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

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3 Salivary side effects after radioiodine treatment for
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7 differentiated papillary thyroid carcinoma: a long-term study.
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19 Running title: Long-term radioiodine salivary side effects after thyroid papillary carcinoma

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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 I¹³¹ 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 I¹³¹ 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 (I¹³¹) 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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11 We tried to reach all 413 included patients, who had previously responded to the
12 questionnaire 74 months ago, on the phone, by mail or, by email in case of failure to inquire
13 on major medical events, exclusion criteria, to give information on the questionnaire and to
14 obtain their permission to send the questionnaire.
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17 This study was conducted in accordance with the Declaration of Helsinki and was approved
18 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 I¹³¹ 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

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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)
33
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
40
41 symptoms in 2019 was 5.3% (8/154) and almost equal to the number of patients who had
42
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%
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52 (20/162) in 2019 vs 24.7% (40/162) in 2013 (p<0.01).
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55 According to the VAS, most of the patients experienced no pain related to parotid or
56
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
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5 in 16% (26/162) of the patients versus 29% (47/162) in 2013.

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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
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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
17
18 related to the radioiodine therapy although they hadn't been operated in our department and
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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
30
31 comparing the weighted averages which go from 1.7 in 2013 to 1.3 in 2019 ($p<0.01$).
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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
56
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 I¹³¹ 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 I¹³¹ 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 I¹³¹ therapy and 5 years later.

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5 Objective imaging observations found a reduction in salivary gland uptake and a reduction of
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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 I¹³¹ 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
4 lemon three times a day, beginning a few hours after I¹³¹ therapy to decrease the residence time
5 of radioiodine within the salivary gland as suggested by Nakada (washout effect).(38)
6
7 Kulkarni and al suggested that lemon juice, due to its sialagogue effect, had reduced the
8 potential radiation absorbed dose in the parotid glands with an average of 34.2%. (39) A
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10 review of natural and synthetic compounds suggested that more studies were needed, and at
11 the time, it was better to use natural compounds over synthetic.(13)(40)(41)(42)(43)
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13 Botulinum toxin seems to confer radioprotective properties to salivary glands in Murine
14 subjects by reducing glandular atrophy and periductal fibrosis during classic external
15 radiation.(44) Botulinum toxin would be an interesting preventive treatment for patients
16 receiving radioiodine to prevent adverse side effects.
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31 Shortcomings

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33 The main shortcoming was related to the duration over which the symptoms were assessed.
34 Patients were asked to remember if they had symptoms related to the oro-facial area in the last
35 three years. We can assume that patients, who never had any symptoms, or few following the
36 I¹³¹ treatment, would not show interest in responding to our questionnaire 6 years later.
37
38 Even if we had gotten a high level of responses from patients we managed to contact (78%),
39 we can assume that symptomatic patients are more willing to respond. Our response rate was
40 better than the classical rate with postal surveys which is around 50%.(45)
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42 Also, one of the main biases would be the difficulty in asserting the correlation between a
43 symptom expressed by the patient and the glandular lesions induced by radioiodine treatment.
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45 For instance, a patient confirmed having a high level of stress, but in the free commentary
46 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 I¹³¹ 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 I¹³¹ therapy. Our study suggests that a significant rate of
6 patients will recover from I¹³¹ 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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34 Conflict of interest: None
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58 Table 1: Results of the 2019 questionnaire. Data are number (%) of patients.

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

Table 3: Visual Analogue scores.

Table 4: Results of question 12 about anxiety and stress due to I¹³¹ therapy

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

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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.

EVA	No of patients (2013)	No of patients (2019)
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.

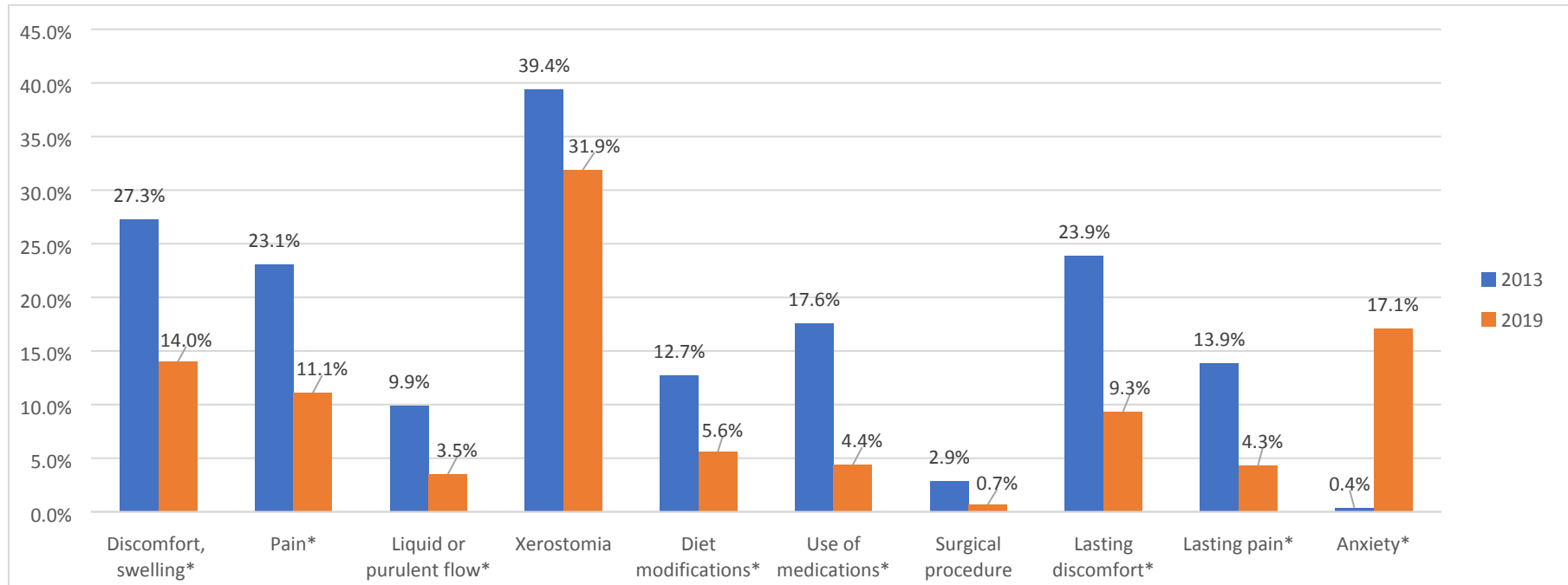
Stress or anxiety	No patients (2013)	No patients (2019)
1 . Not at all	90	129
2. A little	19	13
3. Moderatly	17	8
4. Much	11	6
5. Extremely	3	2
Weighted mean	1,7	1,35

Table 4: Results of question 12 about anxiety and stress du to I¹³¹ therapy

For Peer Review

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For Peer Review



*p<0.05

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