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ORIGINAL ARTICLE

Prevalence of oral side effects of chemotherapy and its relationship with periodontal risk: a cross sectional study

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Abstract

Purpose To determine the prevalence of professionally reported oral side effects of chemotherapy and the self-reported oral side effects and whether both prevalences could be related to the periodontal risk of the patients.

Methods A cross-sectional study with patients undergoing chemotherapy treatment was carried out. Demographic, oral hygiene habits, and cancer-related data were collected while the patient was receiving the chemotherapy infusion. Patient's oral status, measured according to the oral-assessment guide for patients in hospital environments, patient-related outcomes (PROMs), measured by a visual analogue scale, and patient's periodontal risk were analyzed using validated questionnaires. Data was reported in means and standard deviations (SD) in quantitative variables and in counts, prevalence, and 95% confidence intervals (CI) in qualitative variables. ANOVA test and chi-squared tests were used to compare oral side effects among different periodontal risk groups.

Results Three hundred sixty-nine patients were included in the study. The prevalence of professionally reported oral side effects was 86.99% (95% confidence interval CI 83.54%; 90.44%). The prevalence of self-reported oral side effects was 89.70% (95% CI 86.59; 92.82). The most common oral side effects were xerostomia (73.4%), dysgeusia (61.8%), and dry lips (54.2%). More oral alterations were found in patients with worse periodontal risk ($p < 0.001$).

Conclusions The prevalence of oral side effects (professional or self-reported) is higher than 85% in patients undergoing chemotherapy. This prevalence increases as the risk of developing periodontal disease does.

Keywords Chemotherapy · Oral side effects · Xerostomia · Dysgeusia · Periodontal risk

Introduction

In global terms, cancer is characterized by increased cell proliferation and diminished apoptosis. Advances in the treatment of patients with cancer have led to prolonged survival and improved quality of life [1–3]. One of the most used treatments for cancer continues to be nowadays chemotherapy, which is characterized by its lack of selectivity, as it acts upon tumor cells as well as rapidly multiplying normal cells [4].

Although there have been improvements in the chemotherapy clinical outcomes, patients still experience significant side effects, such as gastrointestinal problems, fatigue, and neurological effects [5]. Due to the high cellular turnover rate, the microflora and the oral tissue trauma associated to daily oral function, the oral cavity is very susceptible to the direct and indirect toxic effects from chemotherapy [2, 6]. Oral complications have an estimated prevalence that varies between 31 and 93% [7]. Sweeney et al. stated in a study with 70 patients with terminal cancer under chemotherapy treatment that the most common oral side effects were xerostomia, speech discomfort, and dysgeusia [8, 9]. Cheng et al. determined that about 40% of a sample of 88 patients with solid tumors had experienced dry mouth, distorted taste, and weight loss, and that approximately 45% of the patients reported three or four

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oral dysfunctions simultaneously [10]. This huge variability might be attributed to differences in target populations, chemotherapy treatment, and the moment when the patients are examined as well as to the lack of consensus in the reported outcomes and the lack of sample size calculations [11]. Oral complications may produce severe discomfort and pain, which interferes with oral feeding, delays, or dosage-limitation. Moreover, diminished oral function has a direct and indirect impact on quality of life, affecting daily habits and social relations [12].

Oral side effects of chemotherapy have been associated to treatment (type of chemotherapy or association with local radiotherapy) and patient outcomes (type of tumor, age, sex, previous chemotherapy treatment, previous mouth condition, and daily oral care carried out by the patient) [13]. Furthermore, those patients with worse dental status (caries or periodontal diseases) prior to chemotherapy should be treated before starting the oncological treatment to avoid secondary infections and other complications [14, 15]. It has been shown that patients with low levels of plaque and of gingival inflammation due to correct oral hygiene habits have a reduced likelihood of developing either direct or indirect oral toxic effects of chemotherapy [16, 17]. During chemotherapy, patients with cancer present a more complex oral microbiota, and these may be responsible for different serious local or systemic pathologies [18]. A systematic review by Lalla et al. indicated that most studies examining the use of oral care protocols for the prevention of oral mucositis reported a beneficial effect due to the decrease of the microbiota in the oral cavity, which could provide prevention of secondary infections and consequently a reduction in exacerbation and incidence of mucositis [19]. However, although oral hygiene and periodontal risk are considered important factors related to oral side effects, it is complicated to analyze periodontal indexes in these patients, so the implementation of validated questionnaires could be useful.

Therefore, the main aim of this study was to determine the prevalence of professionally reported oral side effects of chemotherapy on a sample with an adequate size calculation. The secondary objective was to analyze the self-reported oral side effects and whether both prevalences could be related to the periodontal risk of the patients.

Material and methods

Study design

This is a cross-sectional study, whose protocol was approved by the Ethics Committee of the University Hospital La Paz (Code HULP-PI 2485). The design followed the Declaration of Helsinki guidelines. Participation was voluntary, and the data collected was analyzed respecting the patients' privacy. Informed consent was obtained from all individual participants included in the study.

Sample population

Patients were consecutively selected at the oncology service at "University Hospital La Paz" (Madrid, Spain) between October 2016 and June 2017. Subjects were included if they (1) were over 18 years old, (2) were receiving chemotherapy treatment for a solid tumor or hematological cancer, and (3) were able to understand the aim of the study. Patients were excluded if they (1) had received radiotherapy on the head and/or neck or (2) presented other oral disorders (such as leukoplakia or lichen planus). Prior to the start of their chemotherapy treatment, all the patients received information regarding oral hygiene habits from the oncology nurses. None other instructions in order to avoid oral adverse effects, such as sucking ice cubes or using any cytoprotective medicine were given.

Study outcomes

Data collection was completed while the patient was receiving the chemotherapy infusion throughout a questionnaire, hospital medical records, an oral exploration, and evaluating PROMs.

Questionnaire data

Data was collected by a personal interview made by the same researcher (BG) in all patients. Patients were asked about sex, date of birth, systemic diseases, intake of medication, date of their last dental appointment, use of removable prosthesis, and oral hygiene habits. Information about oral hygiene habits included how many times a day they brushed their teeth per day and if they used dental floss, interdental brushes, or mouthwash.

Hospital medical records

Cancer-related information was collected using the hospital medical records. It included information about the location of the tumor, type of treatment, the existence of a previously treated cancer, the chemotherapy agents used, and the number of cycles already received.

Oral examination

An oral exploration was made to assess the existence of mucosal alterations using the validated oral-assessment guide designed by Eilers et al. [14, 20]. It includes assessment of voice, ability to swallow, lips, tongue, saliva, mucous membranes, gums, and teeth/dentures. In order to standardize oral status data, all examinations were made by the same investigator

(BG). Removable dentures, if used, were removed before examination. Assessments were made using a flashlight and a tongue depressor. The examination took place in the armchair while the patients were receiving the chemotherapy infusion, at the Oncologic Day Hospital.

Each category was punctuated with 1, 2, or 3 points according to their intensity. The results of all the categories were added, so that the sum allows to classify the patients as good (< 10points), regular (10–13 points), or bad (> 13 points) oral health patients.

Patient-related outcomes (PROMs)

Patients were asked to evaluate their self perception of oral discomfort through a visual analogue scale (VAS), with questions about having suffered any kind of oral pain, changes in the taste of food and/or drinks, dry mouth, and speech and eating discomfort. The self-reported results were added in order to categorize the side effects: patients with a total result of 0 were classified as no side effects, from 1 to 10 as mild side effects, 11 to 20 as moderate side effects, and over 21, serious side effects.

Periodontal disease risk

The patient's periodontal risk was determined with the use of a questionnaire validated for Spanish population [21], all made by an interview by the same researcher (BG). It consists of 21 multiple choice questions that include information about demographic data, teeth and gums alterations, daily dental self care, healthy habits, family background, and general health. Every topic includes several questions with multiple choice answers, which are punctuated from 0 to 6, so the higher the final result, the higher the patient's risk of having or developing periodontal disease. According to marks, patients were divided into low (< 12 points), medium (12–23 points), and high periodontal risk (> 24 points).

Sample size calculation

The prevalence of professionally reported oral side effects of chemotherapy has been estimated between 40 and 93% [9, 10]. Considering an infinite population, a confidence level of 95%, an absolute precision of 5%, and assuming that a 40% of the patients would suffer oral secondary effects, we estimated that the required sample size for this study was 369 patients.

Statistical analysis

Primary outcome was the prevalence of professionally reported oral side effects. Secondary outcomes include demographic (sex, age, tobacco use, systemic diseases), oral hygiene (last dental checkup, daily toothbrush, use of dental floss, interdental brushes and mouthwash, and use of dental prosthetics), cancer-related (location of the tumor, type of treatment, the existence of a previously treated cancer, the chemotherapy agents used, and the number of cycles), and periodontal disease risk and PROMs (oral pain, changes in the taste of food and/or drinks, dry mouth, and speech and eating discomfort) information. Data was reported in means and standard deviations (SD) in quantitative variables and in counts, prevalence, and 95% confidence intervals (CI) in qualitative variables.

In order to analyze the association between oral side effects and PROMS among different periodontal risk groups, ANOVA and chi-squared tests with Bonferroni corrections were used for quantitative variables and for qualitative variables, respectively.

Results

Sample description

From 641 screened patients, 272 patients were excluded (98 decline to collaborate, 82 had received radiotherapy on their head or neck, and 92 did not speak Spanish or were not capable to collaborate or understand the aim of the study) resulting in 369 included patients.

Demographic data

Out of the 369 included patients, 39.02% ($n = 144$) were men and 60.98% ($n = 225$) were women, with a mean age of 61.03 years (SD = 13.13). Demographic data is reported in Table 1. Most common systemic diseases were hypertension (26.0%) and hypercholesterolemia (17.6%).

Cancer-related data

The study included patients with solid tumors (87.3%) and patients with hematological cancers (12.7%). Nineteen percent of the patients had been previously treated for cancer. Most frequent cancer sites were breast (21.4%), colorectal (19.9%), and lung (17.3%). All of the patients were being treated with chemotherapy, and about 22% had received also radiotherapy (other than head and/or neck). Chemotherapy regimens are described on Table 1. Chemotherapy cycles received varied between 2 and 164 (mean 6.09 (SD 10.73)).

Oral side effects

Prevalence of professionally reported oral side effects was 86.99% (95% CI 83.54%; 90.44%). Oral examination results showed that 30.1% of the patients had good oral health, 58.3% had regular oral health, and 11.7% were

Table 1 Demographic and cancer-related data

		N	%
Sex	Men	144	39.02
	Women	225	60.98
Systemic diseases	Autoimmune disease/allergies	12	3.20
	Bone disease	37	10.00
	Hypercholesterolemia	65	17.60
	Diabetes	35	9.50
	Gastrointestinal disorders	17	4.60
	Heart disease/coagulation disorders	41	11.10
	Hypertension	96	26.00
	Kidney disease	4	1.10
	Liver disease	9	2.40
	Lung disease	16	4.30
	Parkinson's disease	2	0.50
	Prostate disorders	8	2.20
	Psychiatric/psychological disorders	38	10.30
	Thyroid disorder	29	7.90
Cancer location	Breast cancer	79	21.40
	Colorectal cancer	66	17.90
	Lung cancer	64	17.30
	Non-Hodgkin lymphoma	28	7.60
	Other solid tumors	27	7.31
	Liver cancer	19	5.10
	Pancreatic cancer	17	4.60
	Gastrointestinal cancer	16	4.33
	Uterine cancer	15	4.10
	Ovarian cancer	14	3.80
	Hodgkin lymphoma	9	2.40
	Chronic lymphocytic leukemia	7	1.90
	Prostate cancer	5	1.40
	Multiple myeloma	3	0.80
Chemotherapy agents	Antimetabolite	35	9.49
	Anthracycline	5	1.36
	Anthracycline + antitumor antibiotic + non classical alkylating agent + vinca alkaloid.	9	2.44
	Anthracycline + platinum analog	6	1.63
	Anthracycline + alkylating agent	30	8.13
	Anthracycline + alkylating agent + vinca alkaloid	18	4.88
	Anthracycline + alkylating agent + antimetabolite	12	3.25
	Alkylating agent	12	3.25
	Platinum analog	34	9.21
	Platinum analog + antimetabolite	42	11.38
	Platinum analog + antimetabolite + topoisomerase I inhibitor	5	1.36
	Platinum analog + epipodophyllotoxin	8	2.17
	Platinum analog + vinca alkaloid	3	0.81
	Taxane	60	16.26
	Taxane + antimetabolite	6	1.63
	Taxane + platinum analog	27	7.32
	Topoisomerase I inhibitor	11	2.98
	Topoisomerase I inhibitor + antimetabolite	25	6.78
	Vinca alkaloid	3	0.81
	Vinca alkaloid + antimetabolite	3	0.81
	Vinca alkaloid + alkylating agent	4	1.08
	Other chemotherapy treatments	11	2.71

included in the bad oral health group. Specific data from the oral examination are described on Table 2. Most common alterations were dry lips (54.2%), thick or ropy saliva (44.7%), tongue alterations (39.8%), and deeper or raspy voice (27.9%). Almost half of the patients had plaque or calculus between their teeth (39.0%) or generalized along the gingival margin (6.2%), but only about 25% of them showed edematous gums. Most of the patients had no problem to swallow (81.6%) and 82.9% had pink and firm oral mucosa. Patients with uterine cancer and Hodgkin lymphoma were the ones that suffered more professionally reported oral complications (100% of the patients). On the other hand, patients with pancreatic cancer and ovarian cancer were the less affected (appendix Table 7). There was a tendency for an increase in the prevalence of professionally reported oral side effects concomitantly with the number of cycles (appendix Table 8). Prevalence of self-reported oral side effects was 89.70% (95% CI

Table 2 Oral assessment guide

Outcome	Categories	*N*	%
Ability to swallow	Normal swallow	301	81.6
	Some pain on swallowing	68	18.4
	Unable to swallow	0	0
Lips	Smooth, pink and moist	165	44.7
	Dry or cracked	200	54.2
	Ulcerated or bleeding	4	1.1
Tongue	Pink, moist, and papillae present	217	58.8
	Coated or loss of papillae with a shiny appearance with or without redness. Fungal infection.	147	39.8
	Blistered or cracked	5	1.4
Saliva	Watery	204	55.3
	Thick or ropy	165	44.7
	Absent	0	0
Mucous membrane	Pink and firm	306	82.9
	Reddened or coated without ulceration	58	15.7
	Ulceration with or without bleeding	5	1.4
Gingiva	Pink and firm	274	74.3
	Edematous with or without redness, smooth.	92	24.9
	Spontaneous bleeding or bleeding with pressure	3	0.8
Teeth	Clean and no debris	202	54.7
	Plaque or debris in localized areas (between teeth)	144	39.0
	Plaque or debris generalized along gum line	23	6.2
Voice	Normal	265	71.8
	Deeper or raspy	103	27.9
	Difficulty talking or crying, or painful	1	0.3

86.59%; 92.82%). Most common self-reported side effects were xerostomia (271 patients, 73.4%) and dysgeusia (228 patients, 61.8%), followed by oral pain (121 patients, 32.8%), eating discomfort (106 patients, 28.7%) and speech discomfort (74 patients, 20.1%). Highest mean VAS scores were reported in taste alterations and dry mouth (Table 3). Most self-reported oral side effects were expressed by patients with uterine cancer and Hodgkin lymphoma. Patients with chronic lymphocytic leukemia and non-Hodgkin lymphoma reported less oral complications (appendix Table 7). As in the professionally reported oral side effects, the prevalence of self-reported complications increased as the number of cycles did (appendix Table 8).

Periodontal risk assessment

The results of the periodontal risk questionnaire are reported on Table 4. Most of the patients were between 40 and 65 years old (54.2%) and described themselves as medium socioeconomic class (62.6%). The largest group of patients did not report smoking (88.9%) nor alcoholic habits (87.0%). Nearly 80% of the patients reported having had a dental checkup in the previous 2 years (77.2%) and 83.8% stated brushing their teeth at least twice a day. Only 16.3% of the individuals employed dental floss or interdental brushes on a daily basis. A quarter of the study population reported gingival bleeding, whereas almost 15% had tooth mobility and 17.5% had lost a tooth in the previous year. About half of the patients declared having a family history of periodontal disease.

Patients were categorized in three groups according to the risk of having or developing periodontal diseases, resulting in 62 patients (18.4%) included in the low-, 225 (61.0%) in the moderate-, and 50 (13.6%) in the high-risk groups.

Table 3 Self-reported side effects

Secondary effect	*N*	%	Mean VAS score
Xerostomia	271	73.4%	3.85 (SD 3.00)
Dysgeusia	228	61.8%	3.61 (SD 3.51)
Oral pain	121	32.8%	1.34 (SD 2.30)
Eating discomfort	106	28.1%	1.14 (SD 2.09)
Speech discomfort	74	20.1%	0.78 (SD 1.88)

Table 4 Periodontal risk assessment

Outcome	Categories	*N*	%
Sex: are you a man or a woman?	Women (1)	225	61
	Men (2)	144	39
Age: what is your age?	< 40 years (1)	34	9.2
	40–65 years (2)	200	54.2
	> 65 years (3)	135	36.6
Socioeconomic status: what is your family income level?	High class (0)	114	30.9
	Medium class (1)	231	62.6
	Low class (2)	24	6.5
Do your gums bleed?	No (0)	249	73.9
	I do not know (1)	2	0.6
	Sometimes (2)	71	21.1
	Frequently (3)	15	4.5
Have you noticed gum recession or do your teeth appear to be longer?	No (0)	209	62.0
	I do not know (1)	20	5.9
	Yes (3)	108	32.1
Do you have tooth mobility?	No (0)	276	81.9
	I do not know (1)	11	3.3
	Yes (3)	50	14.8
Have you lost a tooth recently?	No (0)	274	81.3
	I do not know (1)	4	1.2
	Yes (3)	59	17.5
Have you visited the dentist in the last two years?	Yes (0)	285	77.2
	I do not know (1)	0	0.0
	No (2)	84	22.8
Do you brush your teeth regularly?	3 times/day (0)	187	50.7
	2 times /day (1)	122	33.1
	< 1 time/day (2)	59	16.0
	Never (3)	1	0.3
How frequently do you use dental floss or interproximal brushes?	Daily (0)	60	16.3
	Weekly (1)	24	6.5
	Sometimes (2)	24	6.5
	Never (3)	261	70.7
Do you have overweight problems?	No (0)	270	73.2
	I do not know (1)	12	3.3
	Maybe (2)	49	13.3
	Yes (3)	38	10.3
Do you smoke?	No smoker (0)	328	88.9
	Occasional smoker (1)	8	2.2
	< 10 cg/day (3)	16	4.3
	> 10 cg/day (6)	17	4.6
Are you stressed?	Absence (0)	208	56.4
	Low(1)	91	24.7
	Moderate (2)	59	16.0
	High (3)	11	3.0
How many alcoholic beverages do you intake daily?	No (0)	321	87
	< 2 units/day (1)	43	11.7
	> 2 units/day (2)	5	1.4
Do your parents or siblings suffer from gum disease?	No (0)	190	51.5
	I do not know (1)	27	7.2
	Yes (3)	152	41.2
Have your parents or siblings lost their teeth early and have to wear dental prosthetics?	No (0)	192	52.0
	I do not know (1)	27	7.3
	Yes (3)	150	40.7
Do you have diabetes?	No (0)	334	90.5
	I do not know (1)	0	0
	Yes, but it is under control (2)	34	9.2
	Yes, and sometimes it is not controlled (6)	1	0.3
Do you have osteoporosis?	No (0)	334	90.5
	I do not know (1)	5	1.4
	Yes (2)	30	8.1
Prior to starting the chemotherapy treatment, did you suffer from oral herpes?	No (0)	303	82.1
	I do not know (1)	6	1.6
	Yes (2)	60	16.3
Did you suffered zoster herpes before starting the chemotherapy treatment?	No (0)	331	89.7
	I do not know (1)	5	1.4
	Yes (2)	33	8.9
Did you use to have frequent infections or low defenses before starting the chemotherapy?	No (0)	326	88.3
	I do not know (1)	10	2.7
	Yes (2)	33	8.9

Association of oral side effects with the periodontal risk assessment

The results from the oral examination analyzed according to the patient's periodontal risk are presented in Table 5. Thirty-two participants (8.7%) were excluded from the periodontal risk assessment because of their edentulism, as the cause of the dental loss was not reported.

More oral alterations were found in patients with worse periodontal risk ($p < 0.001$). Among the 62 patients classified as having low risk of developing periodontal diseases, 58.1% had good results in the oral exploration and 3.2% had severe oral problems. On the other hand, out of the 50 patients with high risk of periodontal diseases, only 6.0% presented a good oral status while 34.0% had severe alterations. Statistical significant differences could be observed when analyzing each of the categories separately, except for voice alterations. Relationship among periodontal risk and tongue, gingival, and saliva alterations were remarkable.

Regarding PROMs, statistical significant relationship was found when analyzing the chemotherapy's side effects reported by the patients and the periodontal risk ($p < 0.001$). Mean VAS results increased as the periodontal risk augmented. Patients with low risk of periodontal disease reported a mean VAS of dysgeusia of 3.03 (SD = 3.04) compared to a mean VAS of 4.90 (SD = 3.89) in patients with high risk. Similarly, patients with lower risk presented a mean VAS of xerostomia of 2.66 (SD 2.79) and patients with higher risk had a mean VAS of 4.98

Table 5 Relationship between oral assessment guide and periodontal risk assessment. [(1)]Low risk versus moderate risk; [(2)]Low risk versus high risk; [(3)]Moderate risk versus high risk

		Periodontal risk			Chi-squared	*p* value (Bonferroni)
		Low	Moderate	High		
Ability to swallow	Normal swallow	60 (96.8%)	179 (79.6%)	36 (72.0%)	0.001	$0.003^{(1)}$
	Some pain on swallowing	2 (3.2%)	46 (20.4%)	14 (28.0%)		$0.000^{(2)}$
	Unable to swallow	0 (0.0%)	0 (0.0%)	0 (0.0%)		$0.726^{(3)}$
Lips	Smooth, pink, and moist	39 (62.9%)	86 (38.2%)	22 (44.0%)	0.045	$0.003^{(1)}$
	Dry or cracked	22 (35.5%)	137 (60.9%)	28 (56.0%)		$0.237^{(2)}$
	Ulcerated or bleeding	1 (1.6%)	2 (0.9%)	0 (0.0%)		$1.188^{(3)}$
Tongue	Pink, moist, and papillae present	48 (77.4%)	131 (58.2%)	19 (38.1%)	0.000	$0.015^{(1)}$
	Coated or loss of papillae with a shiny appearance with or without redness.	14 (22.6%)	90 (40.0%)	31 (62.0%)		$0.000^{(2)}$
	Blistered or cracked	0 (0.0%)	4 (1.8%)	0 (0.0%)		$0.078^{(3)}$
Saliva	Watery	44 (71.0%)	117 (52.0%)	22 (44.0%)	0.008	$0.024^{(1)}$
	Thick or ropy.	18 (29.0%)	108 (48.0%)	28 (56.0%)		$0.012^{(2)}$
	Absent	0 (0.0%)	0 (0.0%)	0 (0.0%)		$0.918^{(3)}$
Mucous membrane	Pink and firm	57 (91.9%)	191 (84.9%)	32 (64.0%)	0.000	$0.381^{(1)}$
	Reddened or coated without ulceration	5 (8.1%)	31 (13.8%)	17 (34.0%)		$0.000^{(2)}$
	Ulceration with or without bleeding	0 (0.0%)	3 (1.3%)	1 (2.0%)		$0.006^{(3)}$
Gingiva	Pink and firm	57 (91.9%)	174(77.3%)	19 (38.0%)	0.000	$0.030^{(1)}$
	Edematous with or without redness, smooth.	5 (8.1%)	50 (22.2%)	29 (58.0%)		$0.000^{(2)}$
	Spontaneous bleeding or bleeding with pressure	0 (0.0%)	1 (0.4%)	2 (4.0%)		$0.000^{(3)}$
Teeth	Clean and no debris	43 (69.4%)	124 (55.1%)	12 (24.0%)	0.000	$0.096^{(1)}$
	Plaque or debris in localized areas (between teeth)	18 (29.0%)	89 (39.6%)	28 (56.0%)		$0.000^{(2)}$
	Plaque or debris generalized along gum line	1 (1.6%)	12 (5.3%)	10 (20.0%)		$0.000^{(3)}$
Voice	Normal	48 (77.4%)	167 (74.2%)	30 (60.0%)	0.052	$1.704^{(1)}$
	Deeper or raspy	14 (22.6%)	57 (25.3%)	20 (40.0%)		$0.138^{(2)}$
	Difficulty talking or crying, or painful	0 (0.0%)	1 (0.4%)	0 (0.0%)		$0.168^{(3)}$
Oral assessment guide	Good oral health	36 (58.1%)	59 (26.2%)	3 (6.0%)	0.000	$0.000^{(1,2,3)}$
	Regular oral health	24 (38.7%)	145 (64.4%)	30 (60.0%)		
	Bad oral health	2 (3.2%)	21 (9.3%)	17 (34.0%)		

(SD2.94). Statistical differences were found between periodontal disease risk groups in xerostomia, dysgeusia, and oral pain (Table 6).

Discussion

This study, designed to determine the frequency of oral complications in 369 patients undergoing chemotherapy, reported that close to 90% of patients had professional or self-reported oral complications. These prevalences are higher than those found by Gomes et al. [22] and Sweeney et al. [8] with values ranging 45.6–65% in hematological or terminal cancer patients (sample sizes 79–80) but similar to those found by Fayle and Curzon [9] in children and Jobbins et al. [23] in terminal cancer patients (89–97%) with bigger sample sizes (43–197 patients).

We found that most common side effects were oral pain (32.8%), lip alterations (55.3%), dysgeusia (61.8%), and xerostomia (73.4%). These values are similar to the percentage reported by Jobbings et al. in a sample of 197 patients [23]. Jensen et al. published in 2010 a systematic review stating that the weighted mean prevalence of xerostomia during chemotherapy was 49.9%, although the results showed divergence due to the heterogeneity on cancer diagnosis, chemotherapy regimens, and the number of previous chemotherapy cycles [24].

The mean VAS score reported by our patients in xerostomia was 3.85 (in a scale from 0 to 10) (SD = 3.0) comparable to 3.66 described by Chan et al. [16]. If we exclude from the mean VAS score analysis those patients that reported not having suffered dry mouth, we find a mean VAS of 5.23 (SD = 2.23), similar to 5.4 described by Mercadante et al. [25]. Out of our 369 patients, 67 (18.15%) reported having severe xerostomia with a mean VAS of 8.34 (SD = 0.84), which seems to represent an important factor in their life quality.

Regarding dysgeusia, our results showed that 61.8% of the patients reported taste disturbances. This comprised changes in the flavor of particular food or beverages as well as all the food tasting the same. Ponticelli et al. analyzed taste changes and its impact in quality of life, concluding that 64% of their participants suffered dysgeusia, with a higher prevalence among women [26]. This coincides with our results, where 63.1% of women suffered dysgeusia compared with 59.7% of men, even though we found no significant statistical differences. Bernhardsson et al. described a 70% prevalence of taste and smell alterations, with alterations appearing

Table 6 Relationship between self-reported side effects and periodontal risk assessment. [(1)]Low risk versus moderate risk; [(2)]Low risk versus high risk; [(3)]Moderate risk versus high risk

Chemotherapy's side effects	Periodontal risk assessment	*N*	Mean	SD	One-way ANOVA (*p* value)	Post-hoc (Bonferroni)			
						Mean difference	95% CI		*p* value
							Low	Upper	
Oral pain	Low	62	0.74	1.639	0.007	− 0.565	− 1.35	0.22	0.248[(1)]
	Moderate	225	1.31	2.328		− 1.358	− 2.39	− 0.32	0.005[(2)]
	High	50	2.10	2.597		− 0.793	− 1.64	0.06	0.077[(3)]
Disgeusia	Low	62	3.03	3.046	0.017	− 0.546	− 1.76	0.67	0.846[(1)]
	Moderate	225	3.58	3.569		− 1.868	−3,48	− 0.25	0.017[(2)]
	High	50	4.90	3.893		− 1.322	− 2.65	0.01	0.051[(3)]
Xerostomia	Low	62	2.66	2.799	0.000	− 1.361	− 2.37	− 0.35	0.004[(1)]
	Moderate	225	4.02	2.941		− 2.319	− 3.65	− 0.99	0.000[(2)]
	High	50	4.98	2.945		− 0.958	− 2.05	0.14	0.109[(3)]
Speech discomfort	Low	62	0.48	1.686	0.311	− 0.387	− 1.06	0.28	0.497[(1)]
	Moderate	225	0.87	2.046		− 0.496	− 1.39	0.39	0.541[(2)]
	High	50	0.98	1.755		− 0.109	− 0.84	0.62	1.000[(3)]
Eating discomfort	Low	62	0.66	1.366	0.103	− 0.610	− 1.33	0.11	0.130[(1)]
	Moderate	225	1.27	2.235		− 0.699	− 1.66	0.26	0.242[(2)]
	High	50	1.36	2.202		− 0.089	− 0.88	0.70	1.000 [(3)]
Total side effects	Low risk	62	7.58	6.525	0.000	− 3.468	− 6.39	− 0.55	0.014[(1)]
	Moderate risk	225	11.05	8.619		− 6.739	− 10.61	− 2.87	0.000[(2)]
	High risk	50	14.32	9.809		− 3.271	− 6.46	− 0.09	0.042[(3)]

just a few days after the first chemotherapy infusion [27]. Other studies showed a lower prevalence of dysgeusia of about 40% [5, 23, 28], which could be due to chemosensory alterations being scarcely reported unless the healthcare professional explicitly ask the patient to provide information about it [27, 29].

One of the most known oral side effects of chemotherapy is mucositis, with an estimated prevalence between 13 and 65% [14, 17]. Patients were evaluated while receiving the chemotherapy infusion, which corresponds to 21 days after the previous chemotherapy infusion (depending on the chemotherapeutic regimen they were under). Mucositis secondary to chemotherapy usually has its peak symptoms 5 to 10 days after the drug intake [30], so when patients were explored, most of the symptoms and signs of the mucositis had disappeared. Nevertheless, in the oral assessment guide, the buccal mucosa and the tongue were evaluated, and in some patients (17.1%), some residual signs of mucositis were found, such as reddened or coated mucous membrane with or without ulceration.

This huge variability could be due to multiple factors, the most important one being the underreporting of mild mucositis, which frequently remains unnoticed, time of oral exploration after the chemotherapy infusion, different type of cancer, and/or chemotherapy regimens analyzed and the diverse diagnosis scales used [11, 24].

In our study, we aimed to evaluate the relationship between periodontal risk and the appearance of oral secondary effects. Having a good oral health and maintaining good oral hygiene have been associated to a lower risk of developing chemotherapy's side effects [7, 17]. We evaluated the patients' periodontal status by using a questionnaire validated for Spanish population that analyzed the risk of having or developing periodontal disease [21]. Our results showed that patients with lower risk of periodontal disease suffered less secondary effects and with less intensity. Statistical differences were found when analyzing the VAS reported by the patient in most of categories according to the periodontal risk. General oral health was evaluated by examining the oral cavity following the guide developed by Eilers et al., which was specifically designed to evaluate oral status in a hospital environment [20]. Our results stated that patients with higher risk of having or developing periodontal disease had worse oral status during chemotherapy and more mucosal complications, which could be due to the important role that oral hygiene plays both in periodontal disease and in the appearance of chemotherapy's side effects. The review by Fitzpatrick and Katz (2010) concluded that there is real potential that the periodontal diseases may be a risk factor for many forms of malignancy, existing a strong degree of evidence of association between periodontitis and oral cancer, although they found that tobacco and alcohol could act as confounding factors [31]. Over 30 years ago, some authors described that chemotherapy could cause an exacerbation of a preexisting periodontal disease [32]. More recently, some studies have shown a relationship between chemotherapy and an increase in some periodontal indexes, such as plaque index, bleeding index, gingival index, and probing depth). Most of these alterations reverted once the chemotherapy treatment finished [33–35].

This study has some limitations, mainly due to the lack of possibility to examine patients in a dental chair, as the place where they received the chemotherapy infusion (Hospital de Día at Hospital Universitario La Paz) had not the adequate facilities. That is the reason why we had to use validated questionnaires to assess the oral status as well as the periodontal disease risk. They are simple, cheap, and easy to use tools that enabled us to evaluate our variables. Another limitation is related to the moment of the examination (while receiving the chemotherapy), as the majority of complications take place 5 to 7 days after the treatment. However, this schedule enabled us to reach a broader sample of patients. Also, this study includes a great variety of cancer types and different treatment regimens, resulting in a very heterogeneous patient's sample. Further studies evaluating patients with the same type and stage of cancer 5 to 7 days after having received the chemotherapy infusion when the side effects are at its peak point, in a dental chair and using periodontal indexes, should be designed.

Conclusions

The most common oral side effects found in patients receiving chemotherapy for solid tumors or hematological cancer were xerostomia and dysgeusia, with a prevalence oral side effects (professional or self-reported) higher than 85%. The risk of the patient of having oral side effects augments as the risk of having or developing periodontal diseases does.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Informed consent Informed consent was signed by all the participants in the study.

Appendix

Table 7 Prevalence of side effects regarding the type of cancer

Type of cancer	*N*	Prevalence of professionally reported oral side effects	Prevalence of self-reported oral side effects
Breast cancer	79	86.1%	91.1%
Colorectal cancer	66	84.8%	90.9%
Lung cancer	64	89.1%	87.5%
Non-Hodgkin lymphoma	28	82.1%	82.1%
Other solid tumors	27	88.8%	92.6%
Liver cancer	19	89.5%	89.5%
Pancreatic cancer	17	82.4%	88.2%
Gastrointestinal cancer	16	87.5%	87.5%
Uterine cancer	15	100.0%	100.0%
Ovarian cancer	14	71.4%	92.9%
Hodgkin lymphoma	9	100.0%	100.0%
Chronic lymphocytic leukemia	7	85.7%	57.1%
Prostate cancer	5	100.0%	100.0%
Multiple myeloma	3	100.0%	100.0%

Table 8 Prevalence of oral side effects regarding the number of cycles already received by the patient

Number of cycles already received	*N*	Prevalence of professionally reported oral side effects	Prevalence of self-reported oral side effects
1	104	82.70%	83.70%
2	71	83.10%	87.30%
3	53	88.70%	94.30%
4	39	89.70%	94.90%
5	14	92.90%	85.70%
6	24	91.70%	91.70%
7	14	85.70%	92.90%
8	6	100.00%	100.00%
9	2	100.00%	100.00%
≥ 10	42	92.85%	95.23%

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