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**Salivary side effects after radioiodine treatment for differentiated papillary thyroid carcinoma: a long-term study.**

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# Salivary side effects after radioiodine treatment for differentiated papillary thyroid carcinoma: a long-term study.

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24 Keywords: Salivary glands, Thyroid cancer, radioiodine therapy, sialadenitis, xerostomia

# Abstract

## *Background*

Although many studies focus on short-term side effects of radioiodine therapy, almost none studied long-term side effects. We assessed radioiodine long-term salivary side effects after radioiodine treatment for differentiated papillary thyroid carcinoma and compared it to short term morbidity within the same population.

## *Methods*

A standardized self-administrated questionnaire was submitted in 2019 by patients treated with radioiodine between 01/2011 and 12/2012. These patients had already answered the same questionnaire 6 years before.

## *Results*

Our study showed a significant reduction for salivary side effects: discomfort in submandibular or parotid area, swelling, pain, a bad or salty taste in the mouth, allowing to get back to a “normal” diet.

## *Conclusions*

Our study suggests that a significant rate of patients will recover from I<sup>131</sup> therapy salivary side effects. As almost 30% of these remissions happened during our late stage follow-up, we highlight the necessity of a long-term follow-up in these patients.

## Introduction

Radioiodine treatment has reached a great rate of success along with surgery in differentiated papillary thyroid carcinoma (DPTC) treatment over the last 70 years. (1) Radioiodine is specifically known to fix to the vesicular thyroid cells but a similar uptake also occurs in the salivary, lacrimal glands and nasal mucosa by the means of the sodium iodide symporter.(2)

Iodine-131 ( $I^{131}$ ) therapy is associated with a high prevalence of side effects, especially salivary and lacrimal gland dysfunction (sicca syndrome), nasal dryness, gustatory dysfunction and dysphagia.(3)(4)(5)(6)(7)(8)(9)

These side effects are benign but have a significant influence on the patient's quality of life.(10) Sialadenitis, pre-parotid alternating swelling, and xerostomia usually occur in the first days after radioiodine treatment but may also occur later on and lead to chronic complications. Candidiasis and dental caries are well known common long-term complications, and some serious late side effects such as; hematotoxic reaction, cancers, leukemia and pulmonary diseases have been identified. (11)(12)

Trials are insufficient to assert the efficacy of interventions to prevent radio-induced salivary dysfunctions by both synthetic or natural agents (lemon, vitamin E, curcumin, chewing gum). (13)

As short-term salivary effects have been well studied, and have found a high rate of side effects with xerostomia as the predominant symptom, no long-term study focusing on salivary side effects and the evolution of the incidence throughout time has been performed.

Our objective was to assess radioiodine long-term salivary side effects after radioiodine treatment for DPTC and compare it to short term morbidity within the same population.

## Materials and methods

## Patients

A prospective comparative within-population study was carried out by having submitted a standardized questionnaire in 2013 and in 2019 to patients which went through radioiodine treatment for a DPTC between January 2011 and December 2012.

The only difference between the 2013 and the 2019 questionnaire was the addition of “During the last 3 years” which is found at the beginning of every question. We consider this study as a long-term evaluation of side effects as symptoms were assessed between 3 to 6 years after radioiodine treatment.

413 patients were included after having responded for the first time to the questionnaire in 2013 and after, exclusion criteria were applied. (14) Exclusion criteria were patients unable to respond due to mental, physical illness or disability, cancer recurrence, or who underwent more than one radioiodine treatment.

Patients were given I<sup>131</sup> capsules, 100 mCi (3.7 GBq, Covidien plc, Dublin, Ireland) during an episode of hypothyroidism or stimulation by recombinant human thyrothropin. During their stay in the department, they were given prophylactic lemon juice three times a day, starting four hours after treatment to increase the salivary discharge and reduce salivary radioiodine (I<sup>131</sup>) uptake. Levothyroxin 2µg/kg was given to hypothyroid patients the day after treatment, and anti-inflammatory drugs were given for five days, if they had pain or tender swelling.

## Questionnaire

The committee members who created the questionnaire were a professor of maxillofacial surgery specialized in salivary gland diseases, a professor of nuclear medicine, a professor of endocrine surgery and an epidemiologist. The questionnaire was elaborated in 2012 after a review of relevant publications following the recommendations of a Cochrane meta-analytic review. It was tested on 10 patients who were asked to comment on every aspect of it,

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2  
3 including content, wording and responses. The final version included a picture; showing the  
4 parotid and submandibular gland areas and 13 items. 9 of the 13 questions used nominal  
5 variables (Yes/No) and two used ordinal variables. It focused on possible salivary or related  
6 symptoms over the past 3 years. A visual analogue scale (VAS) was included into the  
7 questionnaire to evaluate the intensity of pain. The last question (n°13) was an open question  
8 that allowed open-commentary. Gender and age were also collected.  
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12 We tried to reach all 413 included patients, who had previously responded to the  
13 questionnaire 74 months ago, on the phone, by mail or, by email in case of failure to inquire  
14 on major medical events, exclusion criteria, to give information on the questionnaire and to  
15 obtain their permission to send the questionnaire.  
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19 This study was conducted in accordance with the Declaration of Helsinki and was approved  
20 by the local institutional ethics committee (RGPD-AP-HM N°2019-81).  
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### Statistical analysis

The data questionnaire was gathered and compared to the same population in 2013 as in 2019 using McNemar's match test for nominal data and Wilcoxon's test for ordinal data. Our hypothesis was that salivary symptoms would decrease over time. An error rate was set with 95% confidence intervals; p value <.05 was considered significant.

## Results

### Population characteristics

Among the 408 patients who responded to the first questionnaire in 2013, 239 (58%) patients could be reached by phone or mail. 170 patients (79%) responded to the questionnaire and eight were excluded (two died, one from DTTC and six went through iterative I<sup>131</sup> therapy).



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3 There were 36 males (22.2%) and 126 females (77.7%), the sex ratio was 0.29 and the mean  
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5 of the age was 62.4 years  $\pm$  12.5 (min 27, max 86).  
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## 10 11 Questionnaire data and within-population study 12

13  
14 The answers to the 2019 questionnaire are summarized in table 1. (Table 1)  
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16 All evaluations were sent between 92 and 104  $\pm$  99 months after the radioiodine therapy and  
17  
18 74 months after the first study.  
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21 Our within-population comparison between short and long-term salivary side effects found a  
22  
23 significant decrease in all symptoms (swelling, discomfort, pain, bad taste in the mouth, diet  
24  
25 modification, the use of analgesic and anxiety) except for xerostomia, and the rate of patients  
26  
27 who underwent a surgical treatment. (Figure 1)(Table 2)  
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29  
30 The most frequent long-term salivary side effect was xerostomia with 33.1% (53/160) of  
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32 patients complaining about it. We found no significant difference in 2013 with 41% (66/161)  
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34 (p=0.067). There was also no correlation between age or gender and xerostomia in our  
35  
36 sample.  
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39 The rate of patients who were still being treated by analgesics for radioiodine related  
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41 symptoms in 2019 was 5.3% (8/154) and almost equal to the number of patients who had  
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43 reported pain over the last 3 years which was of 4.4% (7/158). There was a significant  
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45 decrease of painkiller medication and reported pain compared to 2013 with a respective 19%  
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47 (28/150) (p<0.01) and 15% (23/153) (p<0.01).  
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50 We found a statistically significant reduction also for pain in the parotid area with 12.4%  
51  
52 (20/162) in 2019 vs 24.7% (40/162) in 2013 (p<0.01).  
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54  
55 According to the VAS, most of the patients experienced no pain related to parotid or  
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57 submandibular glands over the last 3 years. (Table 3) The weighted average showed a  
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59 significant reduction from 1.24 to 0.4 on 10 (p<0.01).  
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3 Discomfort or swelling in the submandibular or parotid area over the last 3 years were present  
4  
5 in 16% (26/162) of the patients versus 29% (47/162) in 2013.

6  
7 6.8% of patients (11/161) had to modify their everyday diet for acidic or sugar foods, this is  
8  
9 almost 2.5 times less than 6 years ago when the rate was of 14.9% (24/161) ( $p<0.01$ ). Only  
10  
11 4.3% (7/162) experienced a flow of salty liquid or a bad liquid taste in their mouth over the  
12  
13 last 3 years while 11.8% (19/161) of the same population experienced it in 2013 ( $p<0.01$ )  
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16 One patient, 0.63% of total population (1/159), had reported a unilateral parotid removal  
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18 related to the radioiodine therapy although they hadn't been operated in our department and  
19  
20 weren't able to provide more information about the operation or the indication. There was no  
21  
22 significant difference in the rate of operation in 2013, which was 1.28% (2/156) ( $p=0.08$ ).  
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25 A total of 18.24% (29/159) of patients still felt at least a little anxious or stressed by the  
26  
27 outcomes of radioiodine treatment in 2019. These symptoms were significantly more frequent  
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29 in 2013 with 38.1% (56/147) ( $p<0.01$ ). (Table 4) The decrease is also significant when  
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31 comparing the weighted averages which go from 1.7 in 2013 to 1.3 in 2019 ( $p<0.01$ ).  
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33

34 33.3% of patients ( $n=54$ ) answered the last question, n°13 (open-commentary) and gave us  
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36 some indication about patients' major concerns that will be examined in the discussion.  
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## 44 Discussion

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47 Our study revealed an important reduction of radioiodine induced salivary side effects over a  
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49 long-term period. The majority of patients, 54.3% (88/162) went through a total recovery of  
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51 salivary symptoms after 6 years. 69.3% (61/88) presented an early stage remission and 30.7%  
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53 (27/88) a late stage remission after the end of our follow-up. After 6 years, there was a  
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55 significant reduction in discomfort, swelling, pain, bad or salty taste in the mouth. There was  
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57 a reduction in stress, medication needs and a normalization of the diet.  
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3 The main strength of this study was the prospective within-population study allowing to  
4 compare the long-term evolution of side effects throughout time in a strictly identical  
5 population. The main remaining symptom was xerostomia with 33.1% (53/160) of patients  
6 suffering from it.  
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15 Some studies analyze mid-term side effects, (15)(16)(17)(18)(19) but few studies were  
16 interested in long-term side effects after 2 years. (3) A 2015 literature review about the main  
17 late side effects of iodotherapy treatment gathered articles with a follow-up mean of 6,12, 18,  
18 and 20 months. This literature review reported a symptomatic “long term” salivary gland  
19 dysfunction in 16-54% of patients.(12) Solans and al, performed a 3 year follow-up, also  
20 using a standardized questionnaire that indicated a strong downward trend for xerostomia that  
21 we did not find even with a follow-up twice as long. But the study’s cohort was two times  
22 smaller, and patients with single or multiplied I<sup>131</sup> therapy were mixed.(3)  
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33 Also, the average age of our sample being high (62.4 years old), we can assume that it might  
34 have an impact on the rate of xerostomia. It is documented that the rate of xerostomia in the  
35 elderly population is high (17-39%) (15)(20)(21)(22) and that xerostomia increases with age  
36 (5.1% at 50 and 18.2% at 75). (23)(24) Hence authors have described that I<sup>131</sup> could even be  
37 more harmful to the altered glands of the elderly in which the glandular part is reduced and  
38 replaced by adipose and fibrovascular tissue. (25)(26)  
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47 We can also think that xerostomia could be more present in a highly medicated elderly  
48 population. For instance, the open commentary section allowed a patient to underline that  
49 xerostomia appears shortly after they began anti-hypertensive therapy. Urinary  
50 antispasmodics, step 2 analgesics, antidepressants, hypnotics, respiratory system, migraine,  
51 smoking withdrawal and gastrointestinal drugs were also reported in our sample and are  
52 known to be responsible for xerostomia. All these xerostomic factors are in balance with the  
53 rate of xerostomia directly due to radioiodine treatment. We previously used an “opinion  
54 expert” dose of 100 mCi to treat patients before the implementation in France of new  
55 guidelines with reduction of administrated RAI activities in low to low-intermediate risks.  
56 (27)  
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3 Jeong and al, performed a comparative scintigraphy before I<sup>131</sup> therapy and 5 years later.

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5 Objective imaging observations found a reduction in salivary gland uptake and a reduction of  
6  
7 ejection fraction of salivary glands in about 20% of parotid glands. Subjective salivary gland  
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9 dysfunction with mainly xerostomia persisted in roughly 40% of cases. These results tend to  
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11 be more in accordance with ours. (28)  
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## 20 Population

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23 Our population was still representative of populations suffering from thyroid carcinoma after  
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25 a second screening with a 1:3 male to female ratio nevertheless, they were obviously older  
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27 with a mean age of  $62,4 \pm 12.5$  years (min 27, max 86). (29) Patients which went through at  
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29 least two radioiodine treatments (n=6) were excluded as global results could worsen. (28)  
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31 Also, patients under 18 at the time of I<sup>131</sup> therapy were initially excluded (n=3) as the pediatric  
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33 population is known to have a higher radio sensitivity. (30)(31) Our survival rate at 5 years  
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35 was above 98% and is in accordance with the rate in the literature. (12)(32)  
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## 45 Preventive agents

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48 The radioactive Iodine was brought to the salivary glands by the means of the adenosine  
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50 triphosphate-dependent  $\text{Na}^+/\text{K}^+/\text{2Cl}^-$  symporter.(33) Researchers have been looking for  
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52 preventive means for this misdirection for over 30 years.(13) It has long been known that the  
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54 richness of parotid in serous tissue and ductal cells favor the absorption of iodine at the  
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56 parotid level more than the submandibular.(34)(35)(36) In recent years, mechanisms of radio-  
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58 induced lesions of the salivary glands have become more clear. Epithelial apoptosis, stem cell  
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3 injuries and lipid peroxidation are among the damage mechanisms.(37) We had administered  
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5 lemon three times a day, beginning a few hours after I<sup>131</sup> therapy to decrease the residence time  
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7 of radioiodine within the salivary gland as suggested by Nakada (washout effect).(38)  
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10 Kulkarni and al suggested that lemon juice, due to its sialagogue effect, had reduced the  
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12 potential radiation absorbed dose in the parotid glands with an average of 34.2%. (39) A  
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14 review of natural and synthetic compounds suggested that more studies were needed, and at  
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16 the time, it was better to use natural compounds over synthetic.(13)(40)(41)(42)(43)  
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18 Botulinum toxin seems to confer radioprotective properties to salivary glands in Murine  
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20 subjects by reducing glandular atrophy and periductal fibrosis during classic external  
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22 radiation.(44) Botulinum toxin would be an interesting preventive treatment for patients  
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24 receiving radioiodine to prevent adverse side effects.  
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## 31 Shortcomings

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34 The main shortcoming was related to the duration over which the symptoms were assessed.  
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36 Patients were asked to remember if they had symptoms related to the oro-facial area in the last  
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38 three years. We can assume that patients, who never had any symptoms, or few following the  
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40 I<sup>131</sup> treatment, would not show interest in responding to our questionnaire 6 years later.  
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43 Even if we had gotten a high level of responses from patients we managed to contact (78%),  
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45 we can assume that symptomatic patients are more willing to respond. Our response rate was  
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47 better than the classical rate with postal surveys which is around 50%.(45)  
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50 Also, one of the main biases would be the difficulty in asserting the correlation between a  
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52 symptom expressed by the patient and the glandular lesions induced by radioiodine treatment.  
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54 For instance, a patient confirmed having a high level of stress, but in the free commentary  
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56 they linked their stress to post reccurrential paralysis dysphonia. Their stress is therefore  
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3 connected to the surgery and not to the I<sup>131</sup> treatment. Another patient relates their actual  
4 stress to the difficulty to balance their hormonal supplementation.  
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10 We chose to focus on subjective symptoms as long term scintigraphic studies had already  
11 been conducted.(28) We'd like to clarify that the discomfort, pain, and changes in eating  
12 habits to assess the repercussion on everyday life are not always correlated to objective  
13 scintigraphic data.(46)(47)(48)  
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22 Our questionnaire did not assess the symptoms that can be consequences of xerostomia; such  
23 as dental caries, dysphagia, dysphonia. Like xerostomia, these symptoms can also have an  
24 impact on one's quality of life.(49)(50) Xerostomia alters the patient's quality of life mainly  
25 by changing their diet habits. Changing diet habits seems to be the greatest factor impacting  
26 one's quality of life.(51)(52)  
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33 It seems difficult to assess the oral health status in a non-dedicated questionnaire. Severe  
34 disabling dysphonia was reported in the open commentary in two cases, however was  
35 attributed to postoperative recurrent paralysis.  
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40 Dysphagia was assessed in question 10 among other disorders by asking for a "lasting  
41 discomfort", but considering that 10 patients (7%) reported suffering from dysphagia in the  
42 open commentary, it should have been the subject of a dedicated question as this symptom  
43 could be linked to xerostomia.  
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52 There was an overall tendency for salivary symptom regression after radioiodine treatment for  
53 DPTC over 6 years. Among salivary symptoms, only the rate of xerostomia did not appear to  
54 drop significantly. This may be linked to shortcomings in our sample or the increasing rate of  
55 xerostomia with the ageing of the population linked to the prolonged follow-up.  
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3 Efforts to increase the effectiveness of preventive treatments for salivary glands must be  
4 maintained and high caution should be applied when processing invasive therapy to treat  
5 salivary dysfunction symptoms after I<sup>131</sup> therapy. Our study suggests that a significant rate of  
6 patients will recover from I<sup>131</sup> therapy salivary side effects. As almost 30% of these remissions  
7 happened during our late stage follow-up, we can only strongly encourage long-term patients'  
8 follow-up. This study should also be used to provide patients with better information about  
9 side effects and their evolution over time.  
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26 Conflict of interest: None  
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34 Table 1: Results of the 2019 questionnaire. Data are number (%) of patients.  
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36 Table 2: Within-population comparison in 2013 and 2019. Data are number (%)  
37 of patients.  
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42 Table 3: Visual Analogue scores.  
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44 Table 4: Results of question 12 about anxiety and stress due to I<sup>131</sup> therapy  
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46 Figure 1: Histogram interpretation of questionnaire responses between 2013 and  
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## 58 References 59 60

1. Seidlin SM, Marinelli LD, Oshry E. Radioactive iodine therapy: effect on functioning metastases of adenocarcinoma of the thyroid. *CA Cancer J Clin.* 1990 Oct;40(5):299–317.
2. Martín M, Geysels RC, Peyret V, Bernal Barquero CE, Masini-Repiso AM, Nicola JP. Implications of Na<sup>+</sup>/I<sup>-</sup> Symporter Transport to the Plasma Membrane for Thyroid Hormonogenesis and Radioiodide Therapy. *J Endocr Soc.* 2019 Jan 1;3(1):222–34.
3. Solans R, Bosch J-A, Galofre P, Porta F, Rosello J, Selva-O'Callagan A, et al. Salivary and Lacrimal Gland Dysfunction (Sicca Syndrome) After Radioiodine Therapy. :7.
4. Lu L, Shan F, Li W, Lu H. Short-Term Side Effects after Radioiodine Treatment in Patients with Differentiated Thyroid Cancer. *BioMed Research International.* 2016;2016:1–5.
5. Lee SL. Complications of Radioactive Iodine Treatment of Thyroid Carcinoma. *Journal of the National Comprehensive Cancer Network.* 2010 Nov;8(11):1277–87.
6. Lee SM, Lee JW, Kim SY, Han SW, Bae WK. Prediction of risk for symptomatic sialadenitis by post-therapeutic dual 131I scintigraphy in patients with differentiated thyroid cancer. *Annals of Nuclear Medicine.* 2013 Oct;27(8):700–9.
7. Hyer S, Kong A, Pratt B, Harmer C. Salivary Gland Toxicity after Radioiodine Therapy for Thyroid Cancer. *Clinical Oncology.* 2007 Feb;19(1):83–6.
8. Fard-Esfahani A, Emami-Ardekani A, Fallahi B, Fard-Esfahani P, Beiki D, Hassanzadeh-Rad A, et al. Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma: *Nuclear Medicine Communications.* 2014 Apr;1.
9. da Fonseca FL, Yamanaka PK, Mazoti L, Arakawa-Sugueno L, Kato JM, Matayoshi S. Correlation among ocular surface disease, xerostomia, and nasal symptoms in patients with differentiated thyroid carcinoma subjected to radioiodine therapy: A prospective comparative study. *Head & Neck.* 2017 Dec;39(12):2381–96.
10. Jensen SB, Vissink A, Andersen E, Brown CG, Davies AN, Dutilh J, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. *Supportive Care in Cancer.* 2010 Aug;18(8):1039–60.
11. Rubino C, de Vathaire F, Dottorini ME, Hall P, Schvartz C, Couette JE, et al. Second primary malignancies in thyroid cancer patients. *British Journal of Cancer.* 2003 Nov;89(9):1638–44.
12. Clement SC, Peeters RP, Ronckers CM, Links TP, van den Heuvel-Eibrink MM, Nieveen van Dijkum EJM, et al. Intermediate and long-term adverse effects of radioiodine therapy for differentiated thyroid carcinoma – A systematic review. *Cancer Treatment Reviews.* 2015 Dec;41(10):925–34.
13. Noaparast Z, Hosseinimehr SJ. Radioprotective agents for the prevention of side effects induced by radioiodine-131 therapy. *Future Oncology.* 2013 Aug;9(8):1145–59.



14. Moreddu E, Baumstarck-Barrau K, Gabriel S, Fakhry N, Sebag F, Mundler O, et al. Incidence of salivary side effects after radioiodine treatment using a new specifically-designed questionnaire. *British Journal of Oral and Maxillofacial Surgery*. 2017 Jul;55(6):609–12.
15. Almeida JP, Sanabria ÁE, Lima ENP, Kowalski LP. Late side effects of radioactive iodine on salivary gland function in patients with thyroid cancer. *Head Neck*. 2011 May;33(5):686–90.
16. An Y-S, Yoon J-K, Lee SJ, Song H-S, Yoon S-H, Jo K-S. Symptomatic late-onset sialadenitis after radioiodine therapy in thyroid cancer. *Ann Nucl Med*. 2013 May;27(4):386–91.
17. Dingle IF, Mishoe AE, Nguyen SA, Overton LJ, Gillespie MB. Salivary Morbidity and Quality of Life following Radioactive Iodine for Well-Differentiated Thyroid Cancer. *Otolaryngol Head Neck Surg*. 2013 May;148(5):746–52.
18. Prendes BL, Orloff LA, Eisele DW. Therapeutic sialendoscopy for the management of radioiodine sialadenitis. *Arch Otolaryngol Head Neck Surg*. 2012 Jan;138(1):15–9.
19. Florenzano P, Guarda FJ, Jaimovich R, Droppelmann N, González H, Domínguez JM. Radioactive Iodine Administration Is Associated with Persistent Related Symptoms in Patients with Differentiated Thyroid Cancer. *International Journal of Endocrinology*. 2016;2016:1–6.
20. Anil S, Vellappally S, Hashem M, Preethanath RS, Patil S, Samaranayake LP. Xerostomia in geriatric patients: a burgeoning global concern. *J Investig Clin Dent*. 2016 Feb;7(1):5–12.
21. Johansson A-K, Johansson A, Unell L, Ekbäck G, Ordell S, Carlsson GE. Self-reported dry mouth in 50- to 80-year-old Swedes: Longitudinal and cross-sectional population studies. *J Oral Rehabil*. 2019 Aug 23;
22. Gentric A. [Sicca syndromes in the elderly]. *Rev Prat*. 2001 Jan 31;51(2):177–80.
23. Johansson A-K, Johansson A, Unell L, Ekbäck G, Ordell S, Carlsson GE. A 15-yr longitudinal study of xerostomia in a Swedish population of 50-yr-old subjects. *European journal of oral sciences*. 2009;117(1):13–9.
24. Johansson A-K, Johansson A, Unell L, Ekbäck G, Ordell S, Carlsson GE. Self-reported dry mouth in Swedish population samples aged 50, 65 and 75 years. *Gerodontology*. 2012;29(2):e107–15.
25. Azevedo LR, Damante JH, Lara VS, Lauris JRP. Age-related changes in human sublingual glands: a post mortem study. *Arch Oral Biol*. 2005 Jun;50(6):565–74.
26. Waterhouse JP, Chisholm DM, Winter RB, Patel M, Yale RS. Replacement of functional parenchymal cells by fat and connective tissue in human submandibular salivary glands: an age-related change. *J Oral Pathol*. 1973;2(1):16–27.

- 1
- 2
- 3 27. Haugen BR. 2015 American Thyroid Association Management Guidelines for Adult
- 4 Patients with Thyroid Nodules and Differentiated Thyroid Cancer: What is new and
- 5 what has changed? *Cancer*. 2017 01;123(3):372–81.
- 6
- 7 28. Jeong SY, Kim HW, Lee S-W, Ahn B-C, Lee J. Salivary Gland Function 5 Years After
- 8 Radioactive Iodine Ablation in Patients with Differentiated Thyroid Cancer: Direct
- 9 Comparison of Pre- and Postablation Scintigraphies and Their Relation to Xerostomia
- 10 Symptoms. *Thyroid*. 2013 May;23(5):609–16.
- 11
- 12 29. Morris LGT, Tuttle RM, Davies L. Changing Trends in the Incidence of Thyroid Cancer
- 13 in the United States. *JAMA Otolaryngol Head Neck Surg*. 2016 01;142(7):709–11.
- 14
- 15 30. Albano D, Bertagna F, Panarotto MB, Giubbini R. Early and late adverse effects of
- 16 radioiodine for pediatric differentiated thyroid cancer. *Pediatr Blood Cancer*. 2017
- 17 Nov;64(11):e26595.
- 18
- 19 31. Selvakumar T, Nies M, Klein Hesselink MS, Brouwers AH, van der Horst-Schrivers
- 20 ANA, Klein Hesselink EN, et al. Long-Term Effects of Radioiodine Treatment on
- 21 Salivary Gland Function in Adult Survivors of Pediatric Differentiated Thyroid
- 22 Carcinoma. *J Nucl Med*. 2019 Feb;60(2):172–7.
- 23
- 24 32. Martínez Trufero J, Capdevilla J, Cruz JJ, Isla D. SEOM clinical guidelines for the
- 25 treatment of thyroid cancer. *Clin Transl Oncol*. 2011 Aug;13(8):574–9.
- 26
- 27 33. Chung J-K, Cheon GJ. Radioiodine therapy in differentiated thyroid cancer: the first
- 28 targeted therapy in oncology. *Endocrinol Metab (Seoul)*. 2014 Sep;29(3):233–9.
- 29
- 30 34. Albrecht HH, Creutzig H. [Salivary gland scintigraphy after radio-iodine therapy.
- 31 Functional scintigraphy of the salivary gland after high dose radio-iodine therapy
- 32 (author's transl)]. *Rofo*. 1976 Dec;125(6):546–51.
- 33
- 34 35. Maheshwari YK, Hill CS, Haynie TP, Hickey RC, Samaan NA. 131I therapy in
- 35 differentiated thyroid carcinoma: M. D. Anderson Hospital experience. *Cancer*. 1981
- 36 Feb 15;47(4):664–71.
- 37
- 38 36. Jonklaas J. Nasal symptoms after radioiodine therapy: a rarely described side effect with
- 39 similar frequency to lacrimal dysfunction. *Thyroid*. 2014 Dec;24(12):1806–14.
- 40
- 41 37. Konings AWT, Coppes RP, Vissink A. On the mechanism of salivary gland
- 42 radiosensitivity. *Int J Radiat Oncol Biol Phys*. 2005 Jul 15;62(4):1187–94.
- 43
- 44 38. Nakada K, Ishibashi T, Takei T, Hirata K, Shinohara K, Katoh S, et al. Does Lemon
- 45 Candy Decrease Salivary Gland Damage After Radioiodine Therapy for Thyroid
- 46 Cancer? :7.
- 47
- 48 39. Kulkarni K, Van Nostrand D, Atkins F, Mete M, Wexler J, Wartofsky L. Does lemon
- 49 juice increase radioiodine reaccumulation within the parotid glands more than if lemon
- 50 juice is not administered?: *Nuclear Medicine Communications*. 2014 Feb;35(2):210–6.
- 51
- 52 40. Jentzen W, Richter M, Nagarajah J, Poeppel TD, Brandau W, Dawes C, et al. Chewing-
- 53 gum stimulation did not reduce the absorbed dose to salivary glands during radioiodine
- 54
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2  
3 treatment of thyroid cancer as inferred from pre-therapy <sup>124</sup>I PET/CT imaging.  
4 EJNMMI Phys. 2014 Dec;1(1):100.  
5
- 6  
7 41. Kim JM, Kim JW, Choi ME, Kim S, Kim Y, Choi J. Protective effects of curcumin on  
8 radioiodine-induced salivary gland dysfunction in mice. *J Tissue Eng Regen Med*. 2019  
9 Apr;13(4):674–81.
- 10  
11 42. Haghghatafshar M, Ghaedian M, Etemadi Z, Entezarmahdi SM, Ghaedian T.  
12 Pilocarpine effect on dose rate of salivary gland in differentiated thyroid carcinoma  
13 patients treated with radioiodine: *Nuclear Medicine Communications*. 2018  
14 May;39(5):430–4.  
15
- 16  
17 43. Upadhyaya A, Zhou P, Meng Z, Wang P, Zhang G, Jia Q, et al. Radioprotective effect of  
18 vitamin E on salivary glands after radioiodine therapy for differentiated thyroid cancer: a  
19 randomized-controlled trial. *Nuclear Medicine Communications*. 2017 Nov;38(11):891–  
20 903.  
21
- 22  
23 44. Zeidan YH, Xiao N, Cao H, Kong C, Le Q-T, Sirjani D. Botulinum Toxin Confers  
24 Radioprotection in Murine Salivary Glands. *International Journal of Radiation  
25 Oncology\*Biology\*Physics*. 2016 Apr;94(5):1190–7.
- 26  
27 45. Breen CL, Shakeshaft AP, Doran CM, Sanson-Fisher RW, Mattick RP. Cost-  
28 effectiveness of follow-up contact for a postal survey: a randomised controlled trial.  
29 *Aust N Z J Public Health*. 2010 Oct;34(5):508–12.  
30
- 31  
32 46. Jonklaas J, Wang H, Esposito G. Salivary Function after Radioiodine Therapy: Poor  
33 Correlation between Symptoms and Salivary Scintigraphy. *Front Endocrinol (Lausanne)*.  
34 2015;6:100.
- 35  
36 47. Wu J, Feng H, Ouyang W, Sun Y, Chen P, Wang J, et al. Systematic evaluation of  
37 salivary gland damage following I-131 therapy in differentiated thyroid cancer patients  
38 by quantitative scintigraphy and clinical follow-up: *Nuclear Medicine Communications*.  
39 2015 Aug;36(8):819–26.  
40
- 41  
42 48. Caglar M, Tuncel M, Alpar R. Scintigraphic Evaluation of Salivary Gland Dysfunction  
43 in Patients with Thyroid Cancer After Radioiodine Treatment: *Clinical Nuclear  
44 Medicine*. 2002 Nov;27(11):767–71.
- 45  
46 49. Baker SR, Pankhurst CL, Robinson PG. Utility of two oral health-related quality-of-life  
47 measures in patients with xerostomia. *Community dentistry and oral epidemiology*.  
48 2006;34(5):351–62.  
49
- 50  
51 50. Strömbeck B, Ekdahl C, Manthorpe R, Wikström I, Jacobsson L. Health-related quality  
52 of life in primary Sjögren's syndrome, rheumatoid arthritis and fibromyalgia compared  
53 to normal population data using SF-36. *Scandinavian journal of rheumatology*.  
54 2000;29(1):20–8.
- 55  
56 51. Hay KD, Morton RP, Wall CR. Quality of life and nutritional studies in Sjogren's  
57 syndrome patients with xerostomia. *The New Zealand dental journal*.  
58 2001;97(430):128–31.  
59  
60

- 1  
2  
3 52. Rostron J, Rogers S, Longman L, Kancy S, Field EA. Health-related quality of life in  
4 patients with Primary Sjögren's Syndrome and Xerostomia: a comparative study.  
5 Gerodontology. 2002;19(1):53-9.  
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For Peer Review

Questions	No	%	Yes	%	Missing data
1. During the last 3 years, have you experienced discomfort or a swelling of your parotids? (around and in front of the ear)	136	84%	20	14%	0
2. During the last 3 years, have you experienced pain in your parotids? (around and in front of the ear)	142	87,6%	16	11,1%	0
3. During the last 3 years, have you noticed a flow of salty liquid or of bad taste liquid in your mouth	155	95,7%	5	3,5%	1
4. During the last 3 years, have you noticed a lack of saliva	107	66,9%	45	31,9%	1
5. During the last 3 years, have you modified your diet because of this discomfort or pain, especially for acidic (tomato, citrus) or sugary foods?	150	93,2%	8	5,6%	0
8. During the last 3 years, have you taken medics for your discomfort or your pain?	146	94,8%	6	4,4%	12
9. During the last 3 years, have you undergone a surgical treatment for your discomfort or pain?	158	99,4%	1	0,7%	6
10. During the last 3 years, did you get a lasting discomfort or swelling?	144	90,6%	13	9,3%	5
11. During the last 3 years, did you feel pain?	151	95,6%	6	4,3%	6
12. During the last 3 years, did you feel anxious because of this symptomatology?	130	81,8%	24	17,1%	10

Table 1: Results of the 2019 questionnaire. Data are number (%) of patients.

Questions	Yes (2013)	%	Yes (2019)	%	Missing data (2012)	Missing data (2019)	p value
1. Have you experienced discomfort or a swelling of your parotids? (around and in front of the ear)	39	27,3%	20	14%	0	0	P< 0.001
2. Have you experienced pain in your parotids? (around and in front of the ear)	33	23,1%	16	11,1%	0	0	p< 0.001
3. Have you noticed a flow of salty liquid or of bad taste liquid in your mouth	14	9,9%	5	3,5%	0	1	p= 0.003
4. Have you noticed a lack of saliva	56	39,4%	45	31,9%	2	1	p= 0.066
5. Have you modified your diet because of this discomfort or pain, especially for acidic (tomato, citrus) or sugary foods?	18	12,7%	8	5,6%	1	0	p= 0.005
8. Have you taken medics for your discomfort or your pain?	23	17,6%	6	4,4%	8	12	p< 0.001
9. Have you undergone a surgical treatment for your discomfort or pain?	4	2,9%	1	0,7%	2	6	p= 0.37
10. Did you get a lasting discomfort or swelling?	33	23,9%	13	9,3%	3	5	p< 0.001
11. Did you felt pain ?	19	13,9%	6	4,3%	3	6	p< 0.001
12. Did you felt anxious because of this symptomatology?	50	38,8%	24	17,1%	3	10	p< 0.001

Table 2: Within-population comparison in 2013 and 2019. Data are number (%) of patients.

<b>EVA</b>	<b>No of patients (2013)</b>	<b>No of patients (2019)</b>
0	108	137
1	6	5
2	8	3
3	6	2
4	5	1
5	4	2
6	2	1
7	2	1
8	4	1
9	2	0
10	0	0
Weighted mean	1,06122449	0,300653595

Table 3: Visual Analogue scores.

<b>Stress or anxiety</b>	<b>No patients (2013)</b>	<b>No patients (2019)</b>
1 . Not at all	90	129
2. A little	19	13
3. Moderatly	17	8
4. Much	11	6
5. Extremely	3	2
Weighted mean	1,7	1,35

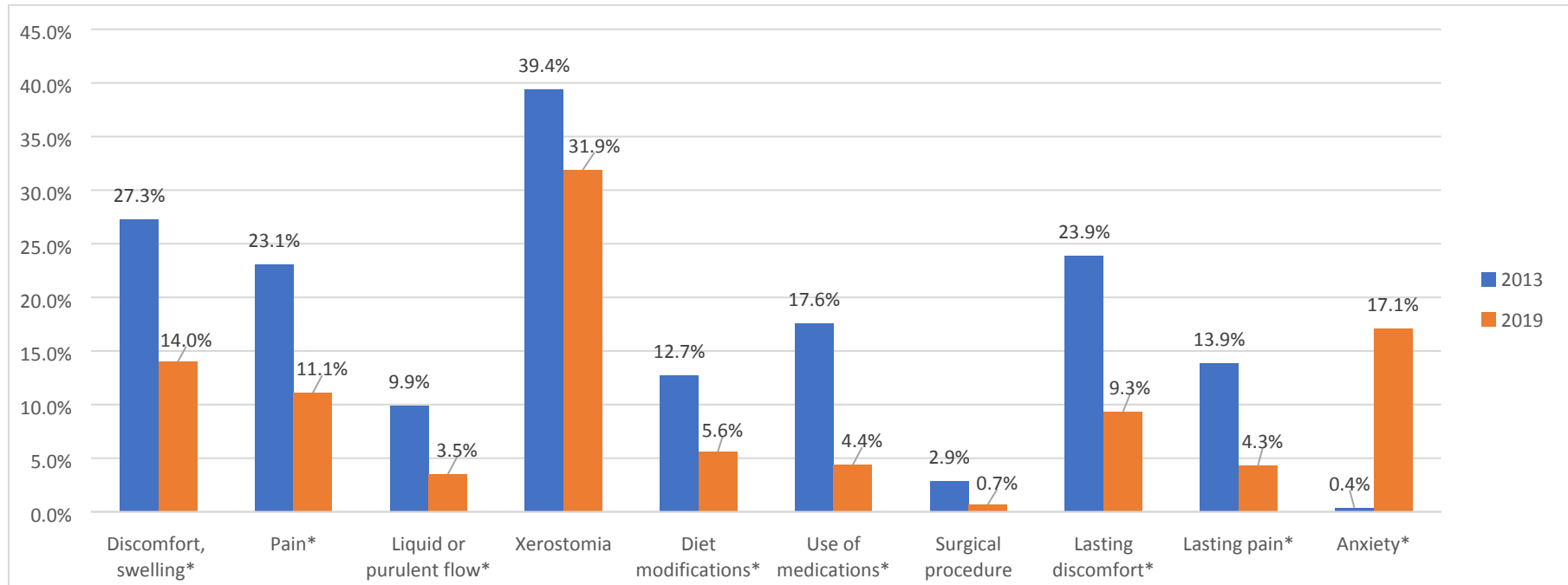
Table 4: Results of question 12 about anxiety and stress du to I<sup>131</sup> therapy

For Peer Review



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\*p<0.05

Figure 1: Histogram interpretation of questionnaire responses between 2013 and 2019