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Correlation among ocular surface disease, xerostomia, and nasal symptoms in patients with differentiated thyroid carcinoma subjected to radioiodine therapy: A prospective comparative study

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Abstract

Background: Some complications of radioiodine therapy have been reported, but the involvement of the eyes and adnexa is rarely discussed. The purpose of this study was to determine the correlation among ocular surface changes, xerostomia, and changes in the nasal mucosa associated with radioiodine therapy.

Methods: Patients subjected to radioiodine therapy (group 1) or not subjected (group 2) were prospectively evaluated by examinations of the ocular surface and tear film, saliva production, and nasal endoscopy. Ocular and nasal symptoms and xerostomia were evaluated using questionnaires.

Results: Evaluation of the ocular surface did not indicate significant differences between the groups. Nasal endoscopy revealed higher mucosal pallor in group 1 and worsening of the endoscopic appearance. Worsening of ocular symptoms and nasal symptoms, xerostomia, and a significant decrease in salivary production was also observed in group 1.

Conclusion: Subjective worsening of xerostomia, xerophthalmia, nasal symptoms, and changes in the nasal mucosa in group 1 was observed.

KEYWORDS

diseases of the lacrimal system, drug-related side effects and adverse reactions, iodine radioisotopes, neoplasms of the thyroid gland/radiotherapy, radiation effects

1 | INTRODUCTION

The use of radioiodine therapy with iodine-131 for treatment of differentiated thyroid carcinomas is a procedure adopted for the ablation of thyroid tissue left after thyroidectomy and of iodine-avid metastasis.[1,2] Its half-life is 8 days; additionally, it emits beta radiation, which is used in therapy, and gamma radiation, which is used in diagnostic imaging tests.[3]

This radiopharmaceutical is frequently used because thyroid cancer accounts for 3.6% of the cases of malignancies worldwide and involves 62 980 new cases in the United States (2014).[4] In Brazil, a study conducted in the capitals of 10 states estimated an incidence of 1.2 cases per 100 000 men and 5.3 cases per 100 000 women.[5] The disease primarily affects women (1:3 male to female ratio) > 45 years old, and papillary and follicular carcinomas are the most common histologic types (75% of cases).[6]

Although mortality due to thyroid cancer has decreased,[7] it is important to note the increase in its incidence worldwide. In the United States, the incidence has increased 2.4 times over the past 30 years, from 3.6 to 8.7 cases per 100 000 inhabitants.[8] In Brazil, a study conducted in a

reference service indicated an increase of 2.766% in the number of patients admitted for thyroid cancer between 1990 and 2010.[9] Although this trend has been attributable to the increased detection of thyroid nodules by imaging studies, treatment of incidental cancers that may not have an effect on patient survival potentially increases the importance of knowing its side effects.

Recent studies in gene therapy have used iodine-131 for the treatment of highly prevalent malignancies, such as breast,[10,11] prostate,[10] and colon cancer,[11] which may indicate a potential increase in the number of patients undergoing this type of treatment in the future.

Although severe complications are rare after treatment,[12,13] adverse effects secondary to salivary gland involvement have been reported, including xerostomia, pain in the parotid glands, and dysphagia, even after administration of low doses of the radiopharmaceutical.[14,15] Ocular complications due to this type of treatment are rarely discussed in the literature[12]; these complications include chronic and recurrent conjunctivitis, keratoconjunctivitis sicca, and xerophthalmia and affect 23% of patients subjected to radioiodine therapy.[1] Lacrimal gland dysfunction,[16,17] especially after high cumulative doses of the drug, has been reported in recent studies. However, the correlation between ocular and extraocular signs and symptoms, including salivary and nasal symptoms, has not been fully elucidated.

Therefore, the purpose of this study was to evaluate the relationship between ocular surface changes and xerostomia and the relationship between changes on the ocular surface and nasal mucosa.

2 | PATIENTS AND METHODS

This study was approved by the Research Ethics Committee of the Clinics Hospital of the Medical School of the University of São Paulo (Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo [HC-FM-USP]), and patients from the Department of Head and Neck Surgery of HC-FM-USP, admitted for thyroidectomy without previous treatment for thyroid cancer, were evaluated between January 2012 and June 2014. All patients were included sequentially before thyroid surgery, when the informed consent form was signed, and the first evaluation (preoperative) was conducted before the beginning of the fasting period. The subjects were divided into 2 groups: group 1 included 44 patients (88 eyes) diagnosed with differentiated thyroid carcinoma with indication for radioiodine therapy and group 2 consisted of 43 patients (86 eyes) diagnosed with differentiated thyroid carcinoma but not subjected to radioiodine therapy. There was no sex or race predilection. All study patients were older than 18 years with records of the histological type of tumor. TNM classification was performed according to the American Joint Committee on Cancer,[18] and disease stage was determined according to the American Thyroid Association.[19] Patients susceptible to the development of dry eye, such as those with autoimmune diseases, users of contact lenses, or antineoplastic drugs, such as 5-fluorouracil and docetaxel, those with history of ocular or lacrimal gland injuries of any nature, those subjected to radiotherapy for treatment of other diseases, those subjected to radiotherapy of the head and neck, and those with a history of hormone therapy or dysthyroid orbitopathy were excluded.

Patients with indication for radioiodine therapy underwent the usual preparation for radiopharmaceutical administration, including dietary counseling, interruption in the use of cosmetics and medications containing iodine, and suspension of the use of thyroid hormone 30 days before admission for radioiodine therapy to increase the serum levels of endogenous thyroid-stimulating hormone (TSH; induced hypothyroidism).[20]

The patients answered questionnaires to assess ocular and nasal symptoms before the examinations. Xerophthalmia (feeling of dry eye, photophobia, burning, and redness) was evaluated using the Ocular Surface Disease Index (OSDI)[21] in Portuguese[22] with a score between 0 (no symptoms) and 100 (maximal symptoms). Nasal symptoms were assessed using the Nasal Obstruction Symptom Evaluation in the Portuguese Language (NOSE-p)[23] with a score between 0 (no symptoms) and 100 (maximal symptoms).

The patients were subjected consecutively to the Tear Film Breakup Time (TBUT) test,[24] Schirmer I test,[25] ocular surface staining with rose bengal, and nasal endoscopy.

The TBUT test was performed after the instillation of 1 drop of a preparation containing fluorescein at 0.25% in the lower conjunctival fornix of each eye. After 4 minutes, the patients were requested not to blink, and the period required for the formation of dark areas corresponding to tear film break-up areas was evaluated via slit-lamp examination (Haag-Streit) under cobalt blue light at $10\times$ magnification. This procedure was repeated 3 times, and the mean values were calculated. The result was considered positive in cases in which the mean value was <10 seconds.

The Schirmer I test was conducted with standard sterile strips (5×60 mm) made of Whatman filter paper 41 (Ophthalmos). The strip was folded in an appropriate place determined by the manufacturer and inserted into the conjunctival fornix between the lateral and middle thirds of the lower eyelid without previous instillation of any eye drop (Schirmer I). The strip was removed after 5 minutes, and the wet area was measured.

The rose bengal test was performed with the instillation of 1 drop of 1% rose bengal (Pharmaceutical Division of HC-FM-USP) in the lower conjunctival fornix of each eye. The result was considered positive in cases in which

TABLE 1 Distribution of the study groups according to age

Group	No. of patients	Mean	SD	Minimum	Median	Maximum	*P* value (*t* test)
1	44	46.9	13.8	21	49.5	82	.05
2	43	52.1	15.5	18	55.0	82	

conjunctival or corneal impregnation was observed after instillation of the eye drop using the slit-lamp at 16 × magnification under a red-free light and graded using the Oxford scale.[26]

Nasal endoscopy was performed by an otorhinolaryngologist blinded to the patient groups by introducing a 4-mm 0-degree rigid nasal endoscope (Karl Storz) into the nasal cavity after topical anesthesia with nebulized 2% lidocaine without a vasoconstrictor. The morphology of the 2 nasal cavities and nasal mucosa was evaluated using the guidelines of the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012[27] for the presence of edema, polyps, and secretion (score between 0 = no changes and 14 = maximum change) and nasal mucosa pallor (indirect sign of atrophy).

The symptoms of xerostomia (dry mouth, cavities, gingivitis, stomatitis, and dysphagia for solids) were evaluated using the Xerostomia Inventory questionnaire[28] in Portuguese,[29] applied by a speech therapist from the Department of Head and Neck Surgery of HC-FM-USP, and the score ranged between 11 (absence of xerostomia) and 55 (maximum xerostomia).

Objective evaluation of saliva production was performed by calculating the difference in the weight of the dry gauze and the gauze moistened with saliva before and after oral stimulation by tongue rotation in the mouth vestibule. The saliva collection before stimulation involved calculation of the weight of a dry gauze using a high-precision scale (model BL2300; Shimadzu), rubbing of the gauze on the tongue, floor of the mouth, lower vestibule, hard palate, upper vestibule, and cheeks, and reweighing of the gauze with the saliva. The difference between the weight of the dry gauze and the gauze containing saliva indicated the production of saliva before stimulation. Similarly, saliva samples were collected after stimulation by rubbing the gauze on the same oral structures after 1 minute without swallowing and with rotation of the tongue around the gums.

All evaluations were performed at the same time of day (between 1:00 PM and 5 PM) to minimize changes secondary to the circadian rhythm.

Each patient underwent examinations and answered questionnaires on the day before thyroidectomy, 1 month after surgery, and 2, 4, 6, and 12 months of follow-up after radioiodine therapy or after surgery.

Statistical analysis was performed by establishing correlations between the values obtained in the various quantitative tests, the positivity or negativity of qualitative tests, and the responses from the questionnaires.

An exploratory data analysis was first performed. This method summarizes a series of related values to estimate the variations in these values, and data were organized and described using tables. For quantitative analysis, the following variables were evaluated: n, mean, SD, minimum, first quartile (25%), median (50%), third quartile (75%), and maximum. This analysis was performed using SAS version 9.0. (SAS Institute, Cary, NC). Fisher's exact test was used for qualitative variables to determine the associations between

TABLE 2 Characteristics of the study patients according to the inclusion group

	Group 1	Group 2
No. of patients	44	43
Mean age (SD), years *P* = .05; Student's *t* test	46.9 (13.8)	52.1 (15.5)
No. of women/men (percentage) *P* = .75; Fisher's exact test	37/7 (84.1/15.9)	38/5 (88.4/11.6)
Histology of the papillary/follicular tumor (percentage)	41/3 (93.2/6.8)	30/13 (69.8/30.2)
Cancer classification		
T	T1: 13 (29.5%) T2: 11 (25.0%) T3: 19 (43.2%) T4a: 1 (2.3%)	T1: 43 (100%)
N	N0: 5 (11.4%) N1: 20 (45.4%) N1a: 12 (27.2%) N1b: 7 (16%)	N0: 10 (23.3%) N1: 2 (4.6%) N1a: 1 (2.3%) Nx: 30 (69.8%)
M	M0: 44 (100%)	M0: 43 (100%)
Disease stages	Stage I: 21 (47.7%) Stage II: 6 (13.6%) Stage III: 15 (34.1%) Stage IVA: 2 (4.6%)	Stage I: 42 (97.7%) Stage III: 1 (2.3%)
Mean follow-up period postradioiodine therapy or postsurgery, months	10.7	10.5

TABLE 3 Distribution of patients per follow-up evaluation

	Follow-up period					
	Before surgery	**After surgery**	**Second month of follow-up**	**Fourth month of follow-up**	**Sixth month of follow-up**	**Twelfth month of follow-up**
Group 1 (N = 44)						
No. of patients	44	44	44	40	38	38
(%)	100	100	100	90.1	86.4	86.4
Group 2 (N = 43)						
No. of patients	43	43	43	40	38	35
(%)	100	100	100	93	88.4	81.4

the groups, and McNemar's test was used to assess the effect of intervention in each group. Student's *t* test was used to compare the ages between the groups. For quantitative variables, a linear regression model with mixed effects (random and fixed effects) was proposed. Linear mixed effect models are used in the analysis of data in which the responses are grouped (more than 1 measurement for the same individual), and the assumption of independence between observations in the same group is not met.[30] This analysis was performed using the PROC MIXED procedure of SAS version 9.0. Comparisons were made using the orthogonal contrasts post hoc test.

3 | RESULTS

With regard to qualitative variables, the mean age was 46.9 ± 13.8 years (range 21-82 years) in group 1 (n = 44; 88 eyes) and 52.1 ± 15.5 years (range 18-82 years) in group 2 (n = 43; 86 eyes; $P = .05$; Table 1). In both groups, there was a predominance of female patients: 84.1% (37 patients) in group 1 and 88.4% (38 patients) in group 2 ($P = .75$).

Table 2 characterizes the study patients according to the inclusion group.

Papillary carcinoma was the predominant histological type in both groups, corresponding to 93.2% (n = 41) patients in group 1 and 69.8% (n = 30) patients in group 2. With regard to the TNM classification, 2.3% of cases (1 patient) were classified as T4a, 43.2% of cases (19 patients) were classified as T3, 25% of cases (11 patients) were classified as T2, and 29.5% of cases (13 patients) were classified as T1 in group 1. In group 2, all 43 patients were classified as T1.

In group 1, 11.4% of cases (5 patients) were classified as N0, 45.4% of cases (20 patients) were classified as N1, 27.2% of cases (12 patients) were classified as N1A, and 16% of cases (7 patients) were classified as N1B. In group 2, 23.3% of cases (10 patients) were classified as N0, 4.6% of cases (2 patients) were classified as N1, 2.3% of cases (1 patient) were classified as N1A, and 69.8% of cases (30 patients) were classified as Nx.

With regard to metastases, all patients from both groups were classified as M0.

With regard to disease stage, 47.7% of cases (21 patients) were classified as stage I, 13.6% of cases (6 patients) were stage II, 34.1% of cases (15 patients) were stage III, and 4.6% of cases (2 patients) were stage IVA in group 1. In group 2, 97.7% of cases (42 patients) were classified as stage I, and 2.3% of cases (1 patient) were classified as stage III.

The distribution of patients in groups 1 and 2 for follow-up evaluations is shown in Table 3. The 12-month follow-up was completed by 38 patients (86.4%) from group 1 and 35 patients (81.4%) from group 2, considering the occurrence of loss of follow-up of the patients who discontinued the study before 12 months. The mean dose of radioiodine therapy was 191.6 ± 37.7 mCi (range 101.2-266.7 mCi). All patients received a single dose of iodine-131.

The TBUT values (Figure 1, Table 4) varied significantly only in the evaluation of the left eyes in group 2 with an increase in the second ($P < .01$) and 12th month ($P = .02$) of follow-up after surgery compared with preoperative values.

The results of the rose bengal test (Table 5) did not differ significantly between the groups in the different evaluation periods.

Schirmer I values were higher after surgery (mean = 14.83; $P = .04$) and in the second month (mean = 15.29; $P = .04$), sixth month (mean = 15.74; $P = .02$), and twelfth month (mean = 14.11; $P < .01$) of follow-up for the right eye in group 2 compared with the preoperative values (mean = 12.93; Figure 2, Table 6).

Nasal endoscopy revealed greater mucosal pallor in group 1 in the second month (odds ratio [OR] 3.61; 95% confidence interval [CI] 1.44-9.09; $P < .01$), fourth month (OR 4.00; 95% CI 1.48-10.79; $P < .01$), and twelfth month of follow-up after radioiodine therapy (OR 3.24; 95% CI 1.14-9.22; $P = .03$; Table 7). Moreover, there was worsening of the EPOS 2012 endoscopic appearance score for edema, polyps, and secretion in the sixth month of follow-up after radioiodine therapy compared with the preoperative values ($P < .01$; Figure 3, Table 8).

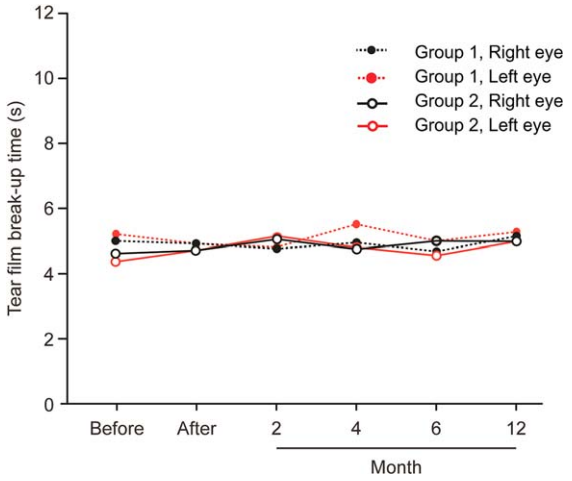

FIGURE 1 Comparison of the mean tear film breakup time between the groups [Color figure can be viewed at wileyonlinelibrary.com]

In group 1, there was 1 case of epistaxis, nasal pain, and nasal congestion 7 days after radioiodine therapy. These symptoms affected a female patient aged 59 years subjected to an iodine dose of 150 mCi and lasted for 2 weeks.

The results of the OSDI questionnaire indicated worsening of the score in group 1 in the second ($P < .01$), fourth ($P < .01$), sixth ($P < .01$), and twelfth month ($P < .01$) of follow-up after radioiodine therapy compared with preoperative values and in the second ($P < .01$), fourth ($P < .01$), and sixth month ($P < .01$) of follow-up after radioiodine therapy compared with the postoperative values. We also observed lower OSDI scores in group 1 before and after surgery ($P < .01$; Figure 4, Table 9).

The subjective evaluation using the NOSE questionnaire indicated worsening of nasal symptoms in group 1 in the second ($P = .02$) and fourth month ($P < .01$) of follow-up after radioiodine therapy compared with preoperative values and in the second ($P = .03$) and fourth month ($P < .01$) of follow-up after radioiodine therapy compared with postoperative values. Additionally, these scores improved between the fourth and twelfth months of follow-up after radioiodine therapy ($P = .03$; Figure 5, Table 10). In group 2, the symptoms improved between the second ($P = .03$) and fourth month ($P = .04$) of follow-up compared with the postoperative values. The individual assessment of each follow-up

TABLE 4 Tear film break-up time (in seconds) between the groups with different follow-up periods

	TBUT	No. of patients	Mean	SD	Minimum	First quartile	Median	Third quartile	Maximum
Group 1									
Before surgery	RE	44	5	2.11	2	3	5	6	12
	LE	44	5.21	2.16	2	4	5	7	10
After surgery	RE	44	4.88	1.76	2	3.5	4	6.5	8
	LE	44	4.93	1.67	2	4	5	6	10
Second month of follow-up	RE	44	4.73	1.72	2	3.5	4	6	9
	LE	44	4.8	1.81	2	3	4.5	6	9
Fourth month of follow-up	RE	40	4.95	2.08	2	4	5	6	14
	LE	40	5.51	2.56	2	4	5	7	16
Sixth month of follow-up	RE	38	4.67	2.04	1	3	4.5	6	10
	LE	38	5.03	2.12	2	3	5	6.5	9
Twelfth month of follow-up	RE	38	5.15	1.86	2	4	5	6	12
	LE	38	5.27	1.74	2	4	5	6	11
Group 2									
Before surgery	RE	43	4.61	1.74	2	3	4	6	8
	LE	43	4.34	1.74	2	3	4	5	9
After	RE	43	4.71	1.95	2	3	4	6	9
surgery	LE	43	4.71	1.72	2	3	5	6	8
Second month of follow-up	RE	43	5.05	1.5	2	4	5	6	8
	LE	43	5.14	1.7	2	4	5	7	8
Fourth month of follow-up	RE	40	4.77	1.97	2	3	4	7	9
	LE	40	4.85	1.87	2	3	5	7	8
Sixth month of follow-up	RE	38	5	1.89	2	4	5	7	8
	LE	38	4.57	1.86	1	3	5	6	8
Twelfth month of follow-up	RE	35	5	1.52	3	4	5	6	8
	LE	35	4.97	1.6	2	4	5	6	8

Abbreviations: LE, left eye; RE, right eye; TBUT, tear film breakup time.

TABLE 5 Comparison of the scores of the rose bengal staining (using the Oxford classification) in each follow-up period (Fisher's exact test)

	Period					
Right eye	**Before surgery**	**After surgery**	**Second month of follow-up**	**Fourth month of follow-up**	**Sixth month of follow-up**	**Twelfth month of follow-up**
Group 1						
0	18	19	13	16	11	13
(%)	(40.91)	(43.18)	(29.55)	(40)	(29.02)	(34.21)
1	26	22	29	18	26	23
(%)	(59.09)	(50)	(65.91)	(45)	(68.42)	(60.53)
2	0	3	2	5	1	1
(%)	0	(6.82)	(4.55)	(12.5	(2.56)	(2.63)
3	0	0	0	1	0	1
(%)	0	0	0	(2.5	0	(2.63)
Total	44	44	44	40	38	38
Group 2						
0	12	10	11	12	7	10
(%)	(27.91)	(23.25)	(25.58)	(30)	(18.42)	(28.57)
1	25	28	30	26	25	24
(%)	(58.14)	(65.11)	(69.77)	(65)	(65.79)	(68.57)
2	6	3	2	2	4	1
(%)	(13.95)	(6.98)	(4.65)	(5)	(10.53)	(2.86)
3	0	2	0	0	2	0
(%)	0	(4.65	0	0	(5.26)	0
Total	43	43	43	40	38	35
	($P = .07$)	($P = .16$)	($P = .93$)	($P = .22$)	($P = .19$)	($P = .85$)
Group 1						
Left eye						
0	17	18	13	12	9	9
(%)	(38.64)	(40.91)	(29.55)	(30)	(23.68)	(23.68)
1	24	22	28	20	25	27
(%)	(54.55)	(50)	(63.64)	(50)	(65.79)	(71.05)
2	3	4	3	7	3	1
(%)	(6.82)	(9.09)	(6.82)	(17.5)	(7.89)	(2.63)
3	0	0	0	1	1	1
(%)	0	0	0	(2.5)	(2.63)	(2.63)
Total	44	44	44	40	38	38
Group 2						
Left eye						
0	11	9	10	9	5	8
(%)	(25.58)	(20.93)	(23.26)	(22.5)	(13.16)	(22.86)
1	28	28	29	26	25	26
(%)	(65.12)	(65.12)	(67.44)	(65)	(65.79)	(74.29)
2	4	4	4	5	5	1
(%)	(9.3)	(9.3)	(9.3)	(12.5)	(13.16)	(2.86)
3	0	2	0	0	3	0
(%)	0	(4.650	0	0	(7.89)	0
Total	43	43	43	40	38	35
	($P = .43$)	($P = .16$)	($P = .79$)	($P = .50$)	($P = .46$)	($P = .99$)

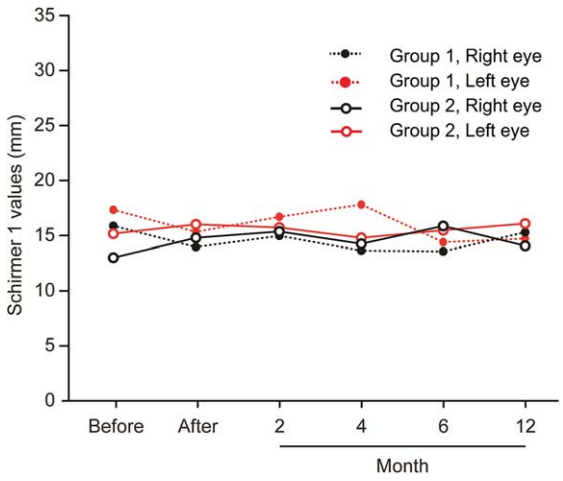

FIGURE 2 Comparison of the mean Schirmer I values between the groups [Color figure can be viewed at wileyonlinelibrary.com]

period between the groups indicated no significant differences in the results.

Evaluation of xerostomia using the Xerostomia Inventory questionnaire indicated worsening of symptoms in group 1 between the second ($P < .01$), fourth ($P < .01$), sixth ($P < .01$), and twelfth month ($P = .01$) of follow-up after radioiodine therapy compared with the preoperative values and in the second ($P < .01$), fourth ($P < .01$), sixth ($P < .01$), and twelfth month ($P = .02$) of follow-up after radioiodine therapy compared with the postoperative values. The symptoms improved in the 12th month compared with the fourth month of follow-up after radioiodine therapy ($P = .01$). However, the symptoms did not vary significantly in group 2 in the different follow-up periods (Figure 6, Table 11).

There was an objective reduction in salivary secretion in group 1 both before and after oral stimulation with tongue rotation in the mouth vestibule in the comparison between the follow-up periods (2, 4, 6, and 12 months) and preoperative values ($P < .01$) and between the follow-up periods (2, 4, 6, and 12 months) and postoperative values ($P < .01$; Figure 7, Table 12).

In addition, there were significant differences in saliva production between the groups in the fourth month ($P < .01$) of follow-up with respect to the saliva production before

TABLE 6 Schirmer I values (in millimeters) for each study group during the follow-up periods

	Schirmer I	No. of patients	Mean	SD	Minimum	First quartile	Median	Third quartile	Maximum
Group 1									
Before surgery	RE	44	15.83	10.66	2	5	15	25	35
	LE	44	17.27	10.47	2	8	17	25	35
After surgery	RE	44	13.97	8.57	1	6.5	14	20	32
	LE	44	15.32	9.13	1	7	15	23	33
Second month of follow-up	RE	44	14.97	10.02	3	6	12	25	34
	LE	44	16.6	10.16	1	9	15	26	35
Fourth month of follow-up	RE	40	13.58	9.92	3	5	10	18	35
	LE	40	17.8	11.72	1	8	12	31	35
Sixth month of follow-up	RE	38	13.52	10.32	1	5	11	21	35
	LE	38	14.35	8.93	1	7	13	22	33
Twelfth month of follow-up	RE	38	15.24	10.61	3	6	10.5	25	35
	LE	38	14.74	10.48	2	6	10	24	35
Group 2									
Before surgery	RE	43	12.93	9.9	1	4	10	19	32
	LE	43	15.21	10.06	1	7	14	24	35
After surgery	RE	43	14.83	9.78	2	6.5	12	23.5	33
	LE	43	15.93	10.71	2	7	15	25	35
Second month of follow-up	RE	43	15.29	9.73	3	8	12	22	33
	LE	43	15.71	9.69	3	8	13	23	35
Fourth month of follow-up	RE	40	14.3	9.89	3	6	11	23	35
	LE	40	14.72	9.44	2	6.5	13.5	20.5	35
Sixth month of follow-up	RE	38	15.74	9.8	2	8	12	27	33
	LE	38	15.5	10.1	3	8	12.5	23	35
Twelfth month of follow-up	RE	35	14.11	9.72	1	7	11.5	16.5	35
	LE	35	16.07	9.74	2	8	15	22	35

Abbreviations: LE, left eye; RE, right eye.

TABLE 7 Nasal mucosal pallor upon endoscopy in the study groups

Second month of follow-up			
Mucosal pallor	**Group 1**	**Group 2**	**Total**
Absent (%)	21 (47.73)	33 (76.74)	54
Present (%)	23 (52.27)	10 (23.26)	33
Total	44	43	87
P value	< .01		
Odds ratio		Case vs control	3.61 (1.44-9.09)
Fourth month of follow-up			
Mucosal pallor	**Group 1**	**Group 2**	**Total**
Absent (%)	20 (50)	32 (80)	52
Present (%)	20 (50)	8 (20)	28
Total	40	40	80
P value	< .01		
Odds ratio		Case vs control	4.00 (1.48-10.79)
Sixth month of follow-up			
Mucosal pallor	**Group Case**	**Control**	**Total**
Absent (%)	23 (58.97)	30 (78.95)	53
Present (%)	16 (41.03)	8 (21.05)	24
Total	39	38	77
P value	.08		
Twelfth month of follow-up			
Mucosal pallor	**Group Case**	**Control**	**Total**
Absent (%)	21 (55.26)	28 (80)	49
Present (%)	17 (44.74)	7 (20)	24
Total	38	35	73
P value	.03		
Odds ratio		Case vs control	3.24 (1.14-9.22)

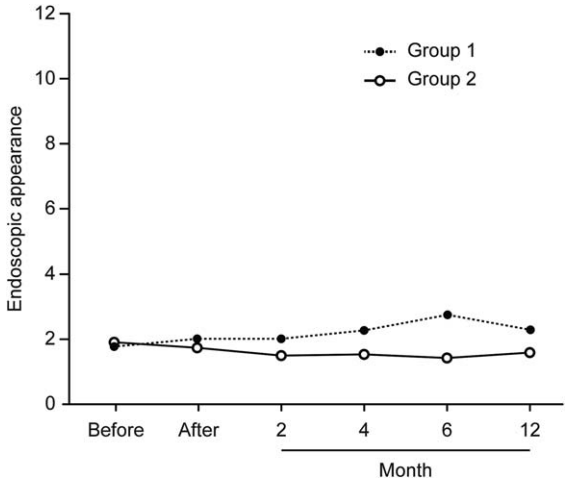

FIGURE 3 Comparison of the mean scores for evaluation of the nasal cavity (according to the European Position Paper on Rhinosinusitis and Nasal Polyps 2012) in each follow-up period

stimulation (Table 12) and in the second ($P = .02$), fourth ($P = .02$), and sixth month ($P = .01$) of follow-up with respect to saliva production after stimulation.

In group 1, the differences in saliva production before and after oral stimulation were lower in all follow-up evaluations until the 12th month compared with the postoperative evaluation in this group ($P < .01$; see Figure 8). In group 2, the differences in saliva production before and after oral stimulation were lower only in the fourth month of follow-up ($P = .02$) compared with the preoperative values.

The difference in saliva production before and after oral stimulation in group 1 was lower than that in preoperative group 2 ($P = .03$) in the second ($P = .02$), sixth ($P = .02$), and twelfth month ($P < .01$) of follow-up (see Figure 8).

4 | DISCUSSION

The histological and functional similarities between the lacrimal and salivary glands and the close relationship between the nasal cavity and lacrimal drainage system supported the design of this study, which is the first to prospectively evaluate the effect of iodine-131 on the lacrimal and salivary physiology jointly.

Descriptive analysis of both groups demonstrated that the epidemiological profile regarding age and sex corroborated findings from other studies for differentiated thyroid carcinoma, including the predominance of female patients (84.1% in group 1 and 88.4% in group 2) and age between 50 and 60 years (mean age of 46.9 years in group 1 and 52.1 years in group 2).[6,8] The lower mean age of patients in group 1 ($P = .05$) may be due to the indication for radioiodine therapy to all patients younger than 45 years and with disease stage II,[19] who were, thus, subjected to treatment with

TABLE 8 Endoscopic appearance (according to European Position Paper on Rhinosinusitis and Nasal Polyps 2012[27]

Group	Period	No. of patients	Mean	SD	Minimum	Median	Maximum
1	Before surgery	44	1.80	3.02	0	0	14
	After surgery	44	2.02	2.57	0	0	9
	Second month	44	2.00	2.01	0	2	6
	Fourth month	40	2.28	2.43	0	2	10
	Sixth month	38	2.77	2.78	0	2	8
	Twelfth month	38	2.32	2.48	0	2	8
2	Before surgery	43	1.91	2.69	0	0	14
	After surgery	43	1.72	2.37	0	0	12
	Second month	43	1.51	2.56	0	0	14
	Fourth month	40	1.53	2.33	0	0	12
	Sixth month	38	1.44	2.29	0	0	12
	Twelfth month	35	1.60	2.32	0	2	12

iodine-131. The presence of patients with advanced stages of the disease in group 1 reflects the current recommendations for ablation using iodine-131 for differentiated thyroid cancer on the basis of the TNM and American Thyroid Association classifications.[19,31]

The presence of sodium-iodide symporter (NIS) in extrathyroidal tissues, including the lacrimal glands[32,33] and exocrine glands,[33,34] may have contributed to the occurrence of adverse effects associated with radioiodine therapy. Among these effects, sialadenitis is the most frequent,[35–37] particularly with the bilateral involvement of the parotid glands because they have a higher proportion of serosal tissue and ductal cells, which absorb more iodine than the mucosal tissue of the submandibular glands.[37,38] Therefore, there is decreased production of saliva, particularly after high doses of radioiodine therapy.[12,37]

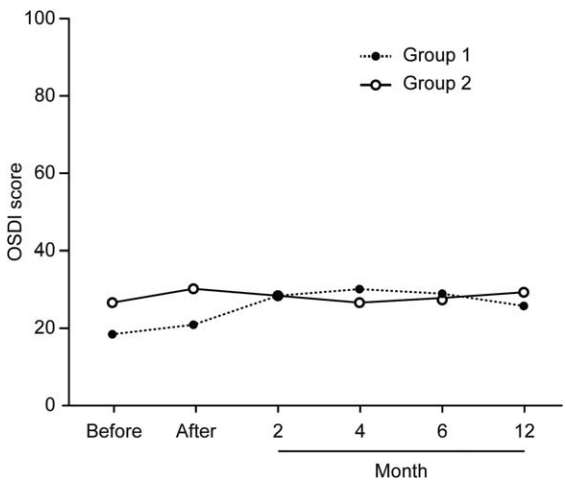

FIGURE 4 Comparison of the mean scores for the evaluation of ocular surface disease (Ocular Surface Disease Index [OSDI] questionnaire) in each follow-up period

The uptake of iodine-131 by the nasal mucosa on scintigraphy is common,[39] even at doses as low as 5 mCi,[40] although this result can be correlated with complications resulting from this form of treatment, including epistaxis and nasal pain in patients subjected to higher doses of radioiodine therapy (up to 150 mCi).[40,41]

The use of the thyroid hormone suspension before radioiodine therapy (induced hypothyroidism) in group 1 may lead to greater uptake of iodine-131 by the nasal mucosa. Some researchers consider the use of recombinant human TSH (rhTSH) in place of this suspension,[42–44] and this technique would avoid induced hypothyroidism and achieve a rate of success similar to that of radioiodine therapy.[4,45] In fact, a recent retrospective study[40] demonstrated that the risk of nasal and ocular adverse effects increased in patients subjected to the withdrawal of thyroid hormone compared with the administration of rhTSH. The ORs (95% CI) for nasal and ocular adverse effects with the use of rhTSH were 0.22 (range 0.11-0.44) and 0.37 (range 0.18-0.76), respectively. Therefore, the potential use of rhTSH to reduce the incidence of adverse effects related to radioiodine therapy should be evaluated in future studies.

Although the association between radioiodine therapy and xerostomia is well established, the association between xerophthalmia and radioiodine therapy has not been fully elucidated. In agreement with previous studies,[12,16] no significant differences in the results of the objective tests that

TABLE 9 Results of the Ocular Surface Disease Index questionnaire

Group	Period	No. of patients	Mean	SD	Minimum	First quartile	Median	Third quartile	Maximum
1	Before surgery	44	18.68	20.91	0	2.30	10.90	30.00	93.2
	After surgery	44	21.03	21.50	0	4.50	12.50	35.25	77.3
	Second month	44	28.23	26.65	0	6.55	21.30	44.65	93.7
	Fourth month	40	30.32	28.23	0	8.30	21.65	44.60	97.9
	Sixth month	38	29.22	26.7	0	8.30	18.70	50.00	100
	Twelfth month	38	25.90	25.55	0	9.10	19.55	45.80	84
2	Before surgery	43	26.82	25.14	0	9.10	16.60	41.70	89.6
	After surgery	43	30.37	26.42	0	10.40	20.80	45.50	85.4
	Second month	43	28.56	25.75	0	10.40	20.80	45.90	83.3
	Fourth month	40	26.46	24.55	0	8.80	19.35	33.05	89.6
	Sixth month	38	27.95	26.28	0	8.30	20.05	45.50	100
	Twelfth month	35	29.36	26.29	0	8.30	17.90	53.60	87.5

were used to evaluate ocular surface disease were observed between the groups. However, worsening of the OSDI scores until the 12th month of follow-up in group 1 indicated a higher frequency of symptoms related to ocular surface disease in patients subjected to radioiodine therapy, although this worsening was not accompanied by significant changes in the TBUT and rose bengal tests.[25,46,47]

The increase in the TBUT values observed in the left eyes in the second and twelfth months of follow-up in group 2 may be because of the higher sensitivity (72%) and lower specificity (62%) of the test[48] with a higher rate of false-positive results and a lower positive predictive value (25%).[46] The TBUT has been shown to present technical variations in its application and to lack consistency for the cut-off values for normality,[46] although it is widely used because of its ease of application and low cost.

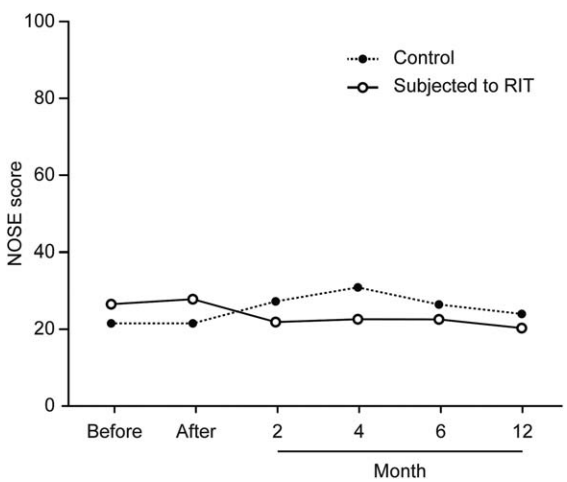

FIGURE 5 Comparison between the mean values of the subjective evaluation of nasal symptoms (Nasal Obstruction Symptom Evaluation [NOSE]) in each follow-up period. RIT, radioiodine therapy

The mean TBUT values ranged between 4.34 and 5.51 seconds, which can be considered abnormal.[46] However, a previous study[49] involving 200 patients suggested a mean value of 7.1 seconds (range 4.7-11.3 seconds) for normal individuals and 2.2 seconds (range 0.9-5.2 seconds) for patients with dry eye, after instillation of 5 microliters of 2% fluorescein. In our study, we used a higher volume and lower concentration of fluorescein, which limits the comparison with other TBUT results, but this volume did not jeopardize the internal validity during follow-up.

The results of the Schirmer I test indicated no significant differences in group 1, suggesting that the aqueous production of the tear film did not decrease, which reduces the likelihood of the concomitant occurrence of lacrimal duct obstruction and xerophthalmia,[50] which would result in an equilibrium between decreased lacrimal production and decreased lacrimal drainage, contributing to the delayed diagnosis of obstructions. Although previous studies suggest the occurrence of dysfunction of lacrimal glands after radioiodine therapy,[17,51] the evaluation of this dysfunction may have been compromised by the predominant inclusion of post-menopausal women, cross evaluation of patients, and the lack of examinations before radioiodine therapy.

The increased production of tears in the Schirmer I test during postoperative follow-up in group 2 supports the results of several studies, which reported high variability, poor reproducibility, and poor correlation between the test

TABLE 10 Results of the Nasal Obstruction Symptom Evaluation questionnaire

Group	Period	No. of patients	Mean	SD	Minimum	First quartile	Median	Third quartile	Maximum
1	Before surgery	44	21.59	25.56	0	0	12.5	32.5	100
	After surgery	44	21.70	23.23	0	5	15.0	27.5	100
	Second month	44	27.39	26.00	0	10	25.0	30.0	100
	Fourth month	40	31.00	28.83	0	7.5	25.0	50	100
	Sixth month	38	26.67	27.92	0	5	15.0	40	100
	Twelfth month	38	24.05	27.54	0	5	10.0	45	90
2	Before surgery	43	26.86	31.03	0	0	15.0	45	100
	After surgery	43	28.14	27.90	0	5	15.0	45	95
	Second month	43	22.14	25.39	0	0	10.0	35	90
	Fourth month	40	22.75	25.54	0	0	10.0	45	90
	Sixth month	38	22.63	27.21	0	0	10.0	30	90
	Twelfth month	35	20.54	21.80	0	0	15.0	35	70

results and other signs and symptoms of ocular surface disease.[25,52,53] However, the possibility of occurrence of stenosis of the nasolacrimal duct cannot be discarded in group 1, and this complication would cause partial obstruction of lacrimal drainage and normal Schirmer I results.

The immunohistochemical analysis of normal tissues of the lacrimal system confirmed the presence of NIS in the basolateral membrane of the epithelium of the lacrimal sac and nasolacrimal duct but the absence of symporters in the accessory and primary lacrimal glands,[32] which could contribute to the decrease of iodine-131 uptake by these structures and the occurrence of less prominent injuries.

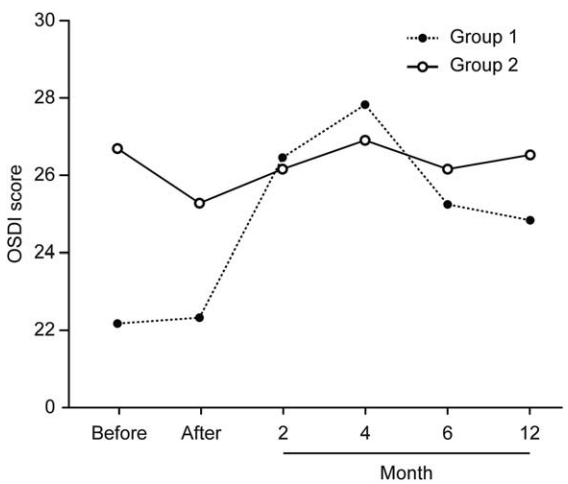

FIGURE 6 Comparison between the mean values of subjective evaluation of xerostomia (Xerostomia Inventory) during each follow-up period. OSDI, Ocular Surface Disease Index

Moreover, the xerostomia evaluation demonstrated worsening of symptoms and an objective decrease in saliva production until the 12th month after radioiodine therapy. The smallest difference in salivary secretion before and after stimulation observed in group 1 indicated the impaired production of saliva with decreased secretion regardless of the stimulus applied.

It is clear in Figures 6 and 7 that there is a significant difference between groups 1 and 2 in xerostomia symptoms and salivary production before stimulation; after radioiodine therapy, both groups have worsened symptoms and salivary production, but reached the same levels. Therefore, we highlight the similarity in the amount of saliva produced in these 2 groups in the different evaluation periods before stimulation, which demonstrates the importance of follow-up of these patients for the detection of xerostomia and indicates the difficult diagnosis of this condition in cross-sectional studies when salivary secretion is not stimulated.

On average, salivary flow without stimulation is 0.3 mL/min,[54,55] which corresponds to 300 mg/min. Salivary flow upon stimulation, which may contribute to 80%-90% of the mean daily production of saliva, may reach 7.0 mL/min[54,55] (or 7 g/min). However, there is significant individual variation in the level of salivary production that is considered normal, and this variation limits the objective characterization of salivary dysfunction, except with the evaluation of previous individual records of secretion,[54] including the method we used for the longitudinal evaluation of patients.

The worsening of nasal symptoms using the NOSE questionnaire until the fourth month of patient follow-up, the worsening of the EPOS 2012 score in the sixth month of

TABLE 11 Results of the Xerostomia Inventory questionnaire

Group	Period	No. of patients	Mean	SD	Minimum	Median	Maximum
1	Before surgery	44	22.21	9.64	14	20	55
	After surgery	44	22.35	9.66	14	20	55
	Second month	44	26.47	9.96	14	26	55
	Fourth month	40	27.83	10.75	14	28	55
	Sixth month	38	25.26	8.95	14	25	55
	Twelfth month	38	24.84	9.76	14	23	55
2	Before surgery	43	26.72	11.91	14	23	55
	After surgery	43	25.28	9.68	14	22	50
	Second month	43	26.16	10.66	14	23	52
	Fourth month	40	26.88	10.26	14	24	52
	Sixth month	38	26.16	9.62	14	24	52
	Twelfth month	35	26.54	9.70	14	24	49

follow-up, and the greater nasal mucosal pallor found in group 1 in the second, fourth, and twelfth months of follow-up after radioiodine therapy indicate the action of iodine-131 in the nasal cavity. The accumulation of iodine-131 in the nasal cavity seems to be normal in patients subjected to radioiodine therapy,[39] and pain and epistaxis have been reported after the use of high radioiodine therapy doses (200-400 mCi), as observed in 1 patient in this study. However, endoscopic findings in patients subjected to radioiodine therapy have not been described. The retention of iodine-131 may contribute to tissue damage of the nasal mucosa and results in an endoscopic appearance suggestive of atrophy, although the uptake mechanism is not entirely understood.

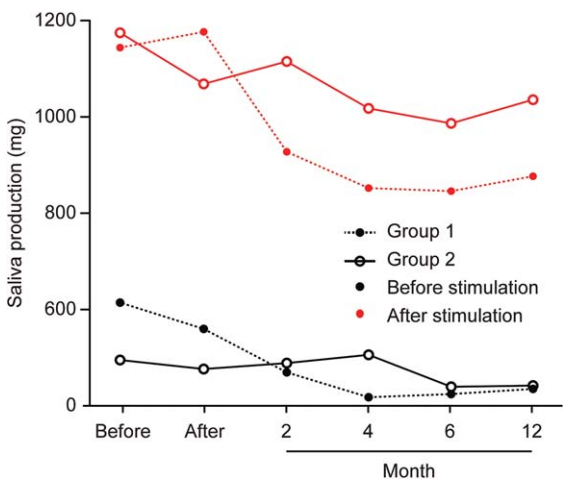

FIGURE 7 Comparison of the mean saliva production before and after stimulation, in milligrams, in each follow-up period [Color figure can be viewed at wileyonlinelibrary.com]

Although the frequency of ocular and nasal symptoms remains uncertain, a recent study[40] warns of the possibility of underreporting the symptoms associated with radioiodine therapy, both because of a lack of familiarity by the physician and the lack of reporting by patients who do not correlate these events to radioiodine therapy.

The main limitation of this study was the small sample size. The use of 0.25% fluorescein drops in the TBUT test was maintained in all evaluations and, although this concentration is not commonly used in clinical practice, it enabled the adequate and standardized comparison of results. Furthermore, the results of the OSDI and NOSE questionnaires may have incurred external influences (seasonal or environmental); we sought to minimize these effects via longitudinal application of these questionnaires to the 2 patient groups.

Although the subjective worsening of xerostomia, xerophthalmia, nasal symptoms, significant decrease in saliva production, and changes in the nasal mucosa were observed in patients from group 1, these observations could not be correlated with objective changes on the ocular surface.

However, these findings demonstrate the importance of alerting health professionals and patients to the possibility of occurrence of these events for early diagnosis and treatment. Although there is no effective method to prevent the adverse effects of radioiodine therapy on the lacrimal system, the use of antioxidants, such as vitamin E,[56] lycopene,[57] and

TABLE 12 Quantification of saliva production in milligrams

Group	Period	Variable	No. of patients	Mean	SD	Minimum	First quartile	Median	Third quartile	Maximum
1	Before surgery	Before stimulation	43	616.07	368.83	115	385.0	482.0	879.0	1516
		After stimulation	43	1146.49	748.34	195	669.0	936.0	1493.0	3808
		Difference	43	530.42	514.95	9	183.0	418.0	656.0	2500
	After surgery	Before stimulation	43	561.88	317.54	153	345.0	521.0	634.0	1543
		After stimulation	43	1178.35	668.33	299	675.0	1040.0	1591.0	3725
		Difference	43	616.47	501.27	16	274.0	481.0	867.0	2199
	Second month of follow-up	Before stimulation	43	470.16	433.05	116	265.0	355.0	482.0	2299
		After stimulation	43	927.28	726.81	245	452.0	676.0	1013.0	3435
		Difference	43	457.12	516.43	22	179.0	312.0	613.0	2960
	Fourth month of follow-up	Before stimulation	40	418.03	236.55	130	275.0	339.0	500.5	1358
		After stimulation	40	851.15	522.92	223	561.5	738.0	944.5	2867
		Difference	40	433.13	416.89	55	215.0	346.0	463.0	2411
	Sixth month of follow-up	Before stimulation	38	424.13	180.78	137	305.0	398.0	512.0	976
		After stimulation	38	847.31	519.89	159	484.0	691.0	998.0	2921
		Difference	38	423.18	435.64	4	88.0	307.0	513.0	2159
	Twelfth month of follow-up	Before stimulation	38	438.08	198.04	117	288.0	426.5	530.0	1156
		After stimulation	38	879.00	430.32	202	532.0	783.0	1207.0	2089
		Difference	38	440.92	371.31	8	151.0	362.0	580.0	1501
2	Before surgery	Before stimulation	43	494.86	337.25	111	266.0	423.0	592.0	1880
		After stimulation	43	1176.70	824.51	195	602.0	988.0	1436.0	4044
		Difference	43	681.84	656.13	–2	191.0	505.0	913.0	3157
	After surgery	Before stimulation	43	477.49	292.62	115	304.0	378.0	612.0	1547
		After stimulation	43	1070.47	737.37	234	554.0	868.0	1334.0	3489
		Difference	43	592.98	587.46	16	123.0	498.0	781.0	2586
	Second month of follow-up	Before stimulation	43	488.44	343.34	89	298.0	412.0	576.0	1789
		After stimulation	43	1118.16	763.77	117	637.0	915.0	1546.0	3134
		Difference	43	629.72	582.76	22	154.0	419.0	1047.0	2448
	Fourth month of follow-up	Before stimulation	40	507.30	321.57	167	303.0	412.5	579.0	1701
		After stimulation	40	1019.33	699.85	202	522.0	802.5	1259.0	3298

(Continues)

TABLE 12 (Continued)

Group	Period	Variable	No. of patients	Mean	SD	Minimum	First quartile	Median	Third quartile	Maximum
		Difference	40	512.03	532.32	4	135.5	316.0	728.5	2586
	Sixth month of follow-up	Before stimulation	38	439.76	224.45	139	265.0	361.5	546.0	913
		After stimulation	38	987.79	631.47	239	478.0	882.0	1324.0	2941
		Difference	38	548.03	520.35	11	165.0	341.0	823.0	2073
	Twelfth month of follow-up	Before stimulation	35	440.97	223.83	81	299.0	396.0	654.0	987
		After stimulation	35	1035.29	728.15	206	489.0	799.0	1429.0	3029
		Difference	35	594.31	571.26	23	153.0	402.0	869.0	2174

montelukast,[58] or NIS blockers, such as perchlorate,[59] are potential therapeutic options.

Prospective studies with a larger sample size and longer follow-up are essential to determine the measures of association, including the relative risk of ocular and nasal adverse effects in patients treated with radioiodine therapy. Furthermore, experimental studies are essential to elucidate the pathophysiological mechanisms associated with these effects and strategies to avoid them without compromising the effectiveness of cancer treatment.

In summary, we could observe a subjective worsening of xerostomia, xerophthalmia, nasal symptoms, and changes in the nasal mucosa. Although it was not correlated with objective measurements, doctors and patients should be aware of these ocular and nasal adverse effects.

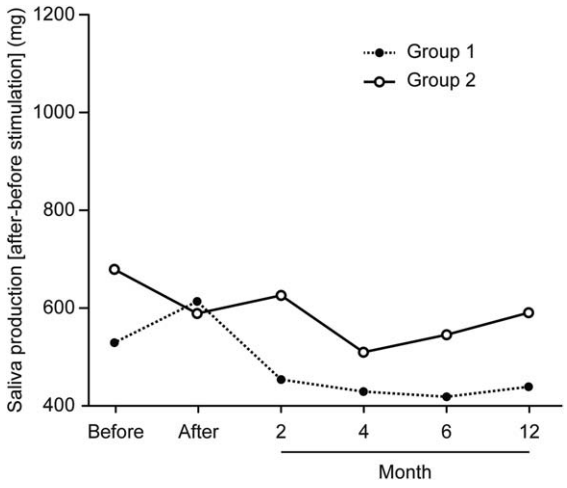

FIGURE 8 Comparison of the mean differences of the production of saliva (poststimulation minus prestimulation), in milligrams, in each evaluation period

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