Original Article

Early Quantification of Salivary Gland Function after Radioiodine Therapy

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Abstract

Purpose of the Study: Radioiodine (I-131) is used as an effective noninvasive treatment for thyroid malignancies. Salivary gland is one of the most affected nontarget organs. The present study aims to perform early quantification of salivary gland function after I-131 therapy (RIT) for thyroid cancer considering I-131 down-scatter in the Tc-99m window. **Materials and Methods:** A total of 20 patients (6 males and 14 females) with differentiated thyroid carcinoma were enrolled in the study. Baseline dynamic salivary scintigraphy was performed in all patients using 185–370 MBq (5–10 mCi) Tc-99m pertechnetate. Posttherapy, salivary scintigraphy was performed 10–25 days after RIT in the range of 1.85–7.4 GBq (50–200 mCi). Time–activity curves obtained from the pre- and posttherapy dynamic salivary scintigraphy were used for semi-quantitative analysis. Uptake ratio (UR), ejection fraction (EF%), and maximum accumulation (MA%) were calculated by drawing regions of interest of individual parotid and submandibular glands over a composite image, after correcting for down-scatter from I-131 in the Tc-99m window. A paired *t*-test was used for comparison of the parameters obtained. **Results:** Significant changes were observed in UR and EF% of both parotid and submandibular glands ($P < 0.05$). No significant changes were found in the value of MA% of left parotid gland and both submandibular glands in the posttherapy scans in comparison to pretherapy scans ($P > 0.05$). However, significant difference was observed in the MA% of the right parotid gland ($P = 0.025$). **Conclusion:** Salivary gland function was found to deteriorate after RIT, with the parotid glands affected more than the submandibular glands.

Keywords: *Radioiodine scatter, radioiodine therapy, salivary gland, salivary scintigraphy, thyroid carcinoma*

Introduction

Thyroid cancer is the fifth most common cancer affecting nearly 3.4% of the world population.[1] Incidence of thyroid carcinoma is increasing in various geographic regions of the world.[2] Thyroid carcinoma is broadly classified into differentiated thyroid carcinoma (DTC) and undifferentiated thyroid carcinoma.[3] Based on survival rates, DTCs are among the most curable cancers.[4] Different treatment options have evolved depending on the type and stage of the thyroid carcinoma, i.e., surgery, thyroid hormone suppression therapy, radioactive iodine (I-131) therapy, targeted therapy, external beam radiation therapy, and chemotherapy.[5]

For the last 50 years, radioiodine (I-131) has been used as an effective noninvasive treatment for thyroid malignancies[6] because of its β-emission of appropriate energy (maximal energy: 606 keV and mean energy: 191 keV) to kill the thyroid cells. Along with β-particle emission, it also emits γ-radiations of 364 and 637 keV (90%). These gamma radiations are used for imaging in nuclear medicine.[7]

The mechanism of iodine uptake in the thyroid gland is based on active transport mediated by sodium iodide symporters (NISs). Apart from thyroid cells, NIS is also expressed in other tissues such as salivary glands, choroid plexus, gastric mucosa, sweat glands, ovaries, placenta, and the mammary glands during pregnancy and lactation.[8] As I-131 is a beta emitter, it causes significant damage to these nontarget organs. The salivary gland is one of the most affected nontarget organs as it concentrates a significant amount of I-131 because of the presence of NIS.[9]

Frequently produced side effects due to I-131 therapy (RIT) include sialadenitis, xerostomia, and xerophthalmia.[10] Radiation causes damage to both the acinar and ductal systems of the salivary glands; however,

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the principal damage is to the acinar parenchyma.[11] This damage causes an apparent increase in salivary sodium and chloride and a decrease in salivary bicarbonate. These changes account for the thick, tenacious, and acidic character of postirradiation saliva.[12]

The loss of salivary gland function affects the quality of life and may lead to impairment of social activities for long-term survivors. Permanent dry mouth may result in sticky saliva and difficulty in eating. Decreased salivary gland output predisposes to mucosal infections and dental caries and may disturb speaking and swallowing as well.[13,14]

Salivary gland scintigraphy is a widely accepted and sensitive method to study the functional status of parenchymal cells of salivary glands. However, image quality in salivary gland scintigraphy is generally compromised due to down-scatter by the 364 keV gamma energy of residual I-131 activity in treated patients. Image degradation due to scatter becomes more pronounced if early imaging is performed. Due to this reason, early quantification becomes challenging. However, the early detection of salivary gland dysfunction may help to prevent further deterioration of salivary gland function. Therefore, considering the importance of early imaging and interference of I-131 down-scatter, the present study aimed to correct for I-131 down-scatter and perform early quantification of salivary gland damage after RIT for thyroid cancer.

Materials and Methods

This prospective study initially enrolled 20 patients (6 males and 14 females) of thyroid cancer (mean age: 38.5 ± 17.45 years), planned for RIT following near-total thyroidectomy. Five patients for whom the salivary scintigraphy was performed within 10–15 days post-I-131 therapy were excluded because of significant down-scatter of I-131, which resulted in nonvisualization of salivary glands. Hence, quantitative analysis of parameters was done in 15 out of 20 patients. Patients finally included in the study had normal biochemical and hematological function except for thyroid function tests. Patients below 18 years of age; pregnant and breastfeeding female patients; those with surgically removed salivary glands, preexisting xerostomia, or any related oral morbidity; and patients taking medications interfering with pertechnetate uptake were excluded from the study. The study was approved by a departmental review committee, and written informed consent was taken from all the patients enrolled in the study. All patients underwent salivary scintigraphy before high dose I-131 RIT ranging from 1.85 to 7.4 GBq (50–200 mCi) for thyroid cancer treatment [Table 1]. After pretherapy salivary scintigraphy, patients were administered I-131 and admitted in the isolation ward till the recorded radiation exposure level was below 5 mR/h. Following I-131 administration, patients were asked to suck on sour candy and hydrate themselves adequately. Before discharge, these patients were instructed to follow radiation safety precautions such as adequate hydration, frequent urination, maintaining a distance of at least 2 m from other people (especially children and pregnant women) at all times, and washing clothes and utensils separately for a week. A posttherapy salivary scintigraphy scan was performed 10–25 days after high-activity I-131 administration.

Table 1: Range of I-131 activity administered to patients

I-131 GBq (mCi)	Number of patients
1.85 (50)	5
3.7 (100)	10
5.55-7.4 (150-200)	5

Imaging protocol

Post-I-131 salivary scintigraphy study was performed using a dual-head gamma camera (Infinia Hawkeye-4; GE Healthcare, USA, or Symbia T16, Siemens, Germany) with a low-energy high-resolution collimator. The patients were instructed not to move during the scan and positioned supine with the head and neck under the anterior head of the gamma camera. A static image was first acquired in the Tc-99m energy window before injection of the radiotracer to account for the down-scatter from residual I-131. Subsequently, following intravenous injection of 185–370 MBq (5–10 mCi) of Tc-99m sodium pertechnetate, sequential dynamic images were acquired at 30 s/frame for 30 min (64 × 64 image matrix, 1.45 zoom). Diluted lemon juice was administered orally 20 min after radiotracer injection to stimulate the salivary glands. After the completion of the dynamic study, a static image was again acquired in the Tc-99m window for the calculation of percentage of I-131 scatter.

Data processing and analysis

In the processing of dynamic salivary scintigraphy data, a summed image was formed by system software using all the acquired serial images. Regions of interest (ROIs) were drawn manually over each of the parotid and submandibular glands, with background ROIs in the temporal region of the head [Figure 1a]. A time–activity curve (TAC) of each salivary gland was generated, and the following points were designated on the TAC: (a) vascular perfusion at 1 min, (b) the maximum count before stimulation, (c) the background count at the time of peak activity, and (d) the minimum count after stimulation [Figure 1b].[15]

The glandular function parameters for each salivary gland were calculated using the TACs, as following:

$$\text{Uptake Ratio (UR)} = \frac{b}{c}$$

$$\text{Maximum accumulation (MA\%)} = \frac{b - a}{c} \times 100$$

$$\text{Ejection fraction (EF\%)} = \frac{b - d}{c} \times 100$$

For correcting I-131 down-scatter in the posttherapy quantitative parameters, percentage down-scatter of I-131 in the Tc-99m window was calculated by dividing the counts obtained in the static image acquired immediately before the start of dynamic salivary scintigraphy [Figure 2a] by the total counts obtained in the static image acquired after the completion of dynamic salivary scintigraphy [Figure 2b].

$$\%\ \text{I-131 Scatter in Tc-99m window (e)} = \frac{\text{I-131 count in Tc-99m window of static image [Figure 2a]}}{\text{Total count in static image [Figure 2b]}} \times 100$$

The posttherapy glandular function parameters for each salivary gland were calculated considering I-131 down-scatter correction, as following:

$$\text{Uptake Ratio (UR)} = \frac{b(1 - e)}{c}$$

$$\text{Maximum accumulation (MA\%)} = \frac{(b - a)\ (1 - e)}{c} \times 100$$

$$\text{Ejection fraction (EF\%)} = \frac{(b - d)(1 - e)}{c} \times 100$$

The salivary gland function was analyzed by comparing the variables of these functional parameters between pretherapy and posttherapy.

Statistical analysis

Statistical analysis was carried out using IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics such as mean, mean difference, and standard deviation were calculated for variables, namely UR, maximum accumulation (MA%), ejection fraction (EF%). A paired *t*-test was performed to find the difference in value of the quantitative parameters before and after RIT. The difference was considered to be significant for $P < 0.05$.

Results

Quantitative analysis of parameters was done in 15 out of 20 patients. Five patients for whom the salivary scintigraphy was performed within 10–15 days post-I-131 therapy were excluded because I-131 down-scatter was very high at posttherapy salivary scintigraphy, resulting in nonvisualization of the salivary glands in the acquired images. Four out of these five patients were given 3.7 GBq (100 mCi), and one was administered 5.55 GBq (150 mCi) of I-131.

Upon assessment, it was found that posttherapy, there was a significant change in the UR of the right parotid gland, left parotid gland, right submandibular (RSM) gland, and left submandibular (LSM) gland ($P = 0.012$, 0.001, 0.005, and 0.002, respectively). No significant change was found in MA% of pre- and posttherapy scans of the left parotid, right, and LSM gland, with $P = 0.132$, 0.127, and 0.595, respectively [Table 2]. However, for the right parotid gland, the difference was found to be significant ($P = 0.025$).

The EF% of the right parotid, left parotid, RSM, and LSM gland was significantly decreased ($P = 0.006$, 0.005, 0.003, and 0.02, respectively).

After I-131 treatment, mean UR and EF% of combined parotid glands (RP and LP) fell significantly from 39.55 ($r = 36.86$, $l = 42.24$) and 63.14 ($r = 60.38$, $l = 65.89$) in the pretherapy scan to 14.39 ($r = 12.76$, $l = 16.01$) and 48.15 ($r = 51.97$, $l = 51.12$) in the posttherapy scans, respectively. Similarly, mean UR and EF% of combined submandibular glands (RSM and LSM) fell significantly from 34.39 ($r = 35.3$, $l = 33.47$) and 51.45 ($r = 51.97$, $l = 51.12$) in the pretherapy scan to 17.52 ($r = 17.36$, $l = 17.69$) and 39.72 ($r = 38.33$, $l = 41.1$) in the posttherapy scan, respectively [Table 2].

A representative image of dynamic salivary scintigraphy study before and after I-131 treatment with TACs demonstrates the deterioration of salivary gland function [Figure 3].

Discussion

Following surgery, I-131 is used to treat DTC for ablation of remnant thyroid tissues and metastatic foci, as iodine gets concentrated into thyroid tissues through NIS.[16] However, iodine is also accumulated in other tissues such

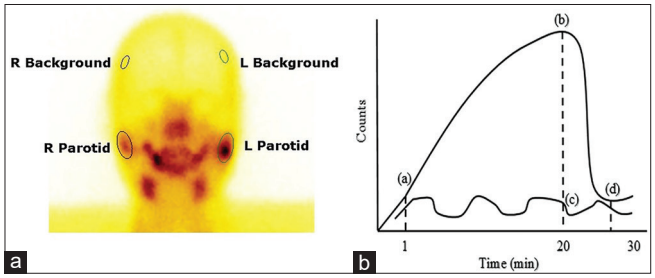

Figure 1: (a) Regions of interest on the summation image obtained by dynamic salivary scintigraphy, (b) schematic presentation of a time–activity curve in a normal pattern of salivary gland scintigraphy

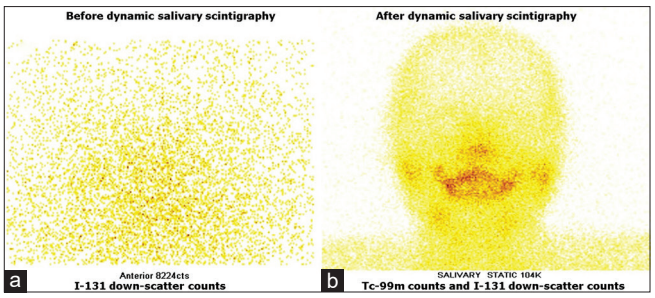

Figure 2: (a) Posttherapy static image showing I-131 down-scatter counts in Tc-99m window before dynamic salivary scintigraphy, (b) posttherapy static image showing Tc-99m with I-131 down-scatter counts after dynamic salivary scintigraphy

as salivary glands, choroid plexus, sweat glands, gastric mucosa, lactating mammary glands, placenta, and ovaries.[8] Because of its localization to nontarget organs, damage due to beta radiation may also occur to these organs. As a significant amount of I-131 gets concentrated in the salivary glands, these are more prone to damage.[9] There are several mechanisms described in literature, including mitotic and interphase cell death, direct DNA damage, or damage to progenitor cells.[17] The specific mechanism responsible for radiation-induced salivary gland dysfunction is still not understood. Trapping mechanism of Tc-99m sodium pertechnetate is similar to iodine trapping by salivary glands. Salivary gland function studies with Tc-99m sodium pertechnetate have, therefore, been used to evaluate salivary gland disorders such as salivary gland tumors, bacterial/viral sialadenitis, sialolithiasis, and Sjogren's syndrome.[18] Several quantitative parameters have been proposed in literature using TACs obtained from dynamic imaging of the salivary glands using Tc-99m sodium pertechnetate. In the present study, three quantitative parameters, such as UR, MA%, EF%, have been evaluated to analyze the damage to the salivary glands after RIT.[15]

The effects of RIT on salivary gland function have been evaluated at different time intervals by different authors. Malpani *et al*. performed salivary scintigraphy with Tc-99m sodium pertechnetate after a month on patients who had received RIT.[18] Bohuslavizki *et al*. performed salivary scintigraphy after 3 months of RIT to evaluate the parenchymal damage to the salivary glands.[19] However, in the present study, posttherapy salivary scintigraphy was performed 10–25 days after RIT to quantitatively analyze the early changes in the functional parameters. These early changes account for initial damage as well as deterioration from the baseline scan. However, the challenge in early imaging and quantification is the interference of I-131 down-scatter due to its 364 keV gamma and longer biological half-life in the body.

Therefore, in the present study, down-scatter of I-131 was calculated and corrected for in 15 patients out of 20, which enabled early quantification of damage to salivary glands. Early protective measures could then be taken for these patients to decrease the damage to the salivary glands. However, in five patients for whom early imaging was done within 10–15 days, quantification was not feasible

Table 2: Salivary gland parameters' comparison before and after high-dose I-131 therapy

Salivary gland	Parameters	Pre I-131 therapy	Post I-131 therapy	Mean difference (pre- and posttherapy)	*t*	*P*
RP	UR	36.86±30.74	12.76±8.22	24.1	2.857	0.013
	MA%	62.09±14.22	46.77±20.39	15.32	2.502	0.025
	EF%	60.38±16.23	46.25±17.44	14.13	3.191	0.007
LP	UR	42.24±25.5	16.01±11.44	26.23	3.969	0.001
	MA%	59.89±13.56	51.17±18.61	8.72	1.597	0.133
	EF%	65.89±16.43	50.01±19.27	15.88	3.252	0.006
RSM	UR	35.3±14.74	17.363±11.47	17.937	3.278	0.005
	MA%	39.65±19.18	30.38±15.22	9.27	1.619	0.128
	EF%	51.97±10.47	38.33±12.33	13.64	3.582	0.003
LSM	UR	33.47±15.22	17.69±12.75	15.78	3.617	0.003
	MA%	36.3±21.18	33.29±16.43	3.01	0.543	0.596
	EF%	51.12±10.18	41.1±14.03	10.02	2.595	0.021

RP: Right parotid, LP: Left parotid, RSM: Right submandibular, LSM: Left submandibular, UR: Uptake ratio, MA: Maximum accumulation, EF: Ejection fraction

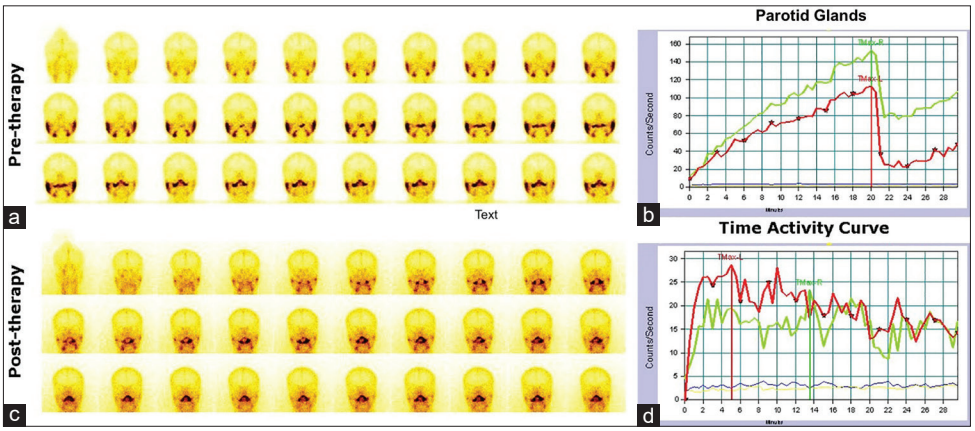

Figure 3: (a) Salivary scintigraphy serial dynamic images before and (c) after I-131 treatment, (b) time–activity curves of parotid glands in pretherapy, and (d) posttherapy salivary scintigraphy

due to significant iodine scatter. This implies that even for early quantification, there is a need for minimum 15 days delay following I-131 treatment. In the present study, UR and EF% were reduced significantly, which can be well appreciated in the bar graphs representing each parameter for an individual [Figures 4-6]. Similar to the present study, Raza *et al*. also found that UR and secretion fraction were sensitive parameters to evaluate salivary gland dysfunction.[16]

Furthermore, UR and EF% in the parotid glands were found to be more affected than submandibular glands. Caglar *et al*. and Liem *et al*. reported similar findings in their studies.[20,21] Malpani *et al*. had also reported that the parotid gland is more affected than the submandibular gland.[18] The difference in the radiosensitivity of the two glands can be attributed to different cell composition. The parotid gland is composed of serous acini, while the submandibular gland consists of mucous and serous cells.[22] The submandibular gland is relatively more radioresistant than the parotid gland because of its ability to secrete mucin continuously without any external stimulation.[23]

As compared to UR and EF%, mean difference of MA% of the parotid and submandibular gland was less and *P* value was also nonsignificant.

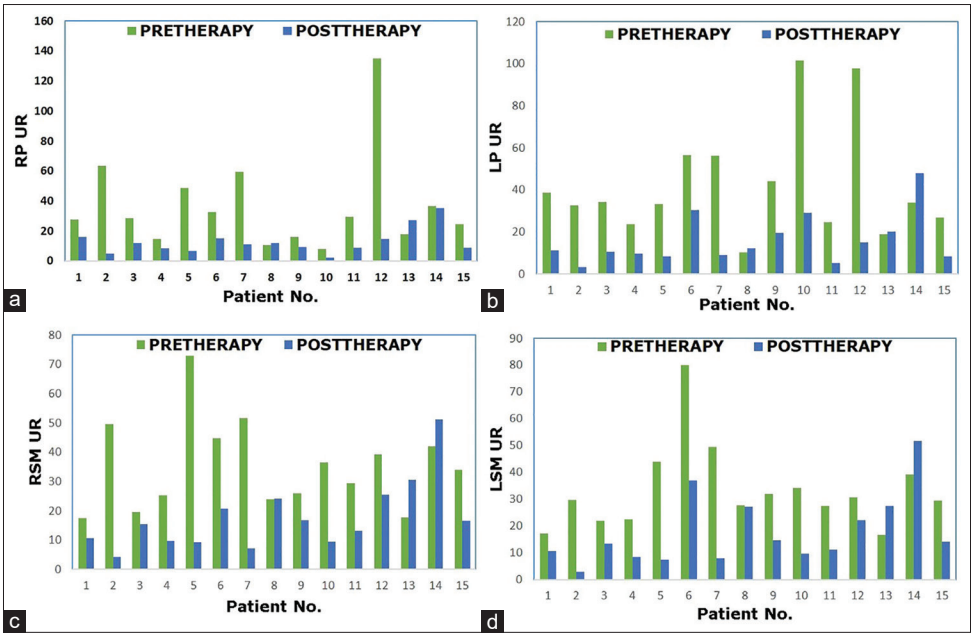

Figure 4: Bar graphs showing uptake ratio scintigraphy parameter for (a) right parotid, (b) left parotid, (c) right submandibular, and (d) left submandibular gland

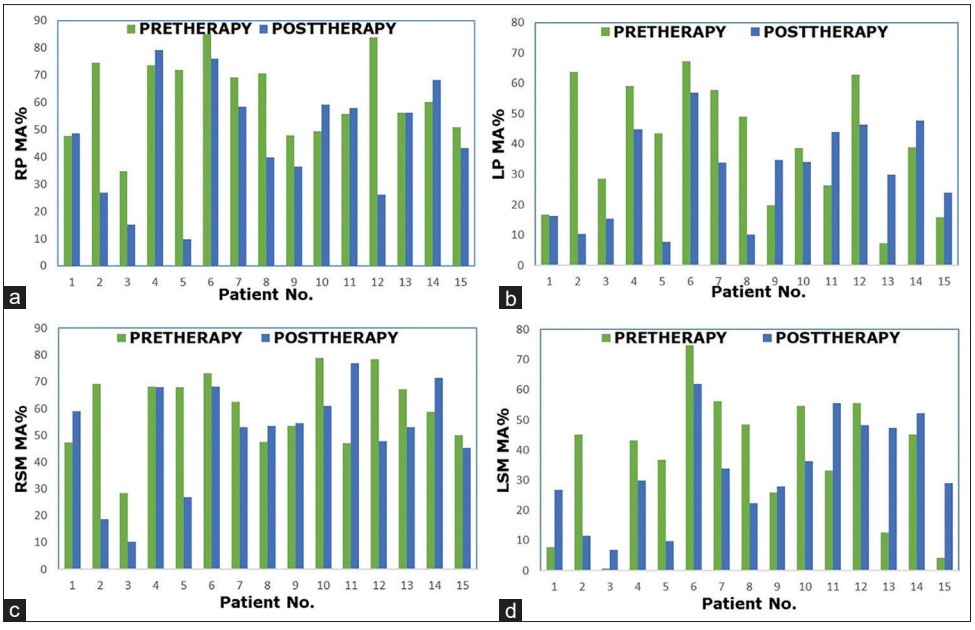

Figure 5: Bar graphs showing maximum accumulation scintigraphy parameter for (a) right parotid, (b) left parotid, (c) right submandibular, and (d) left submandibular gland

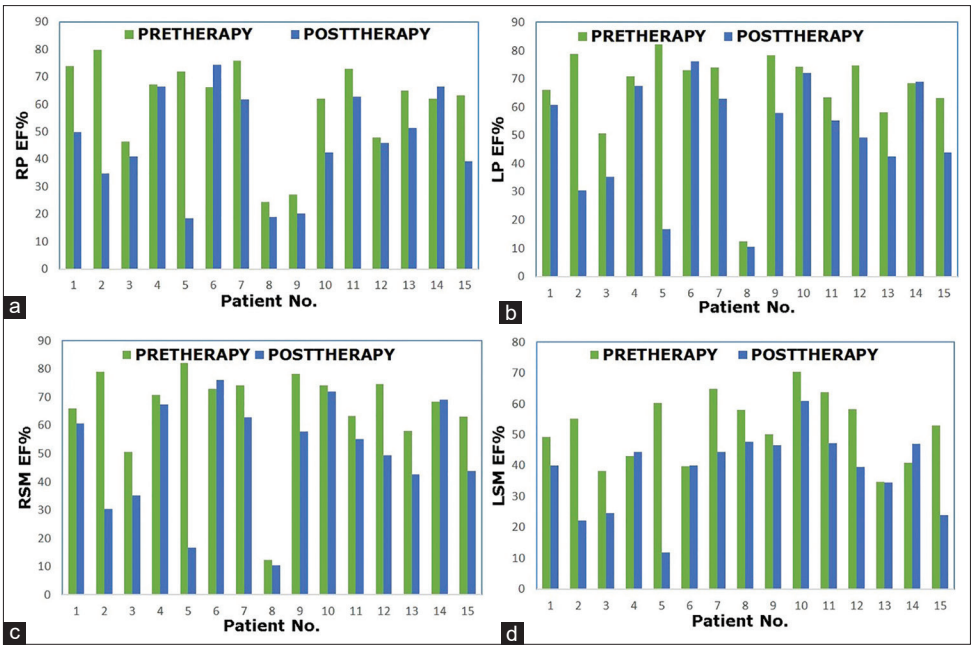

Figure 6: Bar graphs showing ejection fraction scintigraphy parameter for (a) right parotid, (b) left parotid, (c) right submandibular, and (d) left submandibular gland

Several studies have shown that the deterioration of salivary gland function increases with an increase in the dosage of I-131 given to the patients.[10,18] It has been reported that 60%–80% of the patients who had received 18.5 GBq (500 mCi) of I-131 had abnormal salivary gland function. It is difficult to calculate the absorbed dose delivered to the salivary glands as a result of RIT. This is because of parameters required for dosimetry calculations such as effective half-life of I-131, mass of the gland, and iodine uptake, which cannot be measured accurately.[18] Therefore, dosimetry has not been performed in the present study.

Several studies have reported a significant improvement in the quantitative salivary gland function using amifostine and selenium during I-131 treatment for patients with DTC.[24-26] However, other studies have observed no protective effect of amifostine and suggested use of sour candy or lemon juice.[27,28] Therefore, the radioprotective role of amifostine is still controversial. Hence, in the present study, patients were instructed to suck on sour candy to increase salivary secretions and hydrate themselves adequately to protect the salivary glands.

Some studies have observed an increase in blood flow to the salivary glands after stimulation resulting in more absorbed dose to salivary glands. Therefore, the use of sour candy or lemon juice for salivary stimulation needs to be optimized in future studies.[29,30] Other limitations of the study include the small number of patients and the short follow-up time. Furthermore, clinical correlation with symptoms such as pain and dry mouth was not studied. The present study was limited to an attempt to only quantify salivary gland function in the immediate post-I-131 therapy period using salivary scintigraphy.

Conclusion

It can be inferred from this study that early evaluation of salivary gland damage due to RIT can be done after the elimination of down-scatter of I-131 to take early measures to protect salivary glands. The UR and EF% were found to be sensitive quantitative parameters; however, MA% was not affected in posttherapy scans. Furthermore, the parotid gland was found to be more radiosensitive in comparison to the submandibular gland.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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