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# Health-related quality of life and radioiodine therapy in thyroid cancer patients: a before-and-after study

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## 1 **Introduction**

2 Since the early 1980s, there has been a rise in the occurrence of thyroid cancer worldwide,  
3 specifically early papillary thyroid carcinomas <sup>[1]</sup>. The incidence rates vary widely between and  
4 within countries, indicating an uneven global epidemic of thyroid cancer <sup>[1]</sup>. Projections indicate  
5 that within the next ten years, over 1,000,000 people will have been diagnosed with thyroid  
6 cancer <sup>[2]</sup>. However, mortality rates have either remained stable or decreased, with similar lower  
7 rates observed across countries and genders <sup>[1]</sup>. Additionally, the survival rate for this type of  
8 cancer is approximately 97% <sup>[2]</sup>. The growing incidence of this cancer type is leading to an  
9 increase in patients seeking treatments, which may come with accompanying side effects.

10 Apart from the physical aspects related to cancer, the subjective consequences that cancer  
11 survivors experience, such as their quality of life and psychological well-being, are crucial  
12 considerations <sup>[3,4]</sup>. Cancer survivors may undergo various physical, emotional, and  
13 psychosocial changes resulting from their diagnosis and treatment's side effects which can lead  
14 to significant impairments in their health-related quality of life (HRQOL) <sup>[5]</sup>. Thyroid cancer  
15 treatments, such as surgery and radioactive iodine (RAI) ablation, are well-documented to carry  
16 potential complications. For instance, RAI therapy may be associated with short-term or long-  
17 term adverse effects, including dysfunction of salivary or lacrimal glands, bone marrow  
18 suppression, pulmonary fibrosis, and an increased risk of developing secondary malignancies  
19 <sup>[5,6]</sup>.

20 The assessment of HRQOL has gained greater recognition as a mean of gathering more significant  
21 information regarding cancer patients' personal experiences with their treatment process <sup>[7]</sup>.  
22 Concurrently, depression and anxiety are now acknowledged as the most common emotional  
23 issues among individuals with cancer, significantly influencing HRQOL <sup>[7]</sup>. Therefore, some  
24 studies have considered evaluating the psychological impact of a thyroid cancer RAI therapy, and  
25 especially its effect on HRQOL in terms of anxiety and depression symptoms. However, the

26 current research on this topic is limited <sup>[8]</sup>. Only few of the existing studies have included factors  
27 that may contribute to a decrease in HRQOL or psychological well-being after RAI therapy in  
28 comprehensive multivariate analyses, and in a before-and-after design study. Furthermore, the  
29 relationship between the dose or the administered activity and HRQOL or anxiety/depression  
30 symptoms has never been studied. Thus, this study aims 1) to compare HRQOL before and after  
31 RAI therapy in patients treated for a differentiated thyroid cancer, 2) to assess factors statistically  
32 associated with anxiety and depression symptoms or altered HRQOL in these patients, and 3) to  
33 estimate dose-response relationships between RAI therapy and HRQOL or mental health  
34 outcomes.

## 35 **Materials and methods**

### 36 *Patient population*

37 This study is based on the data from the prospective and observational cohort study START (*for*  
38 *Salivary dysfuncTions After Radioiodine Treatment*), as described elsewhere <sup>[9]</sup>. Overall,  
39 analyses were carried out on 136 patients aged 18 and above who were diagnosed with  
40 differentiated thyroid cancer and who had undergone thyroidectomy at Pitié-Salpêtrière Hospital  
41 (Paris, France), while they were awaiting complementary RAI therapy between September 2020  
42 and April 2021. The inclusion of participants was based on a non-randomized approach,  
43 employing a systematic and consecutive selection method. Patients who had previously received  
44 RAI therapy or were anticipated to undergo multiple RAI therapies within the 18 months  
45 following enrollment were excluded from the study. The choice of the administered <sup>131</sup>I-activity  
46 was made by clinicians in the context of cancer treatment according to usual standard of care  
47 and patient prognosis, leading the cohort to be divided into two <sup>131</sup>I-activity groups: 1.1 GBq  
48 (n=44) and 3.7 GBq (n=92). The thyroid-stimulating hormone (TSH) elevation protocol  
49 employed L-thyroxine withdrawal for 35% of patients and recombinant thyroid-stimulating  
50 hormone administration for the remaining 65%.

51 ***Radiation dose assessment***

52 Prior to administration of RAI therapy, three thermoluminescent dosimeters provided by APVL  
53 (Saint-Cyr-sur-Loire, France) were positioned beneath both earlobes and at the sternal notch,  
54 respectively. These dosimeters allowed to measure the radioactivity emitted from the patients,  
55 enabling the dose to the salivary glands to be estimated as accurately as possible, and were  
56 removed after 5 days, just before the post-therapy scan. Dosimeters' records were then converted  
57 into absorbed doses to the right and left salivary glands (Dr and Dl, respectively) according to a  
58 methodology previously described <sup>[10-14]</sup>. Subsequently, a mean dose to the salivary glands (MD)  
59 was calculated based on Dr and Dl for further analysis. The administered <sup>131</sup>I-activity (AA), which  
60 was either 1.1 or 3.7 GBq, was also factored in the analyses.

61 ***Assessment of HRQOL and psychological status***

62 HRQOL, anxiety and depression symptoms, and nutrition were assessed using the following  
63 standardized questionnaires: the Medical Outcome Study Short Form-36 (SF-36), the Hospital  
64 Anxiety and Depression (HAD) scale, and a Visual Analogue Scale (VAS) for nutritional status,  
65 respectively <sup>[15,16]</sup>.

66 The SF-36 comprises 36 items that compose eight sub-scores: physical functioning, role  
67 physical, bodily pain, general health, vitality, social functioning, role emotional, mental health.  
68 These eight sub-scores were standardized following the typical guidelines for interpreting the  
69 SF-36 questionnaire or converted to a scale ranging from 0 to 100 and included in two  
70 component scores: the MCS (mental component score) and the PCS (physical component  
71 score). A higher score reflects a perception of good health, and therefore a lack of functional  
72 deficit or pain <sup>[17]</sup>. As a result, both the two component scores and the eight sub-scores were  
73 examined in this study.

74 The HAD scale is divided into two subscales, for anxiety and depression symptoms separately.  
75 A score ranging from 0 to 7 on either subscale could be considered within the normal range,

76 while a score between 8 and 10 indicated a mild indication of the corresponding emotional state,  
77 and a score above 10 strongly suggested the presence of a mood disorder<sup>[15]</sup>. The overall HAD  
78 score and the two separated subscales after dichotomization (scores <8 vs. ≥8) were analyzed  
79 in this study.

80 The VAS is a 10-point analogue scale, here used as nutritional status, which is a good prognostic  
81 marker in oncology. Patients were asked: “did you reduce your dietary intake since your  
82 surgery?” (0 = I don’t eat anything anymore, 10 = I eat as I always do).

83 All questionnaires were completed at baseline, i.e., right before RAI (T0), and 6 months later  
84 (T6) for all patients. These assessments were conducted during an in-person meeting with a  
85 skilled interviewer as part of the hospital’s treatment follow-up process. Details regarding  
86 possible systemic diseases were obtained from the patients’ medical records and further  
87 corroborated or supplemented through direct questioning during the visits.

88 Table 1 presents the various outcomes used in this study, which were created on the basis of  
89 these questionnaires.

90

### 91 ***Potential confounders***

92 During the enrollment visit, various study covariates identified from the literature were gathered  
93 for the purpose of investigating their role as potential confounders in the studied relationship  
94 between RAI therapy exposure and changes in targeted outcomes between pre- and post-RAI  
95 therapy. The following variables were finally retained for inclusion in the multivariate models:  
96 age, menopause (yes, no, N/A), medication consumption of antidepressants, psycholeptics,  
97 anxiolytics or pain relievers (yes, no) and salivary and/or lacrimal dysfunctions (yes, no). Other  
98 a priori confounders such as body mass index (BMI), history of systemic diseases, TSH  
99 elevation protocol, pTNM staging, histology, marital status and occupation were also initially  
100 considered. However, as they were not associated with the outcomes in the univariate analysis

101 ( $p > 0.10$ ), they were not included in the multivariate analysis.

102

### 103 *Statistical analyses*

104 Logistic and linear random-effects regressions were used both to assess factors statistically  
105 associated with changes in outcomes between pre- and post-RAI, and to investigate associations  
106 between RAI therapy exposure, in terms of administered activity (AA) or mean dose (MD) to  
107 the salivary glands, and changes in outcomes. The multivariate regression models finally  
108 included identified associated factors and subsequent RAI therapy indicators as factors of  
109 interest, providing odds ratios (OR) and beta coefficients ( $\beta$ ), along with their corresponding  
110 95% confidence intervals (95CI%). Salivary dysfunctions and TSH elevation protocol were  
111 investigated as potential modifiers of the relationship between HRQOL or nutrition and RAI  
112 exposure, using interaction terms in multivariate models.

113 The GLIMMIX procedure of SAS V.9.4 statistical software for Windows (SAS Institute, Cary,  
114 NC) was used to conduct the analyses. A significance level of 0.05 was considered statistically  
115 significant for p-values.

116

## 117 **Results**

### 118 *Patient characteristics*

119 Among the 136 patients, the average age at the time of enrollment was 47.1 years ( $\pm 14.1$ ), with  
120 71% of the participants being female. The two RAI activity groups (1.1 and 3.7 GBq) did not  
121 exhibit any significant variations in terms of gender and age. Regarding clinical data, 85% of  
122 the patients had papillary cancer, and 47% had residual thyroid tissue  $^{131}\text{I}$ -fixation in the thyroid  
123 bed following RAI therapy (Table 2). DI and Dr were comparable within each RAI activity  
124 group, respectively.

125

126 ***HRQOL – MOS SF-36***

127 Paired comparison tests did not show any statistical difference in the mental component score  
128 (MCS) between pre- (mean  $\pm$ SD= 44.1  $\pm$ 11.0) and 6-months post-RAI (mean  $\pm$ SD= 44.1  $\pm$ 10.1)  
129 (p=0.73), but showed a statistically significant increase in the physical component score (PCS)  
130 (mean  $\pm$ SD= 47.5  $\pm$ 9.0 and 50.5  $\pm$ 8.5, at T0 and T6 respectively,  $p < 10^{-3}$ ) (Table 3).  
131 Correspondingly, multivariate linear regression analyses did not show any significant  
132 association between RAI exposure and MCS, while a significant positive dose-response  
133 relationship has been found between RAI exposure and PCS ( $\beta = 0.97$ , 95%CI 0.30;1.65 for a  
134 1-Gy MD increase - also significant with AA) (Table 4). Regarding the sub-scores of the SF-  
135 36 questionnaire, those for physical functioning (PF), role physical (RP) and bodily pain (BP)  
136 were significantly higher at T6 compared with T0. However, multivariate analyses revealed a  
137 statistically significant increase only in RP score in relation to RAI exposure ( $\beta = 6.54$ , 95%CI  
138 2.71;10.36 for a 1-Gy MD increase - also significant with AA) (Table 5).

139

140 ***Anxiety and depression symptoms – HAD scale***

141 Paired comparisons in categorial variables showed a non-significant decrease in the proportion of  
142 patients with anxiety symptoms (as per the anxiety component score of the HAD scale) from  
143 47.8% at T0, to 40.4% at T6 (p= 0.15). In contrast, a significant higher proportion of patients with  
144 depression symptoms (as per the depression component score of the HAD) was reported, from  
145 12.5% at baseline to 14.0% at T6 ( $p < 10^{-3}$ ) (Table 3). Nevertheless, paired comparisons for  
146 continuous score showed a significant decrease in the overall HAD score between T0 and T6  
147 (p=0.04), towards a decrease in the level of anxiety-depression symptoms in the patients.  
148 Regarding multivariate analyses, associations between AA or MD and anxiety or depression  
149 symptoms were not statistically significant (OR = 0.86, 95%CI 0.62;1.19, and OR = 1.82, 95%CI  
150 0.84;3.91, for anxiety and depression symptoms respectively, in relation with a 1-Gy increase in



151 MD) (Table 6). No significant dose-response relationship was found either between AA or MD  
152 and the overall HAD score (Table 4).

153

#### 154 *Nutrition – VAS*

155 Paired comparisons did not show any statistical difference in VAS of dietary intake between  
156 T0 (mean  $\pm$ SD= 8.9  $\pm$ 1.8) and T6 (mean  $\pm$ SD= 8.9  $\pm$ 1.9) ( $p=0.69$ ) (Table 3). Moreover, no  
157 significant dose-response relationship was found between AA or MD and the VAS for nutrition  
158 in multivariate analyses (Table 4).

159

#### 160 *Modifying effects*

161 While the interaction between RAI exposure and salivary dysfunction was not significant, it  
162 was between TSH elevation protocol and RAI exposure, showing that patients who underwent  
163 L-thyroxine withdrawal had greater increases in some HRQOL scores between T0 and T6 than  
164 patients who received rTSH (Table 7).

165

#### 166 **Discussion**

167 This study aimed to evaluate a potential association between the dose to the salivary glands or the  
168 administered activity and changes in HRQOL, psychological symptoms, or nutrition in thyroid  
169 cancer patients. Adjusted on confounders, analyses did not find any adverse effects of RAI  
170 therapy on patients' HRQOL by evaluating potential changes in scores assessed immediately  
171 before and 6-months after RAI. A significant positive dose-response relationship was even found  
172 between the activity administered or the dose absorbed by the salivary glands and the physical  
173 component score of the SF-36 questionnaire after adjustment for confounding factors, towards an  
174 improvement in physical HRQOL 6 months after RAI therapy. Similarly, the sub-score related to  
175 role limitations due to physical health problems (RP) showed significant relationships with both

176 the absorbed dose to the salivary glands and administered activity, suggesting fewer physical  
177 disabilities after RAI therapy than before. These relationships were particularly pronounced in  
178 patients who underwent L-thyroxine withdrawal compared with patients who received rTSH,  
179 highlighting the TSH elevation protocol as a potential modifier of this relationship.

180

181 To the best of our knowledge, only few studies have investigated the association between RAI  
182 therapy and HRQOL or psychological status in patients diagnosed with differentiated thyroid  
183 cancer. Banihashem et al. studied trends in HAD and SF-36 scores at different time points in the  
184 patients' treatment (at the time of RAI therapy (T0) and 6 months later (T6)), showing statistical  
185 improvements of HRQOL between T0 and T6, and no significant interaction with RAI activity  
186 (3700 or 5550 MBq). However, they have not provided analyses for the various sub-scores of  
187 the scales, and the processing prior to use of the scores lacks detail for a clear interpretation of  
188 the results <sup>[18]</sup>. A study by van Velsen et al. assessed HRQOL (using the SF-36 with a different  
189 scoring algorithm) before surgery, before RAI therapy, and every 1–2 years thereafter. Using a  
190 random-effects structure, they concluded that HRQOL evolves non-linearly over time in general,  
191 with the lowest HRQOL around RAI therapy, and a return to pre-surgery values 2-3 years later  
192 <sup>[19]</sup>. These results appear to be consistent with those of other studies with different designs <sup>[20–22]</sup>  
193 and could explain the increase in the SF-36 physical component score in our study at 6 months  
194 after RAI.

195 Nevertheless, previous studies have indicated that patients are more likely to suffer from  
196 gastrointestinal discomfort or encounter short-term symptoms such as neck, head or salivary  
197 gland pain immediately after RAI therapy <sup>[23]</sup>. The SF-36 questionnaire employed during the 6-  
198 month follow-up might not have been sensitive enough to detect these transient pains, which  
199 could have potentially disappeared thereafter. Actually, HRQOL in patients treated for thyroid  
200 cancer has also been assessed by various questionnaires in other studies, such as the PROMIS

201 questionnaire <sup>[5,24]</sup>, or the EORTC QLQ-C30 questionnaire <sup>[20,25]</sup>, or the specific questionnaire  
202 designed for evaluating HRQOL in thyroid cancer patients, the EORTC QLQ-THY34 <sup>[26]</sup>.  
203 However, the decision to employ the MOS SF-36 questionnaire was carefully considered to  
204 facilitate comparisons with other studies due to its widespread usage. Whatever the questionnaire,  
205 the subjectivity of the answers is inherent since the questionnaires rely on patients' understanding  
206 and interpretations.

207 The decrease, albeit non-significant, in the number of patients with anxiety symptoms from T0  
208 to T6 may be linked to treatment-related anxiety at baseline, since patient have high anxiety  
209 levels at that time. Social and physical isolation, as part of the requirements post-RAI, may  
210 indeed be a potential anxiety trigger. Stajdugar et al. showed that patients kept in isolated  
211 conditions after RAI are usually extremely stressed <sup>[27]</sup>. Being diagnosed with cancer is an  
212 inherently stressful situation. Research findings indicate that individuals diagnosed with cancer  
213 commonly encounter high levels of anxiety and fear throughout their diagnostic journey,  
214 regardless of the specific type of cancer diagnosis <sup>[28]</sup>. Additionally, there could be a potential  
215 psychological effect not accounted for in the different administered questionnaires related to  
216 the environment in which the treatment is delivered. Therefore, it is not surprising to find  
217 increased anxiety symptoms reported by thyroid cancer patients at T0 compared with T6 in our  
218 study, if potentially attributable to the upcoming treatment, as questionnaires were given prior  
219 to RAI therapy. Including supplementary inquiries regarding the treatment environment and  
220 external factors could prove beneficial in assessing the factors that contribute to patients'  
221 anxiety in a hospital setting.

222 Nevertheless, a significant increase in the number of patients with depressive symptoms at T6,  
223 in parallel with an increase in the depression score on the HAD scale were found. However,  
224 multivariate analyses did not show significant results. These results deserve our attention and  
225 could be taken into consideration if confirmed by other studies.

226

227 The strengths of the START cohort lie in the collection of information about various potential  
228 risk factors as well as HRQOL reports gathered with standardized questionnaires. In the present  
229 study, numerous covariates identified from the literature were tested and confirmed with  
230 univariate analyses and included in multivariate linear and logistic regression models to address  
231 possible confounding effects. Nonetheless, the cohort design employed in this study, where  
232 cases serve as their own controls, offers the advantage of automatically controlling for  
233 individual risk factors that are not time dependent. The implementation of random effects  
234 regression models facilitated the examination of numerous potential cofactors and led to the  
235 identification of age, menopause status, non-use of anxiolytics, psycholeptics, antidepressants,  
236 or pain relievers, and salivary and/or lacrimal dysfunctions as risk or confounding factors for  
237 HRQOL following RAI therapy. The recognition of factors statistically associated with the  
238 outcome could assist healthcare professionals in identifying patients vulnerable to mental health  
239 issues and offer psychological support accordingly. Our study possesses an additional strength  
240 in evaluating adjusted dose-response relationships by considering not just the administered  
241 activity, but also the dose received by the salivary glands, a previously unexplored aspect.  
242 Furthermore, this study analyzed potential modifying effects of certain variables in the studied  
243 relationship, showing that changes in HRQOL differed according to the TSH elevation protocol.

244

245 One of the limitations of this study is the absence of pre-surgery assessment to potentially  
246 confirm that score return to pre-surgery values. Nevertheless, the main objective of this study  
247 was to observe the potential adverse effects of RAI therapy and pre-surgery follow-up would  
248 have provided little information to meet this objective. Moreover, a limitation is the limited  
249 number of patients included, perhaps leading to statistically non-significant but potentially  
250 substantial results. An increase in the number of patients, or joint analyses with international

251 studies could be envisaged to increase the statistical power and scope of the results.

252 **Conclusion**

253 This study did not evidence adverse effects of RAI therapy on the HRQOL and the nutritional  
254 status of thyroid cancer patients, as assessed by the SF-36 questionnaire, the HAD scale and the  
255 VAS, after 6 months. Nevertheless, an increase in the level of depression cannot be ruled out  
256 and deserves our vigilance. A psychological and behavioral intervention strategy could be  
257 considered to help patients overcome the ordeal of therapy. Further research is needed to  
258 explore the long-term HRQOL outcomes. As a result, a prospective follow-up assessment of  
259 these patients at 18 months is already planned. Ultimately, identifying risk factors for HRQOL  
260 in thyroid cancer patients could aid in screening high-risk patients for mental health decrease,  
261 therefore offering suitable psychological support.

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### **Competing Interests**

The authors of this manuscript affirm that they have no affiliations or associations with any companies that produce or provide products or services related to the topic discussed in the article. There are no conflicts of interest to disclose.

### **Authors' contribution**

The financial support acquisition was carried out by CIB and MOB. The START study was conceptualized and designed by CIB, MOB, and CLL. The study itself was conducted by CIB, AB, and MOB. The dosimetry aspect, which involved reading dosimeters, implementing, and validating the method for calculating the dose to the salivary glands, as well as estimating and interpreting the doses, was managed by DB, CéB, and CH. At the Pitié Salpêtrière Hospital, CaB, FM, MS, LL, and CLL served as the clinicians and radiophysicists responsible for treating the patients. CIB and AL performed the statistical analyses and drafted the manuscript. CM reviewed and read the manuscript. All co-authors reviewed and approved the final version of the report. CIB and MOB are the guarantors of this paper and hold overall responsibility for its content.

### **Ethics approval**

Ethical approvals were obtained from the local committee (Comité de Protection des Personnes Sud Méditerranée III (ID: 20.01.24.56149), as well as the Agence Nationale de Sécurité des Médicaments (ID: 2020-A00108-31). The study protocol was registered and made publicly available on the [ClinicalTrials.gov](https://www.clinicaltrials.gov) website (NCT04876287). Informed consent was obtained from all individual participants included in the study.