Dysfunction of the salivary and lachrymal glands after radioiodine therapy for thyroid cancer: Results of the START study after 6-months of follow-up

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Abstract

Background: Understanding of changes in salivary and lacrimal gland functions after radioactive iodine therapy (131I-therapy) remains limited, and, to date, no studies have evaluated dose–response relationships between absorbed dose from 131I-therapy and dysfunctions of these glands. This study investigates salivary/lacrimal dysfunctions in differentiated thyroid cancer (DTC) patients six months after 131I-therapy, identifies 131I-therapy-related risk factors for salivary/lacrimal dysfunctions, and assesses the relationships between 131I-therapy radiation dose and these dysfunctions.

Methods: A cohort study was conducted involving 136 DTC patients treated by 131I-therapy of whom 44 and 92 patients received 1.1 and 3.7 GBq, respectively. Absorbed dose to the salivary glands was estimated using a dosimetric reconstruction method based on thermoluminescent dosimeter measurements. Salivary and lacrimal functions were assessed at baseline (T0, i.e., immediately before 131I-therapy) and six months later (T6) using validated questionnaires and salivary samplings, with and without stimulation of the salivary glands. Statistical analyses included descriptive analyses and random-effects multivariate logistic and linear regressions.

Results: There was no difference between T0 and T6 in the level of parotid gland pain, nor was there difference in the number of patients with hyposalivation, but there were significantly more patients with dry mouth sensation and dry eyes after therapy compared with baseline. Age, menopause, depression and anxiety symptoms, history of systemic disease, and not taking painkillers in the past three months were found to be significantly associated with salivary or lacrimal disorders. Significant associations were found between 131I-exposure and salivary disorders adjusted on the previous variables: for example, per 1-Gy increase in mean dose to the salivary glands, odds ratio = 1.43 [CI 1.02 to 2.04] for dry mouth sensation, ß = -0.08 [CI -0.12 to -0.02] mL/min for stimulated saliva flow, and ß = 1.07 [CI 0.42 to 1.71] mmol/L for salivary potassium concentration.

Conclusions: This study brings new knowledge on the relationship between the absorbed dose to the salivary glands from 131I-therapy and salivary/lacrimal dysfunctions in DTC patients six months after 131I-therapy. Despite the findings of some dysfunctions, the results do not show any obvious clinical disorders after the 131I-therapy. Nevertheless, this study raises awareness of the risk factors for salivary disorders, and calls for longer follow-up.

Introduction

Approximately 10,600 new cases of thyroid cancer were diagnosed in France in 2018; thyroid cancer incidence in France has increased by nearly 5% annually over the past three decades.[1,2] Nevertheless, mortality from thyroid cancer has slightly decreased in recent years, highlighting the good prognosis of this cancer, for which 90% of patients are still alive 10 years after diagnosis.[1,2]

Thyroidectomy followed by vectorized internal radiotherapy (^{131}I-therapy) is the usual treatment for differentiated thyroid cancer (DTC).[3] However, because salivary glands are able to absorb and accumulate iodine, patients might suffer from salivary glands inflammation, and symptomatic or chronic salivary disorders after ^{131}I-therapy.[4] Salivary disorders include any alteration in the quantity or quality of saliva production, i.e., reduced salivary flow and/or altered saliva biochemistry.[5] Subsequent effects can include mouth infections, altered perception of flavors, and impaired ability to swallow and digest food, leading to reduced quality of life. Disorders of the lachrymal glands have also been described following ^{131}I-therapy.[6] However, there is still uncertainty regarding the incidence of such outcomes.[7]

Furthermore, the knowledge of the risk factors for salivary/lachrymal disorders associated with thyroid cancer treated by ^{131}I-therapy is limited by the paucity of studies on the subject, highlighting the need for further studies.[8] A better understanding of these factors may allow the identification of patients likely to develop salivary disorders after ^{131}I-therapy, and thus enable treatment and follow-up to be adapted accordingly.

Finally, the radiation dose-response relationship between ^{131}I-dose and the occurrence of salivary and lachrymal disorders has been poorly studied, with the administered activity used as a proxy for the dose absorbed by the salivary glands.[8,9] However, due to several factors such as iodine biokinetics or the ability of the salivary glands to absorb iodine, the administered activity may not be adequate to accurately characterize the exposure. The use of an appropriate dosimetric method could allow a better estimation of the absorbed dose to the salivary glands, and then a more precise evaluation of the dose-response relationship.

To address these issues, the Salivary dysfuncTions After Radioiodine Treatment (START) study was set up in 2020. This paper describes the incidence of salivary and lachrymal dysfunctions in DTC patients 6 months after ^{131}I-therapy, identifies post-therapy risk factors, and assesses the dose-effect relationship between ^{131}I-exposure and salivary and lachrymal dysfunctions.

Materials and Methods

Study population

The START study has been described in detail elsewhere.[10] Briefly, START is a prospective study, which included 139 DTC patients, aged 18 and over, who have undergone thyroidectomy, and awaiting a

complementary ^{131}I-therapy at Pitié-Salpêtrière Hospital (Paris, France). Inclusion was non-randomized, according to a systematic and consecutive selection of patients. Patients were split into two groups according to the administered ^{131}I-activity: 1.1 GBq (N=45) and 3.7 GBq (N=94). Patients who had previously received ^{131}I-therapy or who were likely to receive several ^{131}I-therapies in the 18-month following enrollment were excluded.

Radiation dose assessment

Three LiF thermoluminescent dosimeters (TLD) from APVL (Saint-Cyr-sur-Loire, France) were placed under both earlobes and at the sternal fork before ^{131}I-therapy, and removed after 5 days, immediately before the post-therapy scan. A computational method was developed to convert the TLD readings, i.e., skin dose, into salivary glands cumulated activity.[10] For that purpose, skin dose per unit nuclear disintegration at the TLD location was calculated using the ICRP female computational phantom and the MCNPX code.[11,12] The computations were checked thanks to dedicated experiments, one consisting in irradiating TLD placed at several locations on a RANDO head phantom with an ^{131}I-capsule inserted at the salivary gland location.[13] The TLD at the sternal fork was used to subtract the contribution of the thyroid remnant to earlobe TLD but it was found to be negligible. The calculated cumulated activity was then converted into absorbed doses to the right and left salivary glands (D_r and D_l, respectively) using S-factor.[14] Then, a mean dose to the salivary glands (MD) was calculated from D_r and D_l to be included in analyses. In addition, the mean dose to the salivary glands per unit of administered activity (MD/A) was calculated. Administered activity (AA) of ^{131}I (1.1 or 3.7 GBq) was also considered in analyses.

Questionnaire-based outcome assessment

Validated questionnaires on salivary complaints (Moreddu et al. questionnaire),[15] lachrymal dryness (OSDI© Questionnaire),[16] anxiety and depression (HAD scale),[17] nutrition (VAS assessment), and quality of life (MOS SF-36)[18] were filled at baseline, i.e., immediately before ^{131}I-administration (T0) and 6 months later (T6) for all patients, during a face-to-face meeting with a trained interviewer, as part of the treatment follow-up at the hospital.

Salivary collection and characterization

Whole saliva was collected for each patient during five minutes at T0 and T6, before and after salivation stimulation, using the Navazesh's standardized method,[19] allowing the calculation of salivary flows before and after stimulation. The concentrations of sodium, potassium, chlorine, calcium, and amylase in the saliva were also assessed at T0 and T6. Salivary and lachrymal dysfunctions were characterized as both binary and continuous outcomes as summarized in Table 1.

[20,21]

[16 22]

Study covariates

Several variables, listed in Table 2, were collected during the enrollment visit to be tested as potential risk factors for salivary and lachrymal dysfunctions. Qualitative and quantitative variables were introduced into the models without being modified.

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Statistical analyses

Patient characteristics at T0 and T6 and exposure descriptions (means and standard deviations, or frequencies and percentages) were examined in relation to the administered activity (1.1 and 3.7 GBq groups). Differences between both groups were assessed using Pearson χ^2 test for categorical data, and t-test for continuous data. Differences for time-varying variables of interest between T0 and T6 were assessed using the McNemar test and T-test for paired comparisons.

Random-effects logistic and linear regressions were used to test established or potential risk factors that may be associated with salivary or lachrymal dysfunctions. Random-effects multivariate logistic and linear regressions, providing odds ratio (OR) and beta coefficients (β) respectively, with their 95% confidence intervals (95CI%), adjusted on the significantly associated risk factors allowed to assess associations between ^{131}I-exposure and salivary and/or lachrymal dysfunctions. Sensitivity analyses were conducted using fixed effect models in which subject effects controlled for explicitly thereby providing control for any characteristic of a study subject that is time-invariant over the period of study T0 to T6.

Analyses were performed using the GLIMMIX procedure of SAS V.9.4 statistical software for Windows (SAS Institute, Cary, NC). An alpha level of 0.05 was considered as significant.

Results

Among the 139 patients in the study, three left the cohort (one exclusion for refusal of ^{131}I-therapy, one death prior to follow-up at T6, one patient lost to follow-up). Thus, analyses included 136 patients, with 44 and 92 patients treated with 1.1 and 3.7 GBq, respectively. The mean age at inclusion was 47.1 (± 14.1) years, 71% were female, 85% had papillary cancer, and 47% had thyroid remnants after ^{131}I-therapy (Table 3). There was no statistically significant difference between the two ^{131}I-activity groups in terms of gender and age.

The mean salivary gland doses were similar for the left and right glands within each ^{131} I- activity group respectively, while the mean dose to the salivary glands per unit of administered activity was similar for both ^{131} I-activity groups (0.6 (± 0.3) mGy/MBq) (Table 3).

Clinically, there was no difference between T0 and T6 in parotid gland pain level and in the number of patients with hyposalivation (Table 4). However, there were significantly more patients with dry mouth sensation and dry eyes after therapy compared to baseline, with 30 (22%) and 23 (17%) new cases at T6, respectively (Table 4). There was no correlation between salivary flows or hyposalivation and dry mouth sensation (p=0.70) (Table S3). Notably, the use of painkillers and the level of anxiety and depression decreased at T6 compared with T0. For paraclinical evaluations, salivary flows decreased at T6, but significantly only for the stimulated flow. Finally, amylase and mineral ion concentrations were significantly higher at T6 compared to baseline (Table 4).

Age, menopause, depression and anxiety symptoms, history of systemic diseases were risk factors for gland disorders, and painkiller intake in the last 3 months was associated with a decrease in salivary disorders (Table S1, Table S2). There was no correlation between salivary and lachrymal outcomes (Table S3).

Multivariate regression analyses quantified relationships between ^{131}I-exposure and salivary or lachrymal dysfunctions, adjusted for age at the time of interview, baseline anxiety and depression score (HAD scale), history of systemic diseases, menopause status, and painkiller use in the last 3 months. For clinical outcomes, no significant association was found between ^{131}I-exposure and stimulated or unstimulated hyposalivation. However, dry mouth sensation was positively associated with mean salivary gland dose (OR = 1.43, 95%CI 1.02–2.04 for a 1-Gy increase), and with the administered ^{131}I-activity (p=0.04). A significant positive association was observed between administered ^{131}I-activity and dry eyes (OR = 3.58 (1.19–10.81) in patients treated with 1.1 GBq versus before treatment), but not for those treated with 3.7 GBq. The latter trend was confirmed when the OSDI© score, used to assess lachrymal dryness, was analyzed using linear analyses. For paraclinical outcomes, the association between mean dose to the salivary glands and stimulated saliva flow was significant after adjustment for confounders, with an average decrease of -0.08 (-0.12;-0.02) mL/min per 1-Gy increase in mean salivary gland dose. The change in saliva biochemical concentrations remained significant only for potassium, with an average increase of 1.07 (0.42;1.71) mmol/L per 1-Gy increase in mean salivary gland dose.

Discussion

The START study is the first study to evaluate salivary disorders, using both objective and subjective indicators, in relation with the absorbed dose to the salivary glands in DTC patients treated by ^{131}I-therapy. The results suggest no clinically-significant impact of ^{131}I-therapy on the salivary glands, but do suggest changes in stimulated saliva flow, salivary potassium concentration, and dry mouth sensation in relation to

the dose absorbed by the salivary glands. Additionally, increased dry eyes as assessed by the OSDI© tool was reported in patients treated in the low administered ^{131}I-activity group.

In the present study, salivary disorders were assessed in a variety of ways, leading to different incidence values (Table 4). In the review by Clement et al. about DTC patients treated with ^{131}I, objective and subjective salivary disorder symptoms ranged between 37% to 72% and 16% to 54%, respectively.[24] Whereas most studies using a subjective criterion reported significant associations with ^{131}I-exposure, conflicting results were found when objective salivary indicators were used.[24] In a prospective study of 25 patients, Viera et al. found a non-significant increase in salivary flows (with and without stimulation) 3 months after ^{131}I-therapy whereas, in a prospective study of 56 patients, Hesselink et al. found a significant decrease in stimulated and unstimulated saliva flows.[9,25] In addition, significantly lower flows were found in ^{131}I-treated patients compared to non-cancer patients,[26] and a significant association was found between ^{131}I-administration (yes/no) and stimulated saliva flow in DTC patients.[8] In our study, we reported a positive and significant association between ^{131}I-exposure and dry mouth sensation 6 months post therapy, and a significant decrease in stimulated flow at T6 in relation to ^{131}I-dose, but not for unstimulated flow. Our study therefore confirms some discrepancies between the results from subjective and objective outcomes, and highlights the lack of reference tools for the assessment of salivary disorders.

In other studies, lachrymal dysfunction, ocular dryness or abnormalities revealed by the Schirmer test were found significantly more frequent in ^{131}I-exposed patients than in unexposed, but no study showed an association between ^{131}I-activity levels and lachrymal gland disorders, assessed both objectively and subjectively, while incidences ranged from 4% to 25.3%.[6,24,27–29] In our study, we observed an increased OR and score for dry eyes after ^{131}I-therapy, with 17% of the patients reporting dry eyes at T6 while they did not before. Surprisingly, associations were higher and significant only for the 1.1 GBq ^{131}I-activity group compared with the 3.7 GBq group. Dose-response analysis was not possible because the absorbed dose to the lacrimal gland was not assessed in this study. We can hypothesize that the dose to the lacrimal gland does not correlate well with the activity delivered. Other risk factors may also obscure this relationship. Nevertheless, our study of lachrymal disorders is based on a subjective assessment using a validated questionnaire. An objective measurement of dry eyes would be useful to confirm these results. Moreover, although the present study shows some significant associations for both lachrymal and salivary disorders with ^{131}I-administration, these disorders were not correlated, suggesting that the sensitivity to iodine and the underlying biological mechanisms are different for these organs. Therefore, the creation of a composite criterion is innovative and interesting, as it allows to consider both objective and subjective indicators, including lachrymal and salivary disorders. The association between ^{131}I-activity and the composite criterion

was positive but non-significant, therefore did not provide evidence of a clinical impact of radioiodine on the salivary and lacrimal glands.

Regarding sialochemistry, significant relationships after adjustment for confounders were found only between ^{131}I-exposure and potassium concentration, among a large set of mineral ions and enzymes tested. To our knowledge, only three studies have assessed salivary composition in DTC patients after ^{131}I-therapy, showing discrepant results, possibly linked to different collection time.[9,30,31]

Very few studies have assessed the dose-response relationship between ^{131}I-exposure and salivary disorders,[8,28,32] and only one study has evaluated this relationship in a well-controlled statistical model: in 179 patients, Almeida et al. found a statistically significant linear relationship between administered ^{131}I-activity (30–450 mCi) and stimulated flow adjusted for age, sex and xerostomic drug use, but not with unstimulated flow.[8] The authors showed that increased age and the use of xerostomic drugs were significantly associated with decreased saliva flows, in particular stimulated flow.[8] Moreover, hypothyroidism and stress can modify the composition and decrease the flow of saliva, although the exact mechanism is unknown.[33,34] In such a study, it is essential to consider risk factors to avoid confusion bias. One of the strengths of our study is its design, where the cases are their own controls, allowing to automatically control for individual risk factors that are not time-dependent.[35,36] In relation to this design, both fixed effect and random effects regression models have been used to assess potential associations between ^{131}I-therapy and dysfunctions. Under random effects models, we do not condition out the unique study identifier (i.e., subject effect); instead, a random effect model where this variable is treated as a random intercept is fitted. An alternative approach is to use conditional logistic regression to obtain fixed effect estimates; this approach also was used, thus conditioning the effect of the subject being "conditioned out" of the model, leading to similar conclusions (results not shown). In our random effects regression models, we were able to test a large number of potential cofactors, and to fit our multivariate models to the significant cofactors. This enabled identifying menopause, history of systemic diseases, not taking painkillers, age, and the level of anxiety-depression as risk factors for salivary disorders after ^{131}I-therapy. This adjusted analysis provides more information about the relationship between the treatment and the studied outcomes than before-and-after studies, which account for most of the studies on the subject.

Other strengths of our studies lie in the assessment of adjusted dose-responses relationships considering not only the administered activity, but also the dose to the salivary glands, which has never been done before. The present study is innovative as it is the first to use calibrated TLD to assess the absorbed doses to the salivary glands, whereas other studies generally use the administered activity as proxy.[8,9] Indeed, iodine uptake by the salivary glands can be modified by the uptake of the thyroid remnants, the "iodine status" of

the patient before the therapy, as well as by other biokinetic parameters. Accurate estimation of absorbed doses to organs is a time and resource-consuming process based on repeated single photon emission computed tomography imaging. The methodology based on TLD measurements has been described elsewhere for several organs, but not for salivary glands.[37–39] In the present study, the dose to salivary glands was found to be 0.6 (± 0.3) mGy/MBq, which is in agreement with previous studies based on imaging where doses ranged between 0.4 and 0.8 mGy/MBq.[40–43] The availability of organ dosimetry has thus provided accuracy in the estimation of dose-response relationships. Nevertheless, the results of logistic and linear regression analyses for the absorbed dose to the salivary glands are consistent with those obtained for the administered activity.

Limitations concern potential biases related to the study design, which were minimized by a rigorous protocol, involving hospital visits that were as similar as possible at baseline and at T6 (face-to-face interview, using identical questionnaire). Patients who received more than one ^{131}I-therapy were excluded from the study even if an evaluation of repeated ^{131}I-therapies would be interesting. Nevertheless, due to the small number of patients with unstimulated or stimulated hyposalivations as described using the validated thresholds for moderate hyposalivation, the results may lack statistical power. In fact, one interpretation of our results might be that ^{131}I-exposure can disrupt stimulated salivary flow, but to too small an extent, i.e. not enough to cause moderate hyposalivation as described by Ericsson and Hardwick.[20]

Conclusion

This study confirms the possible occurrence of salivary and lachrymal disorders in patients treated with ^{131}I for thyroid cancer. Despite the findings of some dysfunctions, the results do not show any obvious clinical disorders after the ^{131}I-therapy. The present study confirms the risk factors of these disorders and brings new knowledge on the dose-response relationships, involving the absorbed dose to the salivary glands based on an accurate dosimetric reconstruction. This study now calls for a longer follow-up, for studying the quality of life of patients after ^{131}I-therapy, and for investigating the epigenetic changes that may contribute to an increased sensitivity to ionizing radiation.[44]

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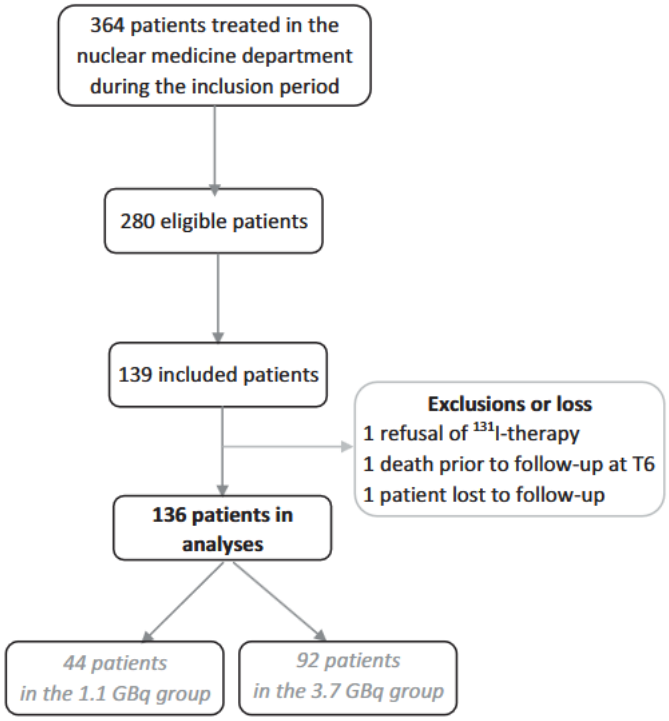

FIG. 1. Flow chart of patients participating in the study.

Table 1: Summary of the different outcomes considered in the START study and their definitions

	Salivary dysfunctions	**Lachrymal dysfunctions**	**Composite criterion**
Binary outcomes (yes/no)	• **Unstimulated hyposalivation**: "yes" when the saliva flow of unstimulated saliva was ≤0.25 mL/min[a] • **Stimulated hyposalivation**: "yes" when the saliva flow of stimulated saliva was ≤1.00 mL/min[a] • **Dry mouth sensation**: having answered "yes" to the question "do you feel that your mouth has been or is dry?"[15] • **Pain in the parotid gland:** having answered "yes" to the question "did you experience pain in the parotid gland?"[15]	• **Dry eyes**: "yes" when the OSDI© score was >12[b]	• **Gland disorders**: "yes" when at least one of the five following outcomes was recorded as "yes": - unstimulated hyposalivation, - stimulated hyposalivation, - dry mouth sensation, - pain in the parotid gland, - dry eyes
Continuous outcomes	• **Unstimulated saliva flow** (mL/min) • **Stimulated saliva flow** (mL/min) • **Salivary biochemical concentrations** in sodium, potassium, chlorine, calcium (mmol/L) and amylase (kU/L)	• **OSDI© score** between 0 and 100[16]	

[a] The thresholds used to define hyposalivation correspond to a moderate hyposalivation;[20,21] [b]an OSDI© score over 12 corresponding to non-normal dryness of the eye;[22] OSDI: Ocular Surface Disease Index

Table 2: List of the potential confounders

	Qualitative data	Quantitative data
Information collected only at the enrollment visit	- tumor histology - presence of residual thyroid tissue - TNM staging - Tg stimulation protocol - family history of thyroid cancer - patient history of cancer or comorbidities	- age - gender
Clinical data collected at T0 and T6	- self-rated menopausal - all medications used during the last 3 months (as coded using the Anatomical Therapeutic Chemical (ATC) code of each medication) - tobacco and alcohol consumption (current/former/no-use)	- self-reported body weight - height
Questionnaires	- changes in drinks/foods[23] - anxiety and depressive symptoms, questionnaire (HAD scale)[17]	

HAD: Hospital Anxiety and Depression scale

Table 3: Baseline characteristics of differentiated thyroid cancer patients, exposure, and factors of interest

Variables	Categories	1.1 GBq group	3.7 GBq group	Total	p^c
Characteristics					
Gender[a]	**women**	35 (79.5)	62 (67.4)	97 (71.3)	0.14
	men	9 (20.5)	30 (32.6)	39 (28.7)	
Age at inclusion (years)[b]		46.6 (13.4)	47.3 (14.4)	47.1 (14.1)	0.77
Cancer histology[a]	**Follicular**	2 (4.5)	18 (19.6)	20 (14.7)	0.02
	Papillary	42 (95.5)	74 (80.4)	116 (85.3)	
pTNM staging[a]	**Tx-T2**	43 (100)	58 (63.0)	101 (74.8)	**<.01**
	T3-T4	0 (0)	34 (37.0)	34 (25.2)	
	Nx-N0	37 (84.1)	39 (42.4)	76 (55.9)	**<.01**
	N1	7 (15.9)	53 (57.6)	60 (44.1)	
Thyroid remnant tissue[a]	**Yes**	16 (36.4)	48 (52.2)	64 (47.1)	0.08
History of systemic disease[a]	**Yes**	13 (29.5)	27 (29.3)	40 (29.4)	0.98
History of salivary dysfunctions[a]	**Yes**	4 (9.1)	3 (3.3)	7 (5.1)	0.15
Score on the HAD scale[b] *at T0*		10.9 (5.5)	11.9 (6.8)	11.6 (6.4)	0.39
Exposure indicators					
D_r (Gy)[b]		0.7 (0.2)	2.2 (0.7)	1.7 (1.0)	**<.01**
D_l (Gy)[b]		0.7 (0.2)	2.4 (1.0)	1.8 (1.1)	**<.01**
MD (Gy)[b]		0.7 (0.2)	2.3 (0.8)	1.8 (1.0)	**<.01**
MD/A (mGy/MBq)[b]		0.6 (0.2)	0.6 (0.3)	0.6 (0.2)	0.32
Salivary and lachrymal variables of interest					
Unstimulated saliva flow *at T0* (mL/min)[b]		0.6 (0.4)	0.8 (0.5)	0.8 (0.5)	**0.03**
Stimulated saliva flow *at T0* (mL/min)[b]		1.9 (0.6)	2.2 (1.0)	2.1 (0.9)	0.06
OSDI score *at T0* [b]		8.0 (12.0)	6.0 (9.5)	6.6 (10.4)	0.31

[a] *N (%);* [b] *Mean (±SD);* [c] *p-value of t-test for continuous variables, or Chi² test for categorical variables between the two activity groups; D_r and D_l: absorbed doses to the right and left salivary glands, respectively; MD: mean of absorbed dose to the right and left salivary glands; MD/A: mean of absorbed dose to the salivary glands per unit of administered activity; T0: evaluation prior to radioiodine treatment; T6: 6 months visit after radioiodine treatment. Statistically significant values in bold.*

Table 4: Comparison tests for time-dependent variables between before (T0) and 6-month (T6) after ^{131}I-therapy

Variables		*T0*	*T6*	*p*
Salivary and lachrymal variables of interest				
Unstimulated hyposalivation [a]	Yes	14 (10.4)	14 (10.4)	1.00[d]
	No	122 (89.6)	121 (89.6)	
New case of unstimulated hyposalivation *at T6* [a]*	Yes	-	8 (5.9)	
Stimulated hyposalivation [a]	Yes	14 (10.4)	14 (10.4)	1.00[d]
	No	122 (89.6)	121 (89.6)	
New case of stimulated hyposalivation *at T6* [a]*	Yes	-	5 (3.7)	
Dry mouth sensation [a]	Yes	24 (17.7)	43 (31.6)	**<.01**[d]
	No	112 (82.4)	93 (68.4)	
New case of dry mouth sensation *at T6* [a]*	Yes	-	30 (22.1)	
Pain in the parotid glands [a]	Yes	15 (11.0)	14 (10.3)	0.83[d]
	No	121 (89.0)	122 (89.7)	
New case of pain in the parotid glands *at T6* [a]*	Yes	-	11 (8.1)	
Dry eyes [a]	Yes	26 (19.1)	38 (28.2)	**0.02**[d]
	No	110 (80.9)	97 (71.9)	
New case of dry eyes *at T6* [a]*	Yes	-	23 (17.0)	
Gland disorders [a]	Yes	66 (48.5)	73 (54.5)	0.21
	No	70 (51.5)	61 (45.5)	
New case of gland disorders *at T6* [a]*	Yes	-	60 (44.8)	
Unstimulated saliva flow (mL/min) [b]		0.8 (0.5)	0.7 (0.4)	0.23[c]
Stimulated saliva flow (mL/min) [b]		2.1 (0.9)	1.9 (0.8)	**<.01**[c]
Amylase concentration (KU/L) [b]		182.5 (132.5)	211.2 (165.1)	**0.01**[c]
Calcium concentration (mmol/L) [b]		0.7 (0.2)	0.8 (0.4)	**0.04**[c]
Chloride concentration (mmol/L) [b]		23.6 (9.5)	25.4 (12.0)	**0.01**[c]

Potassium concentration (mmol/L) [b]		25.4 (9.0)	28.2 (11.5)	**<.01**[c]
Sodium concentration (mmol/L) [b]		9.8 (4.9)	10.1 (4.5)	0.27[c]
OSDI score [b]		6.7 (10.4)	9.4 (14.5)	**0.01**[c]
Time-varying confounders				
HAD score [b]		11.6 (6.4)	10.5 (6.5)	**0.04**[c]
Painkillers intake in the last 3 months [a]	Yes	97 (71.3)	55 (40.4)	**<.01**[d]
	No	39 (28.7)	81 (59.6)	

*[a]N (%); [b]Mean (±SD); [c]T-test for paired comparison; [d]McNemar test for paired comparison; * New cases were coded as "yes" when the outcome was recorded as "yes" at T6 and "no" at T0; OSDI: Ocular Surface Disease Index; HAD: Hospital Anxiety and Depression scale; T0: evaluation prior to radioiodine treatment; T6: 6 months visit after radioiodine treatment. Statistically significant values in bold.*

Table 5: Adjusted odds ratio (ORs) for the relationship between ^{131}I-exposure and salivary and lachrymal disorders (binary variables) at T6

		Unstimulated hyposalivation		Stimulated hyposalivation		Dry mouth sensation		Pain in the parotid gland		Dry eyes		Gland disorders	
^{131}I exposure [a]	**Categories**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
MD (Gy)		0.69	(0.41-1.18)	1.05	(0.56-1.97)	**1.43**	**(1.01-2.04)**	1.40	(0.90-2.18)	n/a		n/a	
AA	Before treatment	1	ref	1	ref	**1**	**ref**	1	ref	1	ref	1	ref
	1100 MBq	0.63	(0.11-3.52)	0.81	(0.09-7.02)	**2.99**	**(1.07-8.39)**	0.48	(0.09-2.53)	**3.58**	**(1.19-10.81)**	1.28	(0.54-3.05)
	3700 MBq	0.57	(0.15-2.14)	0.52	(0.08-3.48)	**2.37**	**(1.01-5.58)**	1.97	(0.7-5.58)	2.12	(0.85-5.28)	1.49	(0.73-3.02)

[a] *Exposure indicators were introduced separately in the models, adjusted for age at the time of interview, anxiety and depression score (HAD scale), history of systemic diseases, menopause status, and painkillers intake in the last 3 months; MD: mean of absorbed dose to the right and left salivary glands; AA: Administered activity of ^{131}I. n/a: not applicable. Statistically significant values in bold.*

Table 6: Adjusted linear regression coefficient for the relationship between ^{131}I-exposure and salivary and lachrymal disorders (quantitative variables) at T6

		Unstimulated saliva flow (mL/min)		Stimulated saliva flow (mL/min)		Amylase concentration (KU/L)		Calcium concentration (mmol/L)		Chloride concentration (mmol/L)		Potassium concentration (mmol/L)		Sodium concentration (mmol/L)		OSDI score	
Variable [a]	**Categories**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**
MD (Gy)		0.00	(-0.03;0.03)	**-0.08**	**(-0.12;-0.02)**	8.56	(-2.31;19.42)	0.00	(-0.02;0.03)	0.59	(-0.04;1.21)	**1.07**	**(0.42;1.71)**	0.10	(-0.17;0.37)	n/a	
AA	Before treatment	1	ref	**1**	**ref**	1	ref	1	ref	1	ref	1	ref	1	ref	1	ref
	1100 MBq	-0.01	(-0.10;0.08)	**-0.26**	**(-0.44;-0.08)**	11.50	(-23.19;46.18)	0.06	(-0.02;0.14)	-0.75	(-2.78;1.27)	-0.05	(-2.08;1.98)	0.18	(-0.71;1.07)	**4.07**	**(0.42;7.73)**
	3700 MBq	-0.01	(-0.07;0.07)	**-0.15**	**(-0.29;-0.02)**	24.95	(-1.42;51.33)	0.04	(-0.02;0.10)	**2.06**	**(0.53;3.59)**	**3.10**	**(1.56;4.64)**	0.32	(-0.35;0.99)	1.57	(-1.24;4.37)

[a] *Exposure indicators were introduced separately in the models, adjusted for age at the time of interview, anxiety and depression score (HAD scale), history of systemic diseases, menopause status, painkillers intake in the last 3 months; OSDI: Ocular Surface Disease Index; MD: mean of absorbed dose to the right and left salivary glands; AA: Administered activity of ^{131}I. n/a: not applicable. Statistically significant values in bold.*

Supplementary data

Table S1: Univariate logistic regression analyses

		Unstimulated hyposalivation		Stimulated hyposalivation		Dry mouth sensation		Pain in the parotid gland		Dry eyes		Gland disorders	
Variable	**Categories**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
D_r (Gy)*		0.85	(0.51-1.42)	1.08	(0.61-1.91)	**1.61**	**(1.15-2.26)**	1.25	(0.86-1.84)	n/a	n/a	n/a	n/a
D_l (Gy)*		0.90	(0.57-1.43)	1.27	(0.79-2.05)	**1.40**	**(1.04-1.88)**	1.14	(0.81-1.61)	n/a	n/a	n/a	n/a
MD (Gy)*		0.88	(0.54-1.43)	1.80	(0.33-9.91)	**1.51**	**(1.10-2.09)**	1.20	(0.83-1.74)	n/a	n/a	n/a	n/a
AA	Before treatment	1	ref	1	ref	**1**	**ref**	1	ref	1	ref	**1**	**ref**
	1100 MBq	0.86	(0.18-4.08)	1.14	(0.17-7.77)	**3.02**	**(1.15-7.93)**	0.34	(0.06-1.75)	**3.36**	**(1.14-9.93)**	1.26	(0.54-2.97)
	3700 MBq	1.11	(0.33-3.71)	0.94	(0.22-4.05)	**2.59**	**(1.19-5.61)**	1.26	(0.52-3.09)	1.77	(0.76-4.11)	1.45	(0.76-2.78)
Gender	men	1	ref	1	ref	1	ref	1	ref	1	ref	1	ref
	women	3.68	(0.62-21.88)	1.91	(0.13-27.65)	1.92	(0.80-4.58)	2.97	(0.87-10.17)	2.20	(0.74-6.54)	1.97	(0.9-4.31)
Age at the time of interview*		**1.11**	**(1.04-1.19)**	1.08	(0.98-1.19)	**1.03**	**(1.00-1.06)**	0.99	(0.96-1.03)	0.98	(0.94-1.01)	**1.02**	**(1.00-1.05)**
BMI*		1.00	(0.87-1.15)	1.08	(0.88-1.31)	1.01	(0.95-1.08)	1.03	(0.95-1.11)	1.05	(0.97-1.13)	1.05	(0.99-1.11)
Anxiety and depression score (HAD scale)*		0.91	(0.80-1.03)	0.92	(0.79-1.07)	1.03	(0.98-1.09)	**1.09**	**(1.01-1.18)**	**1.08**	**(1.01-1.15)**	**1.06**	**(1.00-1.12)**
Menopause	No	**1**	**ref**	1	ref	**1**	**ref**	1	ref	1	ref	**1**	**ref**
	Yes	**9.18**	**(1.57-53.71)**	2.96	(0.17-51.89)	**3.69**	**(1.50-9.10)**	0.79	(0.27-2.28)	0.39	(0.12-1.30)	**2.89**	**(1.19-6.98)**
	Not applicable	0.81	(0.13-5.19)	0.77	(0.05-12.34)	0.91	(0.37-2.26)	0.31	(0.09-1.12)	0.34	(0.11-1.07)	0.75	(0.33-1.67)
Histology	Papillary	1	ref	1	ref	1	ref	1	ref	1	ref	1	ref
	Follicular	0.11	(0.01-2.07)	3.85	(0.16-92.21)	1.25	(0.44-3.51)	0.62	(0.15-2.61)	2.08	(0.57-7.56)	1.45	(0.53-3.92)

		Unstimulated hyposalivation		Stimulated hyposalivation		Dry mouth sensation		Pain in the parotid gland		Dry eyes		Gland disorders	
Variable	**Categories**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
pTNM staging	Nx-N0	1	ref	1	ref	1	ref	1	ref	1	ref	1	ref
N stage													
	N1	0.86	(0.18-3.99)	0.49	(0.04-5.90)	0.94	(0.44-2.00)	0.73	(0.28-1.86)	0.48	(0.19-1.27)	0.63	(0.31-1.28)
T stage	Tx-T2	1	ref	1	ref	1	ref	1	ref	1	ref	1	ref
	T3-T4	1.32	(0.24-7.31)	2.11	(0.19-23.81)	1.03	(0.44-2.43)	2.12	(0.80-5.61)	1.10	(0.37-3.28)	1.62	(0.72-3.64)
History of salivary dysfunctions	No	1	ref	1	ref	1	ref	1	ref	1	ref	**1**	**ref**
	Yes	0.60	(0.02-23.03)	2.02	(0.01-347.8)	3.08	(0.66-14.34)	0.61	(0.06-6.59)	2.58	(0.35-19.10)	5.03	(0.86-29.32)
History of systemic disease	No	1	ref	1	ref	1	ref	1	ref	1	ref	1	ref
	Yes	3.74	(0.80-17.45)	3.37	(0.23-48.68)	1.80	(0.81-4.01)	1.93	(0.75-5.01)	1.20	(0.42-3.40)	2.14	(0.97-4.72)
Family history of thyroid cancer	No	1	ref	1	ref	**1**	**ref**	1	ref	1	ref	1	ref
	Yes	0.26	(0.02-2.66)	0.04	(<0.001-4.47)	**0.28**	**(0.08-0.96)**	0.80	(0.22-2.96)	0.36	(0.09-1.46)	0.39	(0.15-1.02)
Thyroid remnant tissue	No	1	ref	1	ref	1	ref	1	ref	1	ref	1	ref
	Yes	1.23	(0.27-5.63)	0.96	(0.09-10.39)	0.87	(0.41-1.83)	1.79	(0.70-4.55)	0.45	(0.17-1.22)	0.92	(0.46-1.87)
Hypertension drug intake in the last 3 months	No	1	ref	1	ref	1	ref	1	ref	1	ref	**1**	**ref**
	Yes	1.85	(0.39-8.78)	3.34	(0.21-52.02)	1.54	(0.65-3.65)	1.82	(0.65-5.1)	1.10	(0.36-3.38)	**2.81**	**(1.18-6.67)**
Painkillers intake in the last 3 months	No	1	ref	1	ref	1	ref	1	ref	1	ref	1	ref
	Yes	0.28	(0.08-1.00)	0.45	(0.08-2.38)	0.49	(0.23-1.01)	2.52	(0.94-6.78)	1.16	(0.52-2.61)	0.86	(0.46-1.61)

D_r and D_l: absorbed doses to the right and left salivary glands, respectively; MD: mean of absorbed dose to the right and left salivary glands; AA: Administered activity of ^{131}I.

** Continuous variables. n/a: not applicable. Statistically significant values in bold.*

Table S2: Univariate linear analyses

		Unstimulated saliva flow (mL/min)		Stimulated saliva flow (mL/min)		Amylase concentration (KU/L)		Calcium concentration (mmol/L)		Chloride concentration (mmol/L)		Potassium concentration (mmol/L)		Sodium concentration (mmol/L)		OSDI score	
Variable	**Categories**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**
D_r (Gy)*		-0.01	(-0.04;0.02)	**-0.09**	**(-0.14;-0.03)**	**13.61**	**(3.22;23.99)**	0.01	(-0.01;0.03)	**0.85**	**(0.26;1.45)**	**1.47**	**(0.85;2.10)**	0.11	(-0.15;0.36)	n/a	n/a
D_l (Gy)*		-0.01	(-0.04;0.02)	**-0.08**	**(-0.13;-0.03)**	**11.28**	**(1.84;20.72)**	0.01	(-0.01;0.03)	**0.75**	**(0.21;1.30)**	**1.27**	**(0.69;1.84)**	0.12	(-0.11;0.35)	n/a	n/a
MD (Gy)*		-0.01	(-0.04;0.02)	**-0.09**	**(-0.14;-0.03)**	**12.64**	**(2.64;22.63)**	0.01	(-0.01;0.03)	**0.82**	**(0.25;1.39)**	**1.39**	**(0.79;2.00)**	0.12	(-0.13;0.36)	n/a	n/a
AA	Before treatment	0	ref	**0**	**ref**	0	ref	0	ref	**0**	**ref**	**0**	**ref**	0	ref	**0**	**ref**
	1100 MBq	-0.05	(-0.14;0.05)	**-0.31**	**(-0.48;-0.14)**	14.80	(-18.14;47.74)	0.06	(-0.02;0.14)	**-0.40**	**(-2.32;1.53)**	**0.56**	**(-1.40;2.52)**	0.13	(-0.71;0.97)	**4.83**	**(1.22;8.44)**
	3700 MBq	-0.03	(-0.10;0.04)	**-0.16**	**(-0.28;-0.04)**	**32.96**	**(9.18;56.74)**	**0.05**	**(0.00;0.11)**	**2.61**	**(1.25;3.97)**	**3.80**	**(2.41;5.20)**	0.34	(-0.25;0.94)	**1.84**	**(-0.77;4.46)**
Gender	men	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref
	women	-0.05	(-0.20;0.11)	-0.05	(-0.34;0.25)	8.87	(-43.09;60.83)	0.03	(-0.08;0.15)	-3.27	(-7.28;0.73)	-3.68	(-7.46;0.10)	-0.81	(-2.51;0.89)	1.36	(-2.67;5.40)
Age at the time of interview*		-0.01	(-0.01;0.00)	-0.01	(-0.02;0.00)	**3.85**	**(2.29;5.40)**	**0.01**	**(0.00;0.01)**	**0.40**	**(0.29;0.51)**	**0.40**	**(0.29;0.50)**	**0.09**	**(0.04;0.14)**	-0.03	(-0.16;0.10)
BMI*		0.00	(-0.01;0.01)	**-0.02**	**(-0.04;0.00)**	0.13	(-3.76;4.01)	0.01	(-0.00;0.01)	0.14	(-0.15;0.44)	0.22	(-0.06;0.50)	0.02	(-0.11;0.14)	0.19	(-0.12;0.50)
Anxiety and depression score (HAD scale)*		0.00	(-0.01;0.01)	0.01	(-0.01;0.02)	-1.62	(-4.39;1.16)	-0.01	(-0.01;0.00)	-0.18	(-0.36;0.00)	-0.19	(-0.38;-0.01)	-0.04	(-0.12;0.04)	**0.34**	**(0.11;0.58)**
Menopause	No	**0**	**ref**	0	ref	**0**	**ref**	**0**	**ref**	**0**	**ref**	**0**	**ref**	**0**	**ref**	0	ref
	Yes	**-0.19**	**(-0.36;-0.02)**	-0.25	(-0.58;0.08)	**129.18**	**(75.4;182.97)**	**0.17**	**(0.04;0.29)**	**9.04**	**(4.83;13.26)**	7.88	(3.86;11.90)	**2.66**	**(0.81;4.51)**	-2.02	(-6.53;2.49)
	Not applicable	-0.02	(-0.18;0.14)	-0.04	(-0.36;0.27)	37.76	(-14.22;89.75)	0.03	(-0.10;0.15)	**6.53**	**(2.46;10.6)**	6.51	(2.63;10.39)	**1.77**	**(-0.02;3.55)**	-2.09	(-6.44;2.26)
Histology	Papillary	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref
	Follicular	0.10	(-0.10;0.29)	0.00	(-0.37;0.38)	-11.46	(-77.70;54.79)	-0.08	(-0.23;0.07)	-2.13	(-7.28;3.02)	-1.29	(-6.18;3.60)	-0.46	(-2.63;1.71)	2.50	(-2.64;7.64)
pTNM staging[a]																	
N stage	Nx-N0	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref
	N1	0.06	(-0.08;0.20)	0.15	(-0.11;0.42)	-5.50	(-52.81;41.81)	-0.07	(-0.18;0.03)	-1.01	(-4.69;2.68)	-1.16	(-4.64;2.33)	-0.63	(-2.17;0.92)	-2.62	(-6.27;1.04)
T stage	Tx-T2	0	ref	0	ref	0	ref	**0**	**ref**	**0**	**ref**	**0**	**ref**	0	ref	0	ref

		Unstimulated saliva flow (mL/min)		Stimulated saliva flow (mL/min)		Amylase concentration (KU/L)		Calcium concentration (mmol/L)		Chloride concentration (mmol/L)		Potassium concentration (mmol/L)		Sodium concentration (mmol/L)		OSDI score	
Variable	**Categories**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**	**ß**	**95% CI**
	T3-T4	-0.04	(-0.20;0.12)	0.02	(-0.29;0.32)	16.78	(-37.35;70.91)	**0.13**	**(0.01;0.25)**	**5.25**	**(1.10;9.41)**	**5.36**	**(1.43;9.29)**	1.50	(-0.27;3.27)	0.05	(-4.18;4.28)
History of salivary dysfunctions[a]	No	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref
	Yes	-0.17	(-0.48;0.15)	0.08	(-0.52;0.68)	72.98	(-32.49;178.45)	0.07	(-0.17;0.31)	0.34	(-7.93;8.62)	-0.32	(-8.15;7.52)	-0.24	(-3.72;3.24)	2.84	(-5.41;11.09)
History of systemic disease[a]	No	**0**	**ref**	0	ref	**0**	**ref**	**0**	**ref**	**0**	**ref**	**0**	**ref**	0	ref	0	ref
	Yes	**-0.17**	**(-0.32;-0.02)**	-0.12	(-0.41;0.17)	**57.75**	**(7.02;108.48)**	**0.14**	**(0.03;0.26)**	**5.38**	**(1.47;9.30)**	**7.13**	**(3.52;10.74)**	0.30	(-1.39;1.99)	0.12	(-3.90;4.14)
Family history of thyroid cancer	No	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref
	Yes	-0.01	(-0.21;0.18)	-0.01	(-0.37;0.35)	-4.02	(-67.94;59.90)	-0.02	(-0.17;0.12)	-2.65	(-7.62;2.31)	-0.85	(-5.58;3.87)	-1.17	(-3.26;0.92)	-2.85	(-7.79;2.09)
Thyroid remnant tissue[a]	No	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref	0	ref
	Yes	-0.07	(-0.21;0.07)	-0.13	(-0.39;0.14)	-6.44	(-53.50;40.63)	-0.08	(-0.19;0.02)	0.23	(-3.43;3.90)	-0.66	(-4.13;2.82)	-0.57	(-2.11;0.97)	0.34	(-3.32;4.01)
Hypertension drug intake in the last 3 months	No	0	ref	0	ref	0	ref	**0**	**ref**	**0**	**ref**	**0**	**ref**	**0**	**ref**	0	ref
	Yes	-0.04	(-0.20;0.11)	-0.04	(-0.34;0.25)	39.69	(-12.84;92.23)	**0.20**	**(0.08;0.31)**	**7.19**	**(3.49;10.89)**	**6.95**	**(3.37;10.52)**	**1.70**	**(0.09;3.32)**	-0.43	(-4.72;3.86)
Painkillers intake in the last 3 months	No	**0**	**ref**	**0**	**ref**	**0**	**ref**	0	ref	**0**	**ref**	**0**	**ref**	0	ref	0	ref
	Yes	**0.09**	**(0.01;0.16)**	**0.15**	**(0.01;0.30)**	**-33.40**	**(-60.95;-5.84)**	-0.06	(-0.13;0.00)	**-2.24**	**(-3.88;-0.60)**	**-3.44**	**(-5.15;-1.73)**	-0.12	(-0.82;0.58)	-2.16	(-4.99;0.67)

D_r and D_l: absorbed doses to the right and left salivary glands, respectively; MD: mean of absorbed dose to the right and left salivary glands; AA: Administered activity of ^{131}I.

** Continuous variables. OSDI: Ocular Surface Disease Index. n/a: not applicable. Statistically significant values in bold.*

Table S3: Correlogram for the different outcomes studied at T6

	Unstimulated hyposalivation (yes/no)	Stimulated hyposalivation (yes/no)	Dry mouth sensation (yes/no)	Pain in the parotid glands (yes/no)	Dry eyes (yes/no)	Unstimulated saliva flow (mL/min)	Stimulated saliva flow (mL/min)	OSDI score	Gland disorders (≥1) (yes/no)
Unstimulated hyposalivation (yes/no)		0.02	0.70	0.62	0.82	<.01	0.02	0.11	<.001
Stimulated hyposalivation (yes/no)			0.70	0.62	0.34	<.01	<.001	0.63	<.001
Dry mouth sensation (yes/no)				0.33	0.01	0.08	0.06	0.01	<.001
Pain in the parotid glands (yes/no)					0.93	0.08	0.04	0.17	<.001
Dry eyes (yes/no)						0.05	0.22	<.001	<.001
Unstimulated saliva flow (mL/min)							<.001	0.49	<.001
Stimulated saliva flow (mL/min)								0.84	<.001
OSDI score									0.01

Pearson correlation test for two qualitative variables. ANOVA test for one quantitative and one qualitative variables. Chi² test for two qualitative variables. OSDI: Ocular Surface Disease Index.