functions or tumour by-products cause the loss of appetite in cancer patients. Therefore, smell and taste test scores of 12 ovarian cancer patients before chemotherapy were compared with normative data for this study. For smell, there was no significant difference in the mean scores for odour threshold. Mean scores for odour identification and discrimination were higher in ovarian cancer patients than in healthy women. Assuming that odour threshold reflects the function of the peripheral olfactory system to a larger extent than do other olfactory tests [17, 18] and that odour identification and odour discrimination are influenced by cognitive performance, these results indicate no substantial difference in olfactory function between ovarian cancer patients and the controls. For taste, there was a significant decrease in perception of the sour quality on the left side of the patient's tongue compared to normative data. This may be of further interest or may result from variations in the taste strips. Mueller et al. [15] described the percentage of correctly identified taste strips for the highest concentrations of flavours as 100 % for sweet, 99 % for sour, 96 % for salty, and 99 % for bitter. For the lowest concentrations of flavours, averages of correctly identified taste strips were 54 % for sweet, 36 % for sour, 51 % for salty, and 52 % for bitter. Thus, sour in its lowest concentration may be more difficult to identify. Although our study size was small (12 ovarian cancer patients), the taste and smell test results agree with those of a recently published study investigating the olfactory and gustatory function of 69 breast cancer patients before chemotherapy [19].

Buckingham et al. [4] described subjective taste changes in 57 % of 11 ovarian cancer patients undergoing chemotherapy with carboplatinum. Patients are often unaware of olfaction while eating, although 80 % of food information is contributed by olfactory input [20]. In the present study, ovarian cancer patients undergoing chemotherapy with carboplatinum complained of a decrease in olfactory function, with average scores of 20.0 ± 28.2 and 27.3 ± 25.3 in taste, using a visual scale (0 = no complaints, 100 = severe complaints). Buckingham et al. [4] also reported a weight gain in 50 % of the patients. In the present study, weight gain in 50 % of the subjects was not observed. Nevertheless,

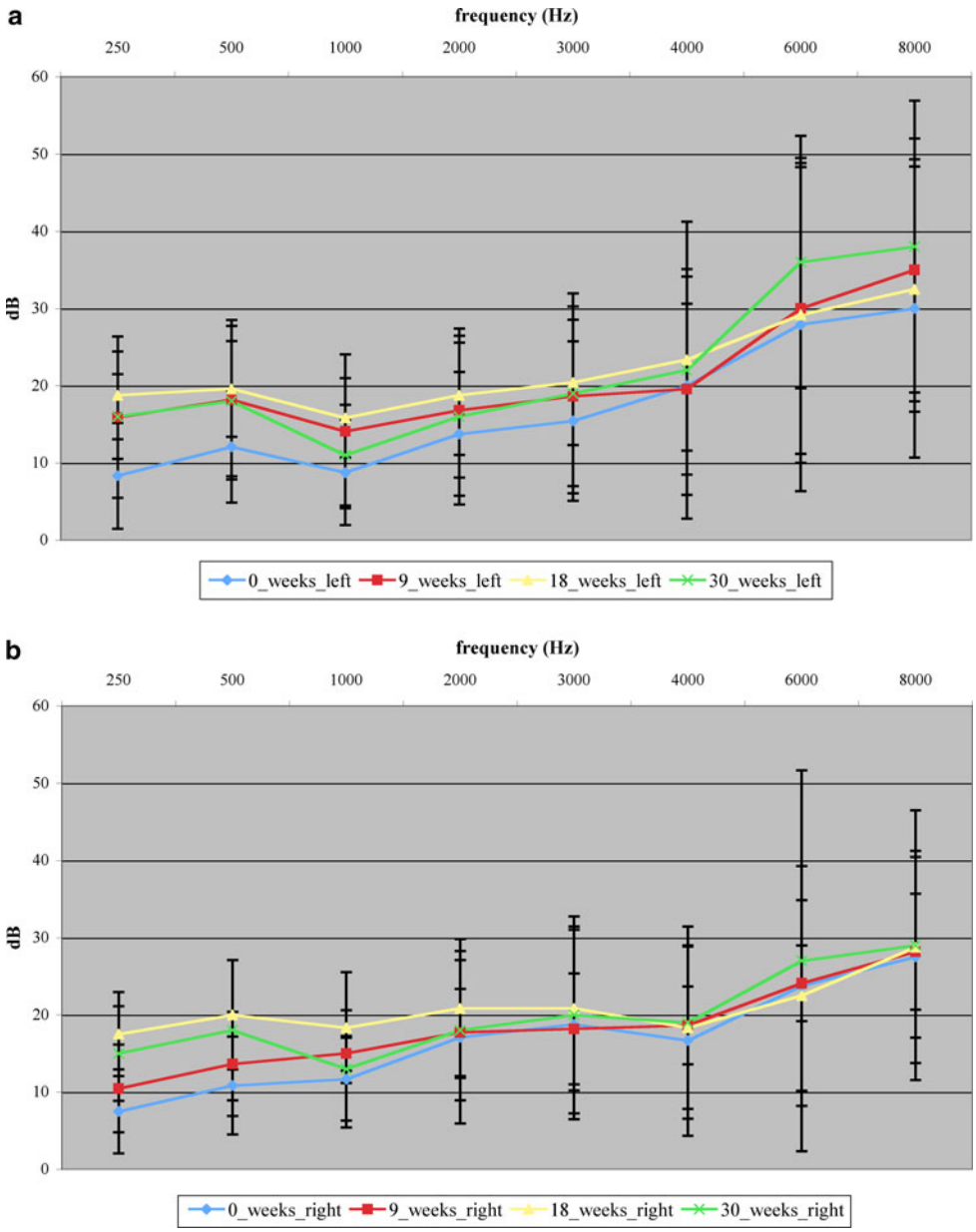

Fig. 3 Average hearing thresholds in the left ear (**a**) and right ear (**b**) of ovarian cancer patients before (0 weeks), during (9 weeks), immediately after (18 weeks), and 3 months after (30 weeks) carboplatinum-containing chemotherapy

patients complained of wanting to sweeten their food much more, which may lead to a weight gain. 3 months after chemotherapy, patients considered their olfactory and gustatory functions as being identical to those before chemotherapy. Similar findings were reported by Bernhardson et al. [21] after interviewing 21 cancer patients undergoing chemotherapy, and by Minakata et al. [9] in a case report of gustatory disorder in a 48-year-old woman with small-cell lung cancer who was receiving chemotherapy.

To substantiate the subjective assessment, olfactory, and gustatory function were measured in validated tests before, during, immediately after, and 3 months after chemotherapy with carboplatinum in 12 ovarian cancer patients. Olfactory and gustatory functions decreased during and after chemotherapy, but recovered 3 months later. Chemotherapeutic agents target rapidly dividing cells in the body. Olfactory receptor cells constantly undergo regeneration after some weeks [22]; the average life of a taste receptor is 10 days but can be months or more [23]. From this viewpoint, the decreases in olfactory and gustatory functions during and after chemotherapy and the recovery 3 months after chemotherapy are well explained. Ovesen et al. [6] focused specifically on changes in olfactory functions of ovarian cancer patients during and after chemotherapy. These authors tested the odour thresholds of six ovarian cancer patients before and 2–3 months after chemotherapy and did not find significant differences. However, testing was performed in the week before the next chemotherapy cycle was scheduled, i.e. at least 2 weeks after the end of the last cycle. In the same study,

electrical taste thresholds were measured and did not change significantly. The period of 2 weeks after the end of the last cycle, as used by Ovesen et al. [6], was probably too long to assess smell and taste changes accurately, in light of the rapid cell-regeneration time discussed above. Berteretche et al. [11] measured the electrical taste thresholds of cancer patients without specifying diagnoses. Measurements were obtained on days 1–11 after chemotherapy began. Beteretche et al. [11] found an elevated threshold; however, electrical taste-threshold measurements obtained 3 weeks after the end of the last chemotherapy cycle showed no significant elevations. These findings are consistent with the results of the present study. Electrical taste thresholds of the chorda tympani or the glossopharyngeal and vagal nerve were measured. An elevation of the electrical taste threshold is not necessarily of clinical significance. However, the present prospective study measured quantitative as well as qualitative taste functions and clearly shows a decrease during and after chemotherapy, which is of clinical significance.

Cisplatin is the most ototoxic drug known [24–26]. High-dose carboplatin can also induce auditory dysfunction with a clinical picture that is roughly similar to that of cisplatinum-containing chemotherapy [12, 13]. In this study, hearing thresholds were measured concurrently with smell and taste tests. There were no significant differences between the hearing thresholds at these specific times in any of the 12 ovarian cancer patients receiving standard carboplatinum dosa at AUC5. Nevertheless, the hearing thresholds of ovarian cancer patients tended to decrease during chemotherapy and recovered in the middle and low frequencies after chemotherapy. In the high frequencies, no such trend was observed.

In conclusion, ovarian cancer patients undergoing platinum-containing chemotherapy should be informed about possible decreases in olfactory and gustatory functions during treatment. Distorted smell and taste functions during chemotherapy could be improved using more spices, a low amount of glutamate, or additional flavours [27–29]. It is also important to inform the patients that the decreases in olfactory and gustatory function are transient and will recover 3 months after chemotherapy. Decrease in hearing thresholds during chemotherapy may also be observed. Nevertheless, this decrease is insignificant and less than 10 dB. Thus, for ovarian cancer patients undergoing carboplatinum-containing chemotherapy, repeated measurement of hearing thresholds is not urgently required. In addition, comparison between normative data and the olfactory and gustatory function of ovarian cancer patients before chemotherapy shows no substantial differences. Thus, weight loss and reduced appetite in ovarian cancer patients before chemotherapy may not necessarily be influenced by distorted taste and smell functions.

Conflict of interest The authors declare that there is no conflict of interest.

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