# Salivary scintigraphy as a pre-treatment diagnostic tool to predict gland dysfunction following $^{131}$I therapy

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## Abstract

**Objective:** To evaluate whether pre-treatment salivary gland scintigraphy (SGS) with technetium-99m pertechnetate ($^{99m}TcO_4^-$) can predict the risk of moderate to severe salivary gland dysfunction and xerostomia in differentiated thyroid cancer (DTC) patients following their first radioiodine-131 ($^{131}$I) therapy. **Subjects and Methods:** We retrospectively enrolled 149 DTC patients (107 females, 42 males; mean age 46.6 ± 12.7 years) who underwent total thyroidectomy between October 2022 and March 2024. All subjects received pre-treatment SGS to measure the uptake index (UI) and excretion fraction (EF) of bilateral parotid and submandibular glands. Patients then underwent $^{131}$I therapy (1.85-5.55GBq) and repeat SGS 6-12 months later under identical conditions. Xerostomia severity was assessed using the xerostomia inventory (XI) score, categorizing patients into no/mild (XI 11-23) versus moderate-extreme xerostomia (XI 24-55). **Results:** Post-therapy, all glands exhibited significant declines in UI (parotid and submandibular glands, $P<0.001$) and EF ($P\leq0.004$). There was no significant correlation between administered $^{131}$I dose and percentage changes in UI (ΔUI%) or EF (ΔEF). However, higher $^{131}$I doses were associated with increased rates of moderate-severe xerostomia ($P=0.015$) and higher mean XI scores ($P=0.008$). Receiver operating characteristic (ROC) analysis demonstrated that pre-treatment UI reliably predicted moderate to severe functional decline (ΔUI% > 20%) with areas under the curve (AUC) of 0.866 for the right parotid, 0.793 for the left parotid, 0.769 for the right submandibular, and 0.816 for the left submandibular glands (all $P<0.001$). Additionally, ΔUI% in both submandibular glands differed significantly between patients with no/mild and moderate–extreme xerostomia (right: $P=0.004$; left: $P=0.012$). **Conclusions:** Pre-treatment $^{99m}TcO_4^-$ SGS uptake index is a dependable predictor of moderate to severe salivary gland dysfunction and xerostomia following $^{131}$I therapy in DTC patients, enabling early identification of individuals at high risk and guiding tailored preventive strategies.

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## Introduction

Thyroid cancer is the most common endocrine malignancy, with its incidence gradually increasing over the past decade [1]. Radioactive iodine (RAI) therapy is typically administered following thyroidectomy in patients with differentiated thyroid carcinoma (DTC) [2]. After oral administration of $^{131}$I, it concentrates not only in residual thyroid tissues and thyroid cancer metastases but also in other tissues, such as the salivary glands, due to their expression of the sodium/iodide symporter (NIS), similar to the thyroid gland [3]. Therefore, $^{131}$I treatment may lead to potential salivary gland dysfunction, which increases the risk of dental caries, periodontal disease, and other oral health complications [4]. Due to differences in research methods, including clinical symptoms and the time of salivary dysfunction, the incidence of salivary dysfunction is still unclear, ranging from 2% to 67% [5].

Additionally, due to the different iodine uptake abilities of the salivary glands and the different protective measures that may be taken after oral administration of $^{131}$I, the activity given to patients may not accurately reflect the dose received by the salivary glands. At the same time, inherent differences between patients can also affect the overall pharmacokinetics of $^{131}$I [6]. Some risk factors for salivary dysfunction are still unclear, and there is still a lack of reliable methods to predict the incidence of salivary gland dysfunction.

Technetium-99m-pertechnetate ($^{99m}TcO_4^-$) is commonly used in clinical settings, exploiting the shared ability of salivary and thyroid glands to actively concentrate $^{99m}TcO_4^-$ thro-

ugh the NIS; this mechanism mirrors the concentration processes of chloride ($Cl^-$) and iodide ($I^-$) [7, 8]. Within 20 minutes of intravenous administration, $^{99m}TcO_4^-$ accumulates in the salivary glands and is excreted with saliva, followed by acid stimulation to assess the salivary glands' secretory and excretory functions. This semi-quantitative method can evaluate glandular dysfunction after RAI therapy [9]. Clinicians can use the salivary gland scintigraphy (SGS)-based functional score as an objective metric to assess salivary gland dysfunction in DTC patients following RAI therapy, thereby facilitating prompt and effective management of complications [9]. However, its potential to predict salivary gland dysfunction before $^{131}I$ treatment has not yet been explored.

In this study, we enrolled a moderate-sized patient cohort and conducted SGS before and 6-12 months after $^{131}I$ therapy. We evaluated the changes in scintigraphy of each salivary gland before and after RAI, subjective symptoms, and factors influencing the development of salivary gland dysfunction in patients who received their first $^{131}I$ treatment. This study aimed to assess whether $^{99m}TcO_4^-$ SGS before treatment predicted salivary gland dysfunction in DTC patients following $^{131}I$ treatment. Increasing understanding of these factors and effectively predicting salivary gland dysfunction will help identify patients at higher risk of developing salivary dysfunction, which may aid in adjusting treatment and protective measures.

## Subjects and Methods

### Patients and clinical data collection

From October 2022 to March 2024, all patients underwent total thyroidectomy at Xuzhou Medical University, with a pathological diagnosis of DTC. A total of 149 patients who underwent $^{99m}TcO_4^-$ salivary gland scintigraphy were retrospectively reviewed. According to relevant guidelines [2], patients requiring $^{131}I$ treatment were selected following a joint assessment by surgeons and nuclear medicine physicians. Four to six weeks post-surgery, patients received their first RAI therapy, with doses ranging from (1.85 to 5.55GBq), guided by intraoperative findings and pathological results [10]. The research protocol was approved by the Ethical Committee of Xuzhou Medical University Affiliated Hospital (approval no. XYFY2023-KL443-01). A comprehensive overview of the study procedures was presented to all participants, who subsequently provided their written informed consent. Exclusion criteria included patients previously treated with chemotherapy or radiotherapy for any other malignancies, as well as those with concurrent conditions such as Sjogren's syndrome, salivary gland tumors, human immunodeficiency virus infection, autoimmune diseases, or a history of sialadenitis.

Before RAI, patients adhered to a low-iodine diet for at least three weeks and underwent SGS. Two hours after oral $^{131}I$ administration, patients were allowed to consume food, encouraged to drink plenty of water, and began taking vitamin C tablets to stimulate salivary gland secretion. Vitamin C was taken every four hours, except during sleep, at a dose of 0.1g for five consecutive days. Salivary gland scintigraphy was repeated 6-12 months after $^{131}I$ treatment under identical conditions to evaluate glandular uptake and excretion function changes. The flowchart of population selection is shown in Figure 1.

### Salivary gland scintigraphy

Imaging was conducted using the GE Infinia VC Hawkeye 4 singly photon emission computed tomography/computed tomography (SPECT/CT) system, equipped with a low-energy, high-resolution parallel-hole collimator set to a 140keV peak and a 20% window width. Technetium-99m-pertechnetate was provided by Beijing Atom HighTech Co., Ltd. Before imaging, patients in a state of hypothyroidism who had fasted for over 4 hours were administered an intravenous dose of 0.37GBq of $^{99m}TcO_4^-$. Imaging of the salivary glands was conducted by covering the head and cervical area (zoom 2.5, one frame per minute). This study captured salivary gland counts 20 minutes post-injection to reflect uptake function, followed by the administration of 0.1g of vitamin C chewed as an acidic stimulant to enhance salivary gland secretion, with data collection continuing for an additional 10 minutes.

### Image analysis

Elliptical regions of interest (ROI) were manually delineated in the bilateral parotid and submandibular gland areas, with equivalent areas of uniform background, also marked in the adjacent bilateral temporal-orbital regions for the parotid glands and in the neck areas for the submandibular glands. Special attention was given to avoiding regions containing residual thyroid tissue and oral areas. The uptake and excretion metrics for $^{99m}TcO_4^-$ were derived from the radioactive counts per minute generated within these ROI. Based on these radioactive counts, the salivary gland function of each gland was calculated, and the uptake index (UI) and excretion fraction (EF) of the parotid and submandibular glands were quantified using formulas referencing previous studies by Upadhyaya, Upadhyaya A et al. (2017) [11] and Fallahi B et al. (2013) [12]. The following functional indices were derived for each salivary gland by the following modified formulas:

$\Delta UI\% = [(\text{pre-treatment UI}) - (\text{post-treatment UI})] / (\text{pre-treatment UI}) \times 100\%$

$\Delta EF = (\text{pre-treatment EF}) - (\text{post-treatment EF})$

Variations in UI ($\Delta UI\%$) and EF ($\Delta EF$) across these glands from pre-treatment SGS to post-treatment SGS were analyzed.

### Assessment of salivary gland dysfunction

Patients' salivary gland status was followed up to 6-12 months after RAI. The study employed an XI to assess the severity of xerostomia in patients; according to the total score of XI, patients are divided into three categories (11-23 points: no to mild xerostomia, 24-39 points: moderate to severe xerostomia, 40-55 points: severe to extreme xerostomia), Selvakumar T et al. (2018) previously used this XI in their research [13]. Functional assessment determined a mild decrease in EF was defined as a decrease in EF of 11%-20%, a moderate decrease was 21%-30%, and a severe decrease was more than 30%, according to the literature [14], this study also defined mild UI decrease as a decrease of 11%-20% in UI,

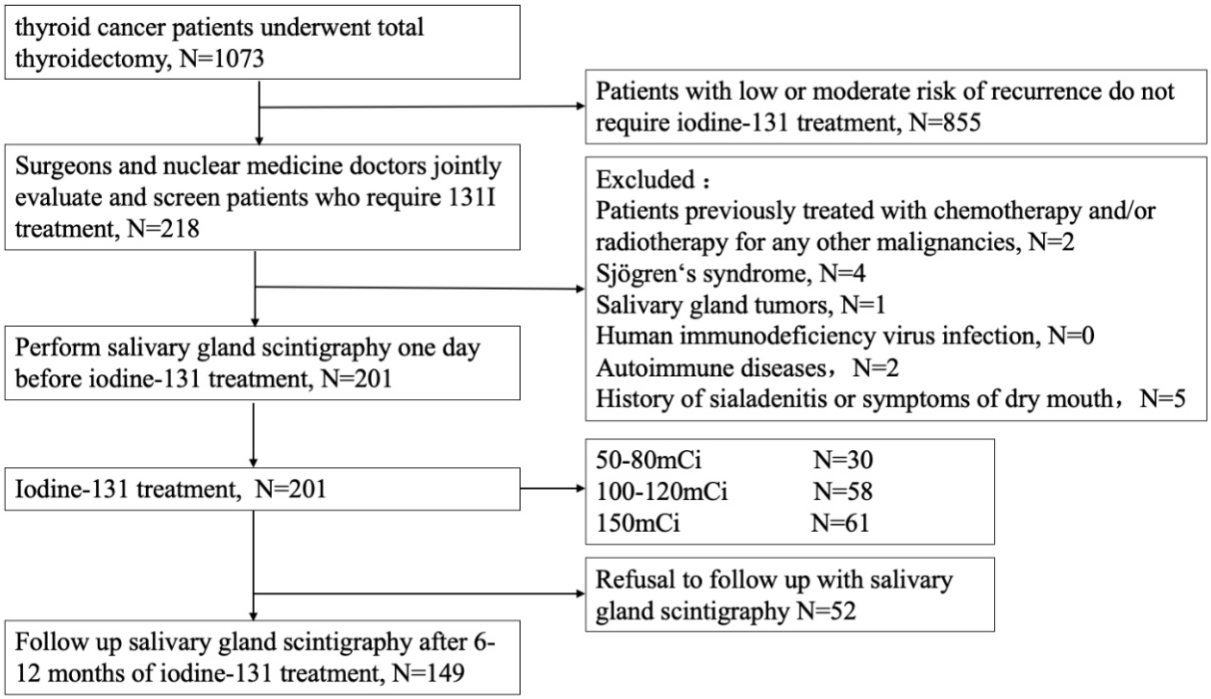


**Figure 1.** Shows the flowchart of population selection.

moderate decrease of 21%-30%, and severe decrease exceeding 30%. Each salivary gland was independently categorized into two groups based on its individual ΔUI% (≤20% or >20%) to assess differences in pre-treatment UI and EF values. This gland-specific approach ensures that variations in functional impairment are analyzed at the level of individual glands rather than aggregated across patients, allowing for a more detailed exploration of glandular responses to $^{131}$I therapy. Image analysis was independently conducted by two experienced nuclear medicine physicians who, blind to original clinical reports and patient information, re-evaluated all studies to reach a consensus on findings.

### Statistical analysis

Data were processed using SPSS 26.0. Normally distributed quantitative data are presented as mean±standard error of the mean (SEM), and comparisons between groups of continuous data adhering to a normal distribution were performed using analysis of variance (ANOVA). Non-normally distributed continuous data are expressed as median [interquartile range (Q1-Q3)] and analyzed using the Mann-Whitney U test, chi-square test, or Fisher's exact test as appropriate. The sensitivity and specificity of pre-UI in predicting moderate to severe functional impairment in salivary glands after $^{131}$I treatment was evaluated using receiver operating characteristic (ROC) curves. Due to salivary gland dysfunction can be influenced by multiple factors, we need consider factors such as age, sex, T stage, risk classification, dose of $^{131}$I therapy, pre-UI, and pre-EF to assess their associations with salivary gland dysfunction. However, in our analysis, these variables may lead to unreliable estimates, given the lack of sufficient variability across categories. Such as the TNM staging (N stage, M stage, and overall TNM stage), their highly skewed distribution in our cohort limited their statistical utility. To ensure robust and interpretable results, we focused on the factors with more balanced distributions. To assess the impact of follow-up duration on salivary gland dysfunction, a sensitivity analysis was conducted using linear regression, with the relationship between follow-up interval and ΔUI% analyzed and $R^2$ and P-values computed for statistical significance. P-value <0.05 was considered statistically significant.

## Results

### Characteristics and symptom evaluation of patients

Data from 596 salivary glands of 149 DTC patients who underwent RAI were fully collected. (107 females, 42 males; mean age 46.58±12.67 years; range, 21-74 years). Thirty patients (20.1%) received low-dose (1.85-2.96GBq), 57 patients (38.3%) received moderate dose (3.7-4.44GBq), and 61 patients (41.6%) received high-dose (5.55GBq) $^{131}$I treatment. The clinical monitoring range after $^{131}$I treatment is 6-12 months. During this period, no $^{131}$I therapy or head and neck radiotherapy was administered. The demographic characteristics of the patients are detailed in Table 1.

### Alterations in salivary gland functionality

Building upon the patient characteristics, salivary gland function was assessed before and after RAI treatment. Fol-

lowing RAI therapy, all salivary glands exhibited significant decreases in both UI and EF compared to pre-treatment levels (Table 2 and Figure 2). Chi-square analysis revealed a significant association between gland type and the degree of UI reduction, with submandibular glands more likely to experience reductions exceeding 30% compared to parotid glands. Furthermore, pairwise comparisons demonstrated that the >30% UI reduction category significantly differed from the ≤10%, 11%-20%, and 21%-30% reduction categories within each gland type (Table 3 and Figure 3). In contrast, the distribution of EF reductions did not differ significantly among the glands.

***Table 1.*** *Characteristics of patients.*

| Variables | Values |
|---|---|
| Total number of patients | 149 |
| Age (years) | 46.58±12.67 |
| Median/Range | 48 (21-74) |
| Sex (Percentage%) | |
| Male | 42 (28.2%) |
| Female | 107 (71.8%) |
| T stage (Percentage%) | |
| Tx | 2 (1.3%) |
| T1 | 69 (46.4%) |
| T2 | 26 (17.4%) |
| T3 | 29 (19.5%) |
| T4 | 23 (15.4%) |
| N stage (Percentage%) | |
| N0 | 5 (3.4%) |
| N1 | 140 (93.9%) |
| Nx | 4 (2.7%) |
| M stage (Percentage%) | |
| M0 | 149 (100%) |
| M1 | 0 (0%) |
| TNM Stage (Percentage%) | |
| I | 112 (75.2%) |
| II | 26 (17.4%) |
| III | 11 (7.4%) |
| Risk classification (Percentage%) | |
| Low | 14 (9.4%) |
| Intermediate | 75 (50.3%) |
| High | 60 (40.3%) |
| Dose of $^{131}$I therapy (GBq) (Percentage%) | |
| 1.85-2.96 | 30 (20.1%) |
| 3.7-4.44 | 57 (38.3%) |
| 5.55 | 62 (41.6%) |
| Median / Range | 3.7 (1.85-5.55) |

*Mean±SEM; Bq, Becquerel*

## Association between the dosage of administered $^{131}$I, salivary gland function and xerostomia severity

To further investigate the potential influence of radioactive iodine dosage on salivary gland function, we examined the association between the administered $^{131}$I dose and salivary gland outcomes. The 149 DTC patients were categorized into three dosage groups: low-dose (1.85-2.96 GBq, n=30, 20.1%), moderate-dose (3.7-4.44 GBq, n=57, 38.3%), and high-dose (5.55GBq, n=61, 41.6%). There were no significant differences in age or gender distribution among the dosage groups, and the distribution of disease stages approached statistical significance (P=0.068). Pre-treatment UI and EF did not differ significantly across dosage groups. Post-treatment analyses revealed no significant differences in UI, EF, ΔUI%, or ΔEF% among the different dosage groups (Table 4), and the distribution of ΔUI% and ΔEF% changes did not vary significantly across dosage levels (Table S1). These findings indicate that the administered $^{131}$I dose was not associated with variations in salivary gland function outcomes.

However, comparison of xerostomia severity scores across different $^{131}$I dose groups revealed that patients in the high-dose group experienced significantly higher rates of moderate to severe xerostomia (50.0%) compared to those in the low-dose (23.3%) and moderate-dose (31.6%) groups (Table 4 and Table S2). Additionally, the mean XI score was significantly higher in the high-dose group compared to the low-dose groups (Figure 4). These results suggest that higher doses of $^{131}$I are associated with more severe subjective symptoms of xerostomia, despite the lack of significant differences in objective salivary gland function indicators.

***Table 2.*** *Salivary gland function before and after RAI.*

| | Uptake Index | | | P value | Excretion Fraction | | | P value |
|---|---|---|---|---|---|---|---|---|
| | Before | After | ΔUI | | Before | After | ΔEF | |
| RPG | 2.35±0.76 | 1.71±0.51 | 0.64±0.79 | **<0.001** | 0.56±0.29 | 0.46±0.32 | 0.10±0.34 | **0.004** |
| LPG | 2.32±0.69 | 1.74±0.51 | 0.57±0.72 | **<0.001** | 0.56±0.29 | 0.45±0.32 | 0.11±0.28 | **0.001** |
| RSMG | 1.32±0.63 | 0.81±0.31 | 0.51±0.50 | **<0.001** | 0.39±0.29 | 0.35±0.24 | 0.05±0.31 | **0.038** |
| LSMG | 1.34±0.66 | 0.83±0.31 | 0.51±0.52 | **<0.001** | 0.37±0.41 | 0.33±0.24 | 0.04±0.39 | **0.031** |

*Mean±SEM; Group comparisons were conducted using the Mann-Whitney U test. The statistically significant P values are highlighted in bold. UI, Uptake Index; EF, Excretion Fraction; RPG, right parotid gland; LPG, left parotid gland; RSMG, right submandibular gland; LSMG, left submandibular gland.*

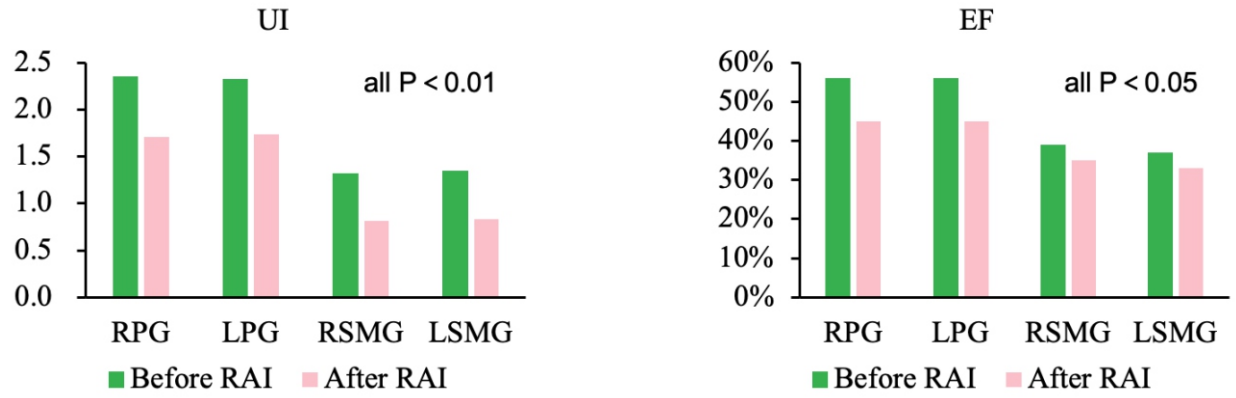


**Figure 2.** Salivary gland function before and after RAI.

***Table 3.*** *Distribution of salivary gland dysfunction by degree of reduction in ΔUI% and ΔEF after RAI (N=149).*

| Parameter | ≤10% decrease | 11%-20% decrease | 21%-30% decrease | >30% decrease | P value |
|---|---|---|---|---|---|
| ΔUI% | | | | | <0.001 |
| RPG (N) | 50a | 20a | 29a | 50b | |
| LPG (N) | 53a | 20a,b | 20a,b | 56b | |
| RSMG (N) | 32a | 13a,b | 20a,b | 84b | |
| LSMG (N) | 34a | 14a,b | 12a | 89b | |
| ΔEF | | | | | 0.584 |
| RPG (N) | 71 | 17 | 13 | 48 | |
| LPG (N) | 63 | 22 | 15 | 49 | |
| RSMG (N) | 72 | 15 | 6 | 56 | |
| LSMG (N) | 68 | 19 | 9 | 53 | |

*UI, Uptake Index; EF, Excretion Fraction; RPG, right parotid gland; LPG, left parotid gland; RSMG, right submandibular gland; LSMG, left submandibular gland. Group comparisons were conducted using the chi-square test. The statistically significant P values are highlighted in bold. P values represent the statistical significance of differences across all subgroups (≤10%, 11%-20%, 21%-30%, >30%) within each salivary gland. Groups marked with the same letter (e.g., a) are not significantly different from each other, whereas groups with different letters (e.g., a and b) indicate statistically significant differences (P < 0.05) in the pairwise comparisons.*

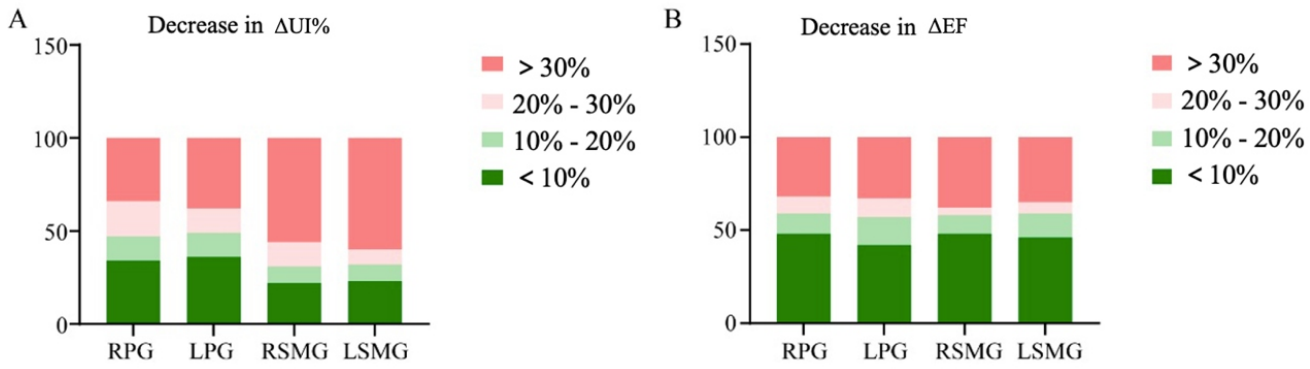


**Figure 3.** Percentage decrease in thyroid uptake and excretion after $^{131}$I therapy. A) Percentage decrease in thyroid uptake. B) Percentage decrease in thyroid excretion. Different colors indicate different change ranges: dark green represents no decrease or a decrease of ≤ 10%, light green indicates a decrease of 11% to 20%, light pink indicates a decrease of 20% to 30%, and dark pink indicates a decrease of >30%.

***Table 4.*** *Comparison of salivary gland function in different dose groups of $^{131}$I.*

| | Dose of $^{131}$I therapy (GBq) | | | P value |
|---|---|---|---|---|
| | (1.85-2.96) | (3.7-4.44) | (5.55) | |
| Sex | | | | 0.353[a] |
| Male | 6 (20.0%) | 15 (26.3%) | 21 (33.9%) | |
| Female | 24 (80.0%) | 42 (73.7%) | 41 (66.1%) | |
| disease stage | | | | 0.068[b] |
| I | 27 (90.0%) | 44 (77.2%) | 41 (66.1%) | |
| II | 3 (10.0%) | 11 (19.3%) | 13 (21.0%) | |
| III | 0 (0.0%) | 2 (3.5%) | 8 (12.9%) | |
| xerostomia inventory | | | | **0.015**[a] |
| No to mild xerostomia | 23(76.7%) | 39(68.4%) | 29(46.8%) | |
| Moderate to severe xerostomia | 7(23.3%) | 18(31.6%) | 31(50.0%) | |
| Age (years) | 46.33±11.33 | 46.28±12.67 | 46.98±13.45 | 0.931[a] |
| Pre-RPG-UI | 2.38±0.86 | 2.37±0.75 | 2.33±0.72 | 0.948 [c] |
| Pre-LPG-UI | 2.41±0.73 | 2.32±0.81 | 2.27±0.55 | 0.682 [c] |
| Pre-RSMG-UI | 1.48±0.62 | 1.28±0.64 | 1.29±0.62 | 0.248 [c] |
| Pre-LSMG-UI | 1.45±0.61 | 1.30±0.69 | 1.32±0.64 | 0.309 [c] |
| Pre-RPG-EF | 0.51±0.33 | 0.59±0.25 | 0.56±0.31 | 0.595 [c] |

*(continued)*

| | | | | |
|---|---|---|---|---|
| Pre-LPG-EF | 0.57±0.27 | 0.58±0.29 | 0.54±0.30 | 0.534 [c] |
| Pre-RSMG-EF | 0.40±0.20 | 0.37±0.37 | 0.41±0.23 | 0.737 [c] |
| Pre-LSMG-EF | 0.44±0.19 | 0.33±0.62 | 0.38±0.21 | 0.490 [c] |
| Post-RPG-UI | 1.88±0.62 | 1.69±0.42 | 1.65±0.52 | 0.167 [c] |
| Post-LPG-UI | 1.84±0.51 | 1.72±0.50 | 1.72±0.54 | 0.391 [c] |
| Post-RSMG-UI | 0.87±0.31 | 0.80±0.30 | 0.80±0.32 | 0.516 [c] |
| Post-LSMG-UI | 0.80±0.23 | 0.82±0.32 | 0.85±0.34 | 0.868 [c] |
| Post-RPG-EF | 0.52±0.30 | 0.50±0.28 | 0.41±0.37 | 0.368 [c] |
| Post-LPG-EF | 0.47±0.35 | 0.46±0.28 | 0.42±0.34 | 0.730 [c] |
| Post-RSMG-EF | 0.37±0.20 | 0.34±0.20 | 0.34±0.28 | 0.678 [c] |
| Post-LSMG-EF | 0.38±0.26 | 0.33±0.18 | 0.32±0.27 | 0.478 [c] |
| RPG-ΔUI% | 0.15±0.25 | 0.23±0.25 | 0.24±0.26 | 0.290 [c] |
| LPG-ΔUI% | 0.19±0.25 | 0.21±0.23 | 0.21±0.27 | 0.893 [c] |
| RSMG-ΔUI% | 0.35±0.24 | 0.30±0.26 | 0.32±0.22 | 0.408 [c] |
| LSMG-ΔUI% | 0.38±0.22 | 0.28±0.27 | 0.30±0.23 | 0.144 [c] |
| RPG-ΔEF | 0.00±0.31 | 0.10±0.33 | 0.15±0.35 | 0.195 [c] |
| LPG-ΔEF | 0.09±0.27 | 0.12±0.31 | 0.12±0.26 | 0.926 [c] |
| RSMG-ΔEF | 0.02±0.19 | 0.03±0.43 | 0.08±0.22 | 0.464 [c] |
| LSMG-ΔEF | 0.06±0.22 | 0.01±0.56 | 0.06±0.23 | 0.964 [c] |
| XI score | 19.57±4.88 | 20.54±4.75 | 23.29±6.57 | **0.008** [c] |

*Pre-UI, pre-treatment Uptake Index; Pre-EF, pre-treatment Excretion Fraction; RPG, right parotid gland; LPG, left parotid gland; RSMG, right submandibular gland; LSMG, left submandibular gland; ΔUI, changes in Uptake Index; ΔEF, changes in Excretion Fraction; XI score, xerostomia inventory score; Mean ± SEM; a: Fisher's exact test was employed to compare the groups. b: The chi-square test was employed to compare the groups, c: The Kruskal-Wallis H test was utilized to compare the groups, and the statistically significant P values are highlighted in bold.*

***Table S1.*** *Distribution of ΔUI% and ΔEF changes across different $^{131}$I therapy doses in salivary glands.*

| Salivary Gland | Metric | Change Category | 1.85-2.96GBq | 3.7-4.44GBq | 5.55GBq | P value |
|---|---|---|---|---|---|---|
| RPG | ΔUI% | -10%< | 43.3 | 31.6 | 30.6 | 0.191 |
| | | -20% to - 11% | 10.0 | 15.8 | 12.9 | |
| | | -30% to - 21% | 23.3 | 19.3 | 17.7 | |
| | | <-30% | 23.3 | 33.3 | 38.7 | |
| | ΔEF | -10%< | 16.7 | 26.3 | 22.6 | 0.100 |
| | | -20% to - 11% | 3.3 | 14.0 | 8.1 | |
| | | -30% to - 21% | 13.3 | 5.3 | 8.1 | |
| | | <-30% | 66.7 | 54.4 | 61.3 | |
| LPG | ΔUI% | -10%< | 36.7 | 31.6 | 38.7 | 0.838 |
| | | -20% to - 11% | 13.3 | 19.3 | 8.1 | |
| | | -30% to - 21% | 16.7 | 12.3 | 12.9 | |
| | | <-30% | 33.3 | 36.8 | 40.3 | |
| | ΔEF | -10%< | 46.7 | 40.4 | 41.9 | 0.972 |
| | | -20% to - 11% | 6.7 | 15.8 | 17.7 | |
| | | -30% to - 21% | 13.3 | 10.5 | 8.1 | |
| | | <-30% | 33.3 | 33.3 | 32.3 | |
| RSMG | ΔUI% | -10%< | 23.3 | 22.8 | 19.4 | 0.919 |
| | | -20% to - 11% | 3.3 | 12.3 | 8.1 | |
| | | -30% to - 21% | 10.0 | 14.0 | 14.5 | |
| | | <-30% | 63.3 | 50.9 | 58.1 | |
| | ΔEF | -10%< | 56.7 | 43.9 | 48.4 | 0.794 |
| | | -20% to - 11% | 10.0 | 5.3 | 14.5 | |
| | | -30% to - 21% | 0.00 | 10.5 | 0.00 | |
| | | <-30% | 33.3 | 40.4 | 37.1 | |

*(continued)*

| | | | | | | |
|---|---|---|---|---|---|---|
| LSMG | ΔUI% | -10%< | 16.7 | 26.3 | 22.6 | 0.789 |
| | | -20% to - 11% | 3.3 | 14.0 | 8.1 | |
| | | -30% to - 21% | 13.3 | 5.3 | 8.1 | |
| | | <-30% | 66.7 | 54.4 | 61.3 | |
| | ΔEF | -10%< | 53.3 | 45.6 | 41.9 | 0.576 |
| | | -20% to - 11% | 10.0 | 8.8 | 17.7 | |
| | | -30% to - 21% | 6.7 | 5.3 | 6.5 | |
| | | <-30% | 30.0 | 40.4 | 33.9 | |

*RPG, right parotid gland; LPG, left parotid gland; RSMG, right submandibular gland; LSMG, left submandibular gland. Categories of change (≤-10%, -20% to -11%, -30% to -21%, and <-30%) represent the magnitude of functional decline. P-values indicate whether the observed differences in functional change across different $^{131}$I therapy doses (1.85-2.96GBq, 3.7-4.44GBq and 5.55GBq) are statistically significant.*

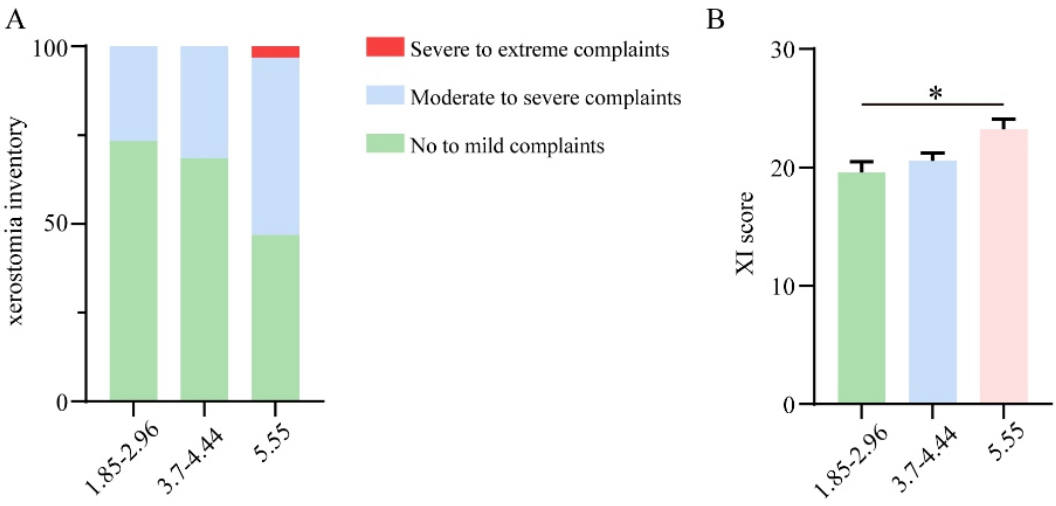


**Figure 4.** Comparison of xerostomia complaints and XI scores among DTC patients receiving different doses of $^{131}$I therapy. A) Distribution of xerostomia complaints: no to mild (green), moderate to severe (blue), and severe to extreme (red). B) Mean XI scores across dosage groups (Kruskal-Wallis H test). *P<0.05.

***Table S2.*** *Comparison of xerostomia severity scores across different $^{131}$I dose groups.*

| | Dose of $^{131}$I therapy (GBq) | | | P value |
|---|---|---|---|---|
| | (1.85-2.96) | (3.7-4.44) | (5.55) | |
| Xerostomia inventory | | | | 0.015[d] |
| No to mild xerostomia | 23 (76.7%)a | 39 (68.4%)a | 29 (46.8%)b | |
| Moderate to severe xerostomia | 7 (23.3%)a | 18 (31.6%)a | 31 (50.0%)b | |

*Group comparisons for xerostomia severity were conducted using the chi-square test, with superscripts (e.g., a, b) indicating pairwise comparisons. Groups with the same letter are not significantly different, while different letters indicate statistical significance (P < 0.05). Statistically significant values are highlighted in bold.*

### Predictive value of Pre-UI for moderate to severe damage to salivary gland function

To assess the predictive potential of the pre-treatment uptake index (Pre-UI) for moderate to severe salivary gland dysfunction, each gland was categorized based on its percentage change in uptake index (ΔUI%) into two groups: ≤20% decrease and >20% decrease. The ≤20% decrease category represents mild or no dysfunction, whereas the >20% decrease category indicates moderate to severe dysfunction. Glands with ΔUI% > 20% exhibited significantly higher Pre-UI values compared to those with ΔUI% ≤ 20% across all gland types (Table 5). In contrast, pre-treatment excretion fraction (Pre-EF) did not consistently differ between the two ΔUI% groups across all glands. Univariate analyses confirmed that Pre-UI is a significant predictor of moderate to severe salivary gland dysfunction in all glands (Table S3-6).

***Table 5.*** *Comparison of Pre-UI in salivary glands between and ΔUI% ≤ 20% and ΔUI%>20% after RAI.*

| | 20% | ΔUI%＞20% | P value |
|---|---|---|---|
| Pre-RPG-UI | 1.92±0.54 | 2.53±0.76 | **<0.001** |
| Pre-LPG-UI | 2.10±0.60 | 2.41±0.71 | **0.007** |
| Pre-RSMG-UI | 1.07±0.65 | 1.39±0.65 | **0.002** |
| Pre-LSMG-UI | 1.07±0.43 | 1.40±0.66 | **<0.001** |
| Pre-RPG-EF | 0.57±0.27 | 0.56±0.30 | 0.990 |
| Pre-LPG-EF | 0.57±0.30 | 0.56±0.29 | 0.837 |
| Pre-RSMG-EF | 0.37±0.17 | 0.38±0.45 | 0.657 |
| Pre-LSMG-EF | 0.39±0.20 | 0.39±0.31 | 0.536 |

*Pre-RPG-UI, pre-treatment right parotid gland uptake; Pre-RPG-EF, pre-treatment right parotid gland excretion; Pre-LPG-UI, pre-treatment left parotid gland uptake; Pre-LPG-EF, pre-treatment left parotid gland excretion; Pre- RSMG -UI, pre-treatment right submandibular gland uptake; Pre-RSMG-EF, pre-treatment right submandibular gland excretion; Pre-LSMG-UI, pre-treatment left submandibular gland uptake; Pre- LSMG-EF, pre-treatment left submandibular gland excretion; ΔUI, changes in Uptake Index; Mean ± SEM. Group comparisons were conducted using the Mann-Whitney U test. The statistically significant P values are highlighted in bold.*

***Table S3.*** *Univariate analysis of risk factors associated with RPG.*

| | Univariate | | |
|---|---|---|---|
| **Variables** | **OR** | **95% CI** | **P value** |
| Age | 0.990 | 0.954-1.026 | 0.572 |
| Sex | 0.714 | 0.279-1.831 | 0.483 |
| T stage | | | 0.443 |
| T1 | 0.992 | 0.013-74.000 | 0.997 |
| T2 | 0.872 | 0.113-6.762 | 0.896 |
| T3 | 2.615 | 0.255-26.777 | 0.418 |
| T4 | 0.535 | 0.110-2.612 | 0.440 |
| Risk classification | | | 0.385 |

*(continued)*

| | | | |
|---|---|---|---|
| Intermediate | 0.204 | 0.021-1.973 | 0.170 |
| High | 0.471 | 0.084-2.641 | 0.392 |
| Dose of $^{131}$I therapy | | | 0.540 |
| 3.7-4.44 | 0.432 | 0.092-1.998 | 0.283 |
| 5.55 | 0.792 | 0.247-2.543 | 0.695 |
| Pre-RPG-UI | 5.884 | 2.651-13.061 | 0.000 |
| Pre-RPG-EF | 0.545 | 0.120-2.481 | 0.433 |

*Pre-RPG-UI, pre-treatment right parotid gland uptake; Pre-RPG-EF, pre-treatment right parotid gland excretion.*

***Table S4.*** *Univariate analysis of risk factors associated with LPG.*

| | Univariate | | |
|---|---|---|---|
| **Variables** | **OR** | **95% CI** | **P value** |
| Age | 0.989 | 0.957-1.023 | 0.529 |
| Sex | 0.491 | 0.213-1.135 | 0.096 |
| T stage | | | 0.330 |
| T1 | 0.197 | 0.007-5.839 | 0.348 |
| T2 | 0.223 | 0.039-1.277 | 0.092 |
| T3 | 0.293 | 0.043-2.023 | 0.213 |
| T4 | 0.213 | 0.049-0.934 | 0.040 |
| Risk classification | | | 0.891 |
| Intermediate | 1.046 | 0.122-8.956 | 0.967 |
| High | 0.772 | 0.188-3.164 | 0.720 |
| Dose of $^{131}$I therapy | | | 0.469 |
| 3.7-4.44 | 2.419 | 0.552-10.591 | 0.241 |
| 5.55 | 1.707 | 0.572-5.093 | 0.338 |
| Pre-LPG-UI | 2.571 | 1.277-5.173 | 0.008 |
| Pre-LPG-EF | 0.928 | 0.226-3.810 | 0.917 |

*Pre-LPG-UI, pre-treatment left parotid gland uptake; Pre-LPG-EF, pre-treatment left parotid gland excretion*

Additionally, to ensure that the follow-up interval did not confound the observed associations, a sensitivity analysis using linear regression was performed. This analysis assessed the relationship between the follow-up interval (treated as a continuous variable) and ΔUI% for each gland. The results indicated no significant associations between follow-up duration and ΔUI% across all glands with minimal $R^2$ values (Table S7). Receiver operating characteristic (ROC) curve analyses further demonstrated that Pre-UI effectively predicts moderate to severe salivary gland dysfunction. The Pre-RPG-UI achieved an area under the curve (AUC) of 0.866 with a cut-off value of 2.30, sensitivity of 79.7%, and specificity of 81.4% (Figure 5A). Similarly, the Pre-LPG-UI yielded an AUC of 0.793, a cut-off value of 2.13, sensitivity of 84.2%, and specificity of 67.1% (Figure 5B). The Pre-RSMG-UI demonstrated an AUC of 0.769, a cut-off value of 0.87, sensitivity of 84.9%, and specificity of 55.8% (Figure 5C). Lastly, the Pre-LSMG-UI showed an AUC of 0.816, a cut-off value of 0.86, sensitivity of 90.1%, and specificity of 64.6% (Figure 5D). These ROC analyses confirm that Pre-UI is a reliable predictor of significant salivary gland dysfunction following $^{131}$I therapy.

***Table S5.*** *Univariate analysis of risk factors associated with RSMG.*

| | Univariate | | |
|---|---|---|---|
| **Variables** | **OR** | **95% CI** | **P value** |
| Age | 1.026 | 0.985-1.069 | 0.217 |
| Sex | 0.523 | 0.173-1.586 | 0.252 |
| T stage | | | 0.630 |
| T1 | 306205465.2 | 0.000 | 0.999 |
| T2 | 1.125 | 0.177-7.160 | 0.900 |
| T3 | 0.419 | 0.058-3.046 | 0.390 |
| T4 | 1.144 | 0.233-5.617 | 0.869 |
| Risk classification | | | 0.486 |
| Intermediate | 0.252 | 0.019-3.338 | 0.296 |
| High | 0.868 | 0.160-4.698 | 0.869 |
| Dose of $^{131}$I therapy | | | 0.561 |
| 1.85-2.96 | 2.020 | 0.322-12.667 | 0.453 |
| 3.7-4.44 | 2.007 | 0.538-7.495 | 0.300 |
| Pre-RSMG-UI | 3.552 | 1.220-10.340 | 0.020 |
| Pre-RSMG-EF | 0.834 | 0.127-5.462 | 0.850 |

*Pre-RSMG-UI, pre-treatment right submandibular gland uptake; Pre-RSMG-EF, pre-treatment right submandibular gland excretion*

***Table S6.*** *Univariate analysis of risk factors associated with LSMG.*

| | Univariate | | |
|---|---|---|---|
| **Variables** | **OR** | **95% CI** | **P value** |
| Age | 1.005 | 0.969-1.043 | 0.781 |
| Sex | 0.409 | 0.145-1.151 | 0.090 |
| T stage | | | 0.972 |
| T1 | 2405814504 | 0.000 | 0.999 |
| T2 | 1.201 | 0.215-6.712 | 0.835 |
| T3 | 1.051 | 0.154-7.155 | 0.959 |
| T4 | 1.645 | 0.381-7.098 | 0.505 |
| Risk classification | | | 0.472 |
| Intermediate | 0.217 | 0.019-2.504 | 0.221 |
| High | 0.564 | 0.115-2.777 | 0.482 |
| Dose of $^{131}$I therapy | | | 0.453 |
| 1.85-2.96 | 3.015 | 0.517-17.597 | 0.220 |
| 3.7-4.44 | 1.655 | 0.512-5.350 | 0.400 |
| Pre-LSMG-UI | 6.656 | 2.330-19.012 | 0.000 |
| Pre-LSMG-EF | 0.677 | 0.188-2.439 | 0.551 |

*Pre-LSMG-UI, pre-treatment left submandibular gland uptake; Pre- LSMG-EF, pre-treatment left submandibular gland excretion*

### Predictive value of Pre-UI for xerostomia severity

Building upon the predictive role of Pre-UI in salivary gland dysfunction, we investigated whether Pre-UI also predicts the severity of xerostomia symptoms. Based on XI scores, 38.9% (58/149) of patients experienced moderate to extreme xerostomia. Significant differences were observed between patients with no to mild xerostomia and those with moderate to extreme xerostomia in the Pre-UI of the right submandibular gland and left submandibular gland, as well as in the percentage change in uptake index of the right submandibular gland and left submandibular gland (Table 6). In contrast, there were no significant differences in the Pre-UI, ΔUI%, EF, or ΔEF% of the bilateral parotid glands between the two groups. Further analysis categorized salivary gland dysfunction and xerostomia severity for each gland type based on xerostomia severity (no to mild vs. moderate to extreme xerostomia). The results indicated that dysfunction in RPG, LPG, RSMG, and LSMG was not significantly associated with xerostomia severity (Table 7).

Univariate logistic regression analyses revealed that female sex and high-risk classification were significantly associated with increased severity of xerostomia. In contrast, other variables-including age, T stage, intermediate risk classification, dose of $^{131}$I therapy, and pre-treatment uptake indices-did not show significant associations with xerostomia severity (Table S8).

## Discussion

Salivary gland dysfunction is a common complication of $^{131}$I therapy after thyroidectomy in DTC patients [13]. This dysfunction is attributed to $^{131}$I retention within the salivary glands, driven by increased capillary permeability due to inflammatory responses and further exacerbated by inflammatory-induced ductal wall damage and luminal obstruction [15, 16]. Conservative measures such as adequate hydration, salivary stimulation, gland Massage, and the use of

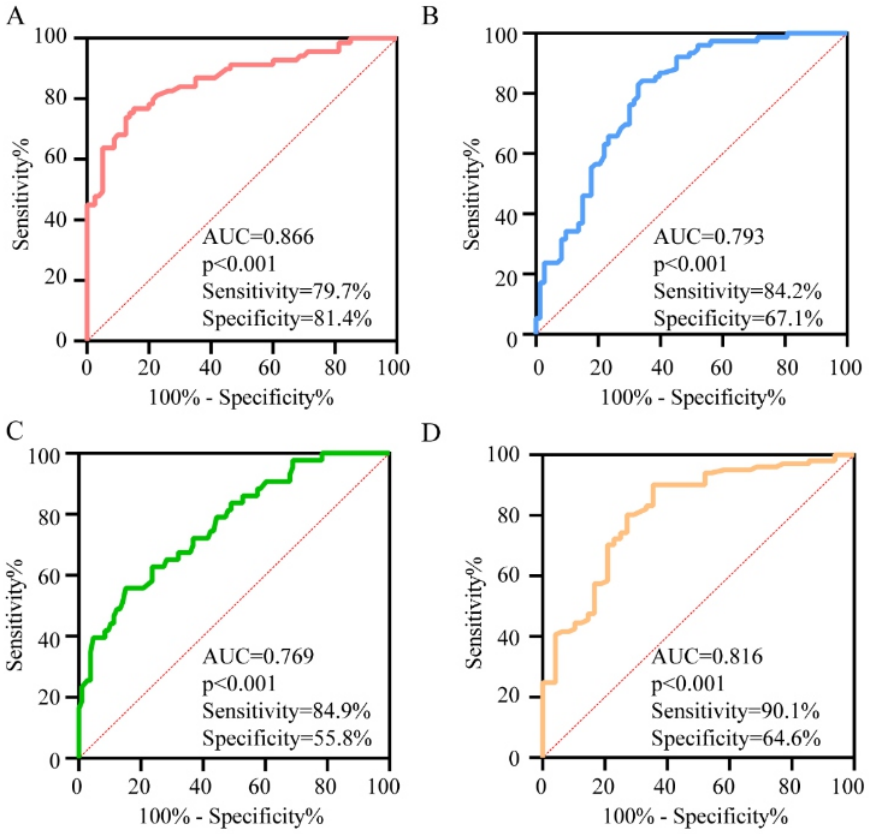


**Figure 5.** ROC curve analysis for predicting parotid gland dysfunction using pre-UI. A) ROC curve for Pre-RPG-UI in predicting RPG dysfunction. B) ROC curve for Pre-LPG-UI in predicting LPG dysfunction. C) ROC curve for Pre-RSMG-UI in predicting RSMG dysfunction. D) ROC curve for Pre-LSMG-UI in predicting LSMG dysfunction.

***Table S7**. Sensitivity analysis of follow-up interval on salivary gland dysfunction using linear regression.*

| Variables | $R^2$ | P value |
|---|---|---|
| RPG-ΔUI% | 0.001 | 0.734 |
| LPG-ΔUI% | 0.006 | 0.355 |
| RSMG-ΔUI% | 0.001 | 0.715 |
| LSMG-ΔUI% | 0.007 | 0.313 |

*RPG, right parotid gland; LPG, left parotid gland; RSMG, right submandibular gland; LSMG, left submandibular gland.*

NSAID, anticholinergics, or corticosteroid therapy generally alleviate these conditions [17]. However, in refractory cases, invasive methods such as saliva endoscopy treatment have limitations, particularly in patients with small ductal lumens [18]. Therefore, predicting salivary gland dysfunction is crucial for identifying patients who require stringent post-treatment surveillance and for minimizing the impact of dysfunction. Previous studies have utilized SGS to evaluate gland function post-$^{131}$I therapy in DTC patients, highlighting its non-invasive, convenient nature, capability to quantitatively or semi-quantitatively assess individual gland uptake and secretion functions with high repeatability [19, 20]. This study further demonstrates the potential of $^{99m}TcO_4^-$ SGS before treatment to predict salivary gland dysfunction caused by RAI therapy.

The salivary gland dysfunction incidence rate observed in this study is slightly higher than previously reported [14, 21], potentially due to differences in follow-up durations. For example, Solans et al. (2001) followed-up 79 patients who received $^{131}$I therapy, and SGS showed that 50.6% (40/79) of

***Table 6.*** *Comparison of functional parameters between no to mild and moderate to extreme xerostomia.*

| | Xerostomia Inventory | | P value |
|---|---|---|---|
| | No to mild xerostomia | Moderate to extreme xerostomia | |
| Pre-RPG-UI | 2.29±0.08 | 2.46±0.10 | 0.184 |
| Pre-LPG-UI | 2.26±0.10 | 2.40±0.10 | 0.245 |
| Pre-RSMG-UI | 1.18±0.05 | 1.56±0.09 | **<0.001** |
| Pre-LSMG-UI | 1.21±0.05 | 1.55±0.10 | **0.006** |
| Pre-RPG-EF | 0.57±0.03 | 0.54±0.04 | 0.663 |
| Pre-LPG- EF | 0.57±0.03 | 0.54±0.04 | 0.344 |
| Pre-RSMG- EF | 0.40±0.03 | 0.38±0.03 | 0.591 |
| Pre-LSMG- EF | 0.37±0.05 | 0.38±0.03 | 0.214 |
| RPG-ΔUI% | 0.20±0.03 | 0.26±0.03 | 0.070 |
| LPG-ΔUI% | 0.18±0.03 | 0.24±0.02 | 0.080 |
| RSMG-ΔUI% | 0.27±0.02 | 0.40±0.03 | **0.004** |
| LSMG-ΔUI% | 0.27±0.02 | 0.37±0.03 | **0.012** |
| RPG-ΔEF | 0.10±0.04 | 0.11±0.05 | 0.483 |
| LPG-ΔEF | 0.12±0.03 | 0.10±0.04 | 0.898 |
| RSMG-ΔEF | 0.04±0.04 | 0.06±0.03 | 0.586 |
| LSMG-ΔEF | 0.03±0.05 | 0.06±0.03 | 0.994 |

*Mean ± SEM. Group comparisons were conducted using the Mann-Whitney U test. The statistically significant P values are highlighted in bold.*

the patients had changes in glandular function in the first year after $^{131}$I treatment. Only 13.9% (11/79) of the patients had changes in glandular function in the second year [22]. Jeong et al. (2013) followed up about 5 years after RAI ablation[14], and the results showed that only 21.3% of the glands showed a decrease in UI, and 20.3% showed a decrease in glandular EF.

Thyroid remnants are capable of absorbing high radiation doses due to prolonged iodine uptake, whereas salivary glands, lacking iodine organification, can excrete absorbed $^{131}$I, particularly under conditions such as acid stimulation or mastication. This excretion process is independent of thyrotropin levels or thyroid function [14]. Differences in NIS-mediated uptake and secretion determine the retention of $^{131}$I in salivary glands. This indicates that patients with stronger uptake ability have higher radiation doses, leading to more severe damage [23, 24]. Previous studies have reported that even with relatively low levels of $^{131}$I administered, salivary gland damage can still be observed [11, 25]. This study evaluated salivary gland function across different iodine treatment dose groups, revealing no significant differences in Pre-UI and Pre-EF. Similarly, no statistical differences were found in Post-UI and Post-EF or the change in ΔUI% or ΔEF across different dosage groups. Consistent with Son et al. (2019) [3], their logistic reg-

***Table 7.*** *Distribution of salivary gland dysfunction and xerostomia severity across different salivary glands.*

| Injury site | Xerostomia Inventory | | P value |
|---|---|---|---|
| | No to mild xerostomia (90) | Moderate to extreme xerostomia (59) | |
| RPG | 62 | 44 | 0.465 |
| LPG | 63 | 43 | 0.854 |
| RSMG | 74 | 51 | 0.649 |
| LSMG | 70 | 47 | 0.841 |

*RPG, right parotid gland; LPG, left parotid gland; RSMG, right submandibular gland; LSMG, left submandibular gland.*

***Table S8.*** *Univariate logistic regression analysis of factors associated with xerostomia severity.*

| Variables | Univariate | | P value |
|---|---|---|---|
| | OR | 95% CI | |
| Age | 0.992 | 0.962-1.024 | 0.629 |
| Sex | 2.747 | 1.080-6.985 | 0.034 |
| T stage | | | 0.844 |
| T1 | 8336364752 | 0.000 | 0.999 |
| T2 | 2.020 | 0.451-9.044 | 0.358 |
| T3 | 2.720 | 0.514-14.395 | 0.239 |
| T4 | 1.469 | 0.445-4.845 | 0.528 |
| Risk classification | | | 0.093 |
| Intermediate | 0.395 | 0.048-3.249 | 0.388 |
| High | 0.211 | 0.050-0.898 | 0.035 |
| Dose of $^{131}$I therapy | | | 0.391 |
| 1.85-2.96 | 0.359 | 0.083-1.557 | 0.171 |
| 3.7-4.44 | 0.667 | 0.238-1.870 | 0.442 |
| Pre-RPG-UI | 0.957 | 0.518-1.765 | 0.887 |
| Pre-LPG- UI | 1.214 | 0.625-2.357 | 0.567 |
| Pre-RSMG-UI | 2.210 | 0.731-6.678 | 0.160 |
| Pre-LSMG- UI | 1.270 | 0.443-3.636 | 0.656 |

*Pre-RPG-UI, pre-treatment right parotid gland uptake; Pre-LPG-UI, pre-treatment left paro-tid gland uptake; Pre-RSMG-UI, pre-treatment right submandibular gland uptake; Pre-LSMG-UI, pre-treatment left submandibular gland uptake.*

ression analysis revealed that parotid dysfunction 8 months after treatment was not associated with the $^{131}$I dose (OR= 0.9959; P=0.536). Furthermore, no statistically significant differences were observed in the incidence of parotid dysfunction between varying doses of $^{131}$I, as indicated by the $\chi^2$ test (P=0.658) and the $\chi^2$ test for trend (P=0.554). They indicated that variables other than dosage contribute to salivary gland dysfunction, such as individual glandular uptake capacity, retention time, gland size, radiosensitivity, and post-therapeutic protective strategies. This study observed a strong correlation between pre-treatment uptake levels and post-treatment decreases, underscoring the critical role of glandular uptake in the mechanism of salivary gland damage. Lee et al. (2013) also found that the initial uptake intensity of $^{131}$I in salivary glands was associated with the risk of glandular damage rather than the clearance rate of $^{131}$I, which aligns with our research findings [26]. In this study, Pre-UI was used to predict moderate to severe salivary gland dysfunction (ΔUI%>20%) after $^{131}$I treatment, and the predictive sensitivity of RPG, LPG, RSMG, and LSMG reached 79.7%, 84.2%, 84.9%, and 90.1%, respectively.

In our study, 6.5% (39/596) of glands exhibited a change from a Pre-EF > 0 to a Post-EF <0, indicating an increase in $^{99m}TcO_4^-$ accumulation following acid stimulation, a phenomenon typically induced by $^{131}$I therapy [27]. In human salivary glands, the NIS is predominantly expressed in ductal cells, not in acinar cells [24]. Iodine-131 concentrates in the ductal system, where beta radiation can cause damage leading to ductal narrowing due to luminal fragmentation, potentially resulting in ductal obstruction and subsequent damage [16]. This obstruction may cause retention of secreted saliva within the ducts, triggering salivary gland inflammation. Technetium-99m-pertechnetate uptake and washout reflect the functions of the parenchyma and ducts, respectively [28]. Since radiation primarily damages ductal walls, leading to subsequent vascular fibrosis, salivary excretion could be impaired earlier and more severely than parenchymal uptake at early stages [23]. Previous research suggested the parotid gland is more vulnerable to $^{131}$I therapy due to higher concentrations of radiation-sensitive serous cells, unlike the submandibular gland, which contains both mucous and serous cells, possibly offering some radiation protection [14]. Contrary to these findings, this study observed more pronounced uptake function impairment in the submandibular glands, challenging previous conclusions. This difference may be linked to the timing of iodine intake and subsequent activities, including ingestion time, hydration, and spontaneous glandular secretion. In this study, almost all patients always ingested $^{131}$I at 4pm and began resting around 10pm; the submandibular gland is responsible for the majority of saliva secretion during rest, might accumulate higher radiation doses due to prolonged periods without stimulation, leading to increased radiation absorption [3, 24, 29]. Jo KS et al. (2014) also found that the submandibular gland accumulated more radioactive $^{131}$I after treatment, but the reason is uncertain [23]. The absorbed radiation dose to an organ is directly related to the amount taken up by the organ and the duration of radiation that remains in that organ but is inversely related to the volume of the organ [30]. Therefore, higher NIS expression and the smaller size of the submandibular gland could result in greater radiation exposure than the parotid gland. In addition, the measurement of submandibular gland uptake is easily affected by residual uptake from the strong thyroid gland, which may affect the results of quantitative analysis [26].

In terms of xerostomia, 38.9% (58/149) of patients in this study experienced moderate to extreme xerostomia, a percentage similar to that reported in the literature [31, 32]. Significant differences were observed in xerostomia complaints (P=0.015) and XI scores (P=0.008) among different $^{131}$I treatment dose groups, indicating that higher doses of $^{131}$I were associated with more severe xerostomia. Hollingsworth B et al. (2016) reported that the mean cumulative $^{131}$I activity was (1.702GBq) higher in patients with xerostomia than in patients without xerostomia, and the mean first administration $^{131}$I activity was (0.777GBq) higher than in patients without xerostomia [33]. These findings suggest that while general characteristics remain similar, higher doses may lead to increased dry mouth symptoms, highlighting the need for further research to manage these side effects effectively. Notably, there were significant differences in the Pre-UI and ΔUI% of bilateral submandibular glands between patients without mild dry mouth symptoms and those with moderate to severe dry mouth symptoms, suggesting that the uptake function of bilateral submandibular glands before treatment and the degree of their damage may have a significant impact on dry mouth symptoms. This is similar to previous reports that dysfunction of the submandibular gland might be closely related to dry mouth symptoms [14, 34]. In our study, the pre-treatment uptake function of the submandibular gland was an important influencing factor for xerostomia after $^{131}$I treatment. The higher the Pre-UI value, the higher the incidence of xerostomia after treatment. This may be related to the significant decrease of submandibular gland uptake function caused by the increase of $^{131}$I dose in the gland due to high uptake function. Although most patients with submandibular and parotid gland dysfunction report dry mouth, there are also a few patients who do not have symptoms, and the absence of apparent dry mouth symptoms in these patients may result from the compensatory function of other salivary glands [35]. About 90% of saliva is produced by the three pairs of significant salivary glands (parotid gland, submandibular gland, and sublingual gland). The remaining 10% is produced by hundreds of minor salivary glands widely scattered throughout the oral mucosa [36]. The small (minor) salivary glands produce 70% of the mucin in saliva, crucial for maintaining mucosal lubrication and oral comfort. The sublingual gland and submandibular gland produce the remaining mucin. Evidence shows that although patients receiving radiation therapy for laryngeal cancer have radiation doses exceeding the tolerated dose to their parotid and submandibular glands, their complaints about dry mouth are lower because the function of small oral glands is protected. In comparison, there are more complaints about dry mouth after radiation therapy for oropharyngeal and nasopharyngeal cancer [37]. Future studies should include more sophisticated analyses and control for confounding variables to understand these relationships better. The results also indicated that the lack of a significant change in EF in the submandibular glands bet-

ween the groups with and without xerostomia might appear to be inconsistent with the observed association between higher UI and increased risk of xerostomia. The reason may be the following: (1) Differentiating uptake and secretion functions: While uptake (UI) and secretion (EF) are closely related, they assess different aspects of salivary gland function. A reduction in uptake capacity may lead to glandular dysfunction, even if secretion remains relatively unaffected. Submandibular glands with higher pre-treatment UI values are more vulnerable to radiation-induced damage, which primarily affects their ability to accumulate iodine (i.e., impaired uptake). However, this dysfunction may not immediately result in a detectable decline in secretion (EF), which is more directly linked to the gland's ability to release saliva in response to stimulation. In this case, a decline in uptake may be an early sign of dysfunction, preceding any noticeable changes in secretion; (2) Impact of radiation on glandular tissue: The impairment in UI suggests that the submandibular glands are absorbing more $^{131}I$, which can cause radiation-induced damage to glandular tissue, particularly the ductal system. This damage, often characterized by ductal narrowing and potential blockages, may not be reflected in EF, which primarily measures the gland's secretion capacity under stimulation. Therefore, even though the ability to concentrate on iodine is reduced, this does not necessarily translate into an immediate or measurable decline in saliva secretion, especially in the early post-treatment phase. (3) Threshold effects and compensatory mechanisms: Xerostomia could be related to a threshold effect, where even small or subclinical impairments in glandular function, such as reduced uptake, are sufficient to trigger dry mouth symptoms, even if secretion remains relatively unaffected. Furthermore, other salivary glands may compensate for the loss of function in the submandibular glands, which could help alleviate the subjective experience of xerostomia in the short term. This compensatory effect might mask the early stages of secretion dysfunction, even when there are significant changes in uptake function.

There are certain limitations to the present study. Firstly, in our study, individual gland evaluation is used, because different salivary glands have distinct functional properties, and in clinical practice, there is currently no universally defined metric that combines the function of all salivary glands. Future study could analyze an aggregate metric representing overall salivary gland function may provide a more holistic perspective Secondly, patients with higher pre-therapy uptake index (Pre-UI) values exhibit greater declines in uptake function (ΔUI%) post-therapy. This outcome may be expected, as glands with higher initial uptake are inherently more likely to experience larger proportional decreases. However, we argue that this does not undermine the predictive utility of Pre-UI. In fact, it reinforces its importance as a tool for identifying glands at higher risk of significant damage. By recognizing glands with stronger baseline uptake, clinicians can better stratify risk and implement more targeted interventions to mitigate the impact of RAI therapy. Therefore, while the relationship between Pre-UI and ΔUI% may reflect a natural tendency, it remains a valuable predictor for anticipating salivary gland dysfunction and guiding patient management. Thirdly, the study was conducted at a single center with a small patient cohort, which may introduce selection bias and limit the generalizability of the findings. In our analysis, we conducted univariate regression analyses for each salivary gland, given that only Pre-UI was identified as a significant factor in the univariate analyses, we did not proceed with multivariate logistic regression. To further explore the factors influencing ΔUI% and salivary gland dysfunction, performing a multivariate logistic regression analysis may be better, future study may be needing larger samples and multiple centersto conduct a more stability analysis. Fourthly, the overall low administered radioiodine activities in our cohort might explain the absence of a clear activity-dependent relationship in salivary gland impairment. Finally, the present study did not observe an activity- dependent salivary gland impairment, and the overall low administered activity. Sialagogues stimulate salivary flow, potentially enhancing iodine retention in the glands during the critical period of high radiation exposure, thereby increasing the absorbed dose and exacerbating glandular damage. However, in our study, the timing and frequency of sialagogue use were not systematically recorded, limiting our ability to directly evaluate its impact. This may play a role, it does not fully account for the observed widespread functional decline across all salivary glands. The frequent decline in gland function is likely a result of the interplay between higher baseline uptake capacity and cumulative radiation effects, potentially amplified by the timing of sialagogue use.

*In conclusion*, our finding that the Pre-UI of the salivary glands correlates with a decrease in ΔUI% after RAI therapy in DTC patients is of clinical significance. This finding indicates that pre-treatment $^{99m}TcO_4^-$ SGS can be a predictive tool for identifying patients at risk of severe salivary gland dysfunction, facilitating close monitoring and proactive preventive strategies. Thus, pre-treatment SGS effectively predicts severe salivary gland dysfunction, allowing for targeted interventions in high-risk DTC patients.

*The authors declare that they have no conflicts of interest.*

**Ethics approval and consent to participate**

The research protocol was approved by the Ethical Committee of Xuzhou Medical University Affiliated Hospital. A comprehensive overview of the study procedures was presented to all participants, who subsequently provided their written informed consent.

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