



PSMA PET/CT Identifies Inpatient Variation in Salivary Gland Toxicity From Iodine-131 Therapy

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Abstract

Introduction: Xerostomia is a well-known complication after iodine-131 (¹³¹I) therapy for thyroid carcinoma. It is currently insufficiently understood how the dose and biodistribution of ¹³¹I relates to salivary gland toxicity, and whether this is consistent for all salivary glands within a single patient. Prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) was recently introduced as a new tool to evaluate the relative loss of vital acinar cells in individual salivary glands. We aimed to assess gland-specific salivary gland toxicity after ¹³¹I-therapy using PSMA PET/CT.

Methods: Five patients with differentiated thyroid cancer underwent [⁶⁸Ga]Ga-PSMA-II PET/CT to evaluate their eligibility for peptide radioligand therapy with [¹⁷⁷Lu]Lu-PSMA-617. Uptake patterns in salivary glands were evaluated visually and quantitatively as an indicator of vital acinar cell loss after prior ¹³¹I-therapy.

Results: Four of 5 patients demonstrated significant lowered uptake in at least one salivary gland, after receiving at least 2 ¹³¹I-treatments. Asymmetric loss of vital acinar cells occurred by gland type (parotid/submandibular) and location (right/left). The other salivary glands in these patients and all salivary glands in the fifth patient showed normal uptake, demonstrating high inpatient and interpatient variability.

Conclusions: ¹³¹I-therapy can induce salivary gland toxicity with high inter- but also high inpatient variation among separate gland locations, which can be assessed with PSMA PET/CT. This new technique offers potential to guide further development and evaluation of protective measures in patients receiving ¹³¹I-therapy.

Keywords

salivary glands, toxicity, PSMA PET/CT, radionuclide therapy, thyroid carcinoma, ¹³¹I, case series

Introduction

Radiation-induced salivary gland toxicity is a well-known issue in patients who receive radionuclide therapy with iodine-131 (¹³¹I), with a reported prevalence of 16% to 54%.¹⁻⁶ ¹³¹I is accumulated in salivary glands due to the presence of the sodium iodide symporter.^{7,8} The locally emitted radiation can cause damage to the glands, resulting in a dry mouth (ie, xerostomia) or painful inflammation (ie, sialadenitis) along with significant impact on quality of life.⁶

Functional loss of the salivary glands is difficult to quantify. An objective decrease in parotid and/or submandibular gland function as seen with scintigraphic or sialometric techniques does not necessarily correlate with the subjective feeling of xerostomia in patients.^{2,3,6} One study⁹ showed in a group of

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45 patients with differentiated thyroid cancer (DTC) who received ^{131}I -therapy, only 54% reported xerostomia, of which 86% exhibited loss of function. In addition, while most patients (67%) with salivary gland dysfunction reported xerostomia, 23% reported no symptoms. This indicates that a complex interplay of salivary gland functions affects the feeling of a dry mouth (or the lack thereof) in patients. Different glands contribute to different types of saliva production; for example, the submandibular glands are mostly used for continuous saliva production to moisten the mouth throughout the day, whereas the parotid glands are primarily activated when food is being ingested.¹⁰ The role of minor and mucosal gland locations is less clearly defined. It is currently insufficiently known how much damage to which types of glands results in the subjective feeling of xerostomia. Better quantification of salivary gland damage after ^{131}I -therapy and its relation to a dry mouth are needed to allow further development of protective strategies.

Functional imaging of expression of the prostate-specific membrane antigen (PSMA) with radiolabeled PSMA ligands is commonly used for (re)staging of prostate cancer.¹¹ The PSMA epitope is also abundantly expressed by vital acinar and ductal cells in salivary glands.¹² Therefore, [^{68}Ga]Ga-PSMA-11 positron emission tomography/computed tomography (PET/CT) can also be used to visualize and quantify functional salivary gland tissue with very high sensitivity and specificity in three dimension. Since PSMA-ligand binds only to vital gland cells, a loss of these cells from radiation damage would result in a loss of signal on the PET scan. This permits its use as an objective measure of salivary gland damage.¹²

The aim of this study was to visualize and evaluate patterns of ^{131}I -therapy induced salivary gland toxicity using PSMA PET/CT. This would allow a better understanding of the relation between glandular cell loss and clinical xerostomia and also provide a means to screen for potential new protective measures for patients receiving radionuclide therapy.

Methods

Patient Selection

The 5 patients included in this evaluation were diagnosed with progressive DTC after previous ^{131}I -treatment. They were referred for [^{68}Ga]Ga-PSMA-11 PET/CT on clinical indication to evaluate their eligibility for peptide radioligand therapy with [^{177}Lu]Lu-PSMA-617, since PSMA expression in DTC has been documented before.¹³ As such, baseline PSMA PET/CT scan data for this patient group before ^{131}I -treatments do not exist. Any comparisons to a normal reference control are based on well-established data from literature.

Ethics Approval and Consent to Participate

The Medical Research Ethics Committee of University Medical Center Utrecht waived the need for approval of the study and the need to obtain informed consent for retrospective evaluation of the salivary glands on the acquired PET/CT scans.

Table 1. Patient Treatment History.

Patient number	Sex & Age	Type	Treatment history		
			Year	Activity (MBq)	Target region
1	M 54	^{131}I -Therapy	2008	7400	–
		^{131}I -Therapy	2008	7400	–
		Radiotherapy	2009	–	Cervical spine
		^{131}I -Therapy	2009	7400	–
		^{131}I -Therapy	2011	7400	–
		^{131}I -Therapy	2013	7400	–
2	F 71	^{131}I -Therapy	1996	3700	–
		^{131}I -Therapy	1999	7400	–
3	F 43	^{131}I -Therapy	2013	1100	–
		^{131}I -Therapy	2014	7400	–
		^{131}I -Therapy	2016	7400	–
4	F 75	^{131}I -Therapy	2008	3700	–
		Radiotherapy	2016	–	Left neck and TH4
5	F 65	^{131}I -Therapy	1995	148	–
		^{131}I -Therapy	2010	5550	–
		Radiotherapy	2014	–	Right neck and mediastinum

Prostate-Specific Membrane Antigen PET/CT

[^{68}Ga]Ga-PSMA-11 was administered intravenously in a dose of 2 MBq/kg. Combined PET and CT images were acquired approximately 60 minutes later, from skull vertex to the thighs using a TruePoint Biograph mCT40 scanner (Siemens). A low-dose CT scan was performed using Care Dose 4D and Care kV, reference parameters: 40 mAs, 120 kV. Positron emission tomography was acquired according to the European Association of Nuclear Medicine recommendations. Salivary gland uptake on the reconstructed PET scans was evaluated visually and quantitatively. For standard uptake value (SUV) measurements, the lean body mass corrected values were used. The left and right parotid and submandibular glands were delineated and the SUV_{max} within each gland was obtained. The SUV_{max} values were compared with a recent study to ascertain if they were within the normal range for healthy salivary glands.

Results

Patient Characteristics

The characteristics of the 5 patients in this study are detailed in Table 1. They were diagnosed with metastatic papillary thyroid carcinoma and had received at least 2 treatments with ^{131}I , the last of which was given at least one year ago and had resulted in negative ^{131}I post-therapy scintigraphy. Thus, the study assessed long-term damage to salivary glands, inflicted by cumulative ^{131}I -treatments. In 2 cases, external beam radiotherapy (EBRT) has also been applied to a part of the neck. Since the focus of this study is on salivary gland damage,

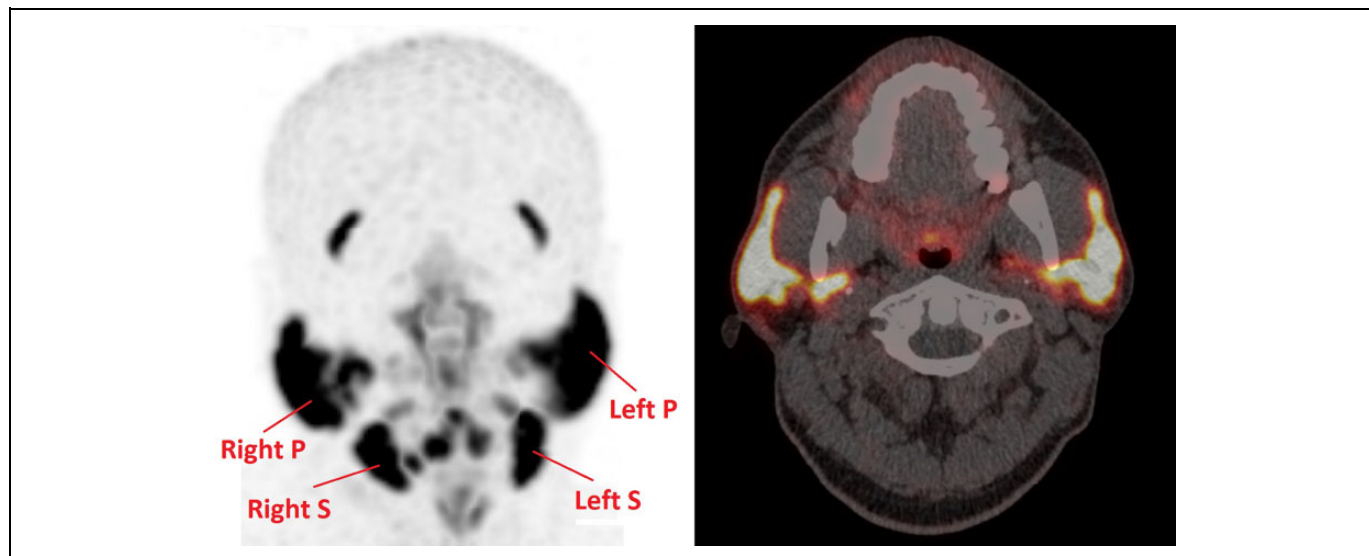


Figure 1. Images from patient 1. P indicates parotid gland; S submandibular gland.

further characteristics of the thyroid cancers were considered beyond the scope of the manuscript.

Gland Evaluation

Four patients showed evidence of extensive loss of viable gland cells in at least one major salivary gland, as seen in Figures 1 to 5. Distinct gland locations are indicated in Figure 1, with P (parotid glands) or S (submandibular glands). A recent study with 30 patients who underwent [^{68}Ga]Ga-PSMA-11 PET/CT reported that the mean (\pm standard deviation) SUV_{max} values in healthy parotid and submandibular glands of patients are $12.3 (\pm 3.9)$ and $11.7 (\pm 3.5)$, respectively.¹² For comparison, the SUV_{max} values for the evaluated salivary glands are reported in Table 2.

Patient 1 (Figure 1) demonstrated normal symmetric uptake and distribution of PSMA ligand despite receiving 6 ^{131}I -treatments, indicating viable gland cells in the left and right parotid and submandibular glands.

Patient 2 (Figure 2) demonstrated normal uptake in all glands except the left parotid, which showed no activity at all, compatible with complete loss of viable gland cells, and this was attributed to 2 ^{131}I -treatments.

Patient 3 (Figure 3) showed normal uptake in both submandibular glands, but extensive and diffuse loss in both parotid glands which was attributed to 3 ^{131}I -treatments. However, the center of the right parotid gland showed a hotspot of activity, which could suggest a focal area of spared gland cells or local regeneration from stem cells.¹⁴

Patient 4 (Figure 4) demonstrated normal uptake in the left parotid and right submandibular glands and complete loss of uptake in the right parotid and left submandibular glands. This is attributed to ^{131}I -treatments, and additionally, to EBRT for the left submandibular gland, since the left neck received a mean dose of 48 Gy.

Table 2. Uptake in Individual Glands.^a

Patient number	Glandular Ga-PSMA SUV_{max}			
	Left parotid	Right parotid	Left submandibular	Right submandibular
1	15.3	14.9	12.0	13.4
2	0.9	12.0	10.5	11.7
3	1.9	4.9	11.0	12.4
4	12.3	0.7	2.4	8.5
5	1.3	17.9	8.8	1.1

Abbreviations: PSMA, prostate-specific membrane antigen; SUV, standard uptake value.

^aNormal SUV_{max} values in healthy parotid and submandibular glands of patients are $12.3 (\pm 3.9)$ and $11.7 (\pm 3.5)$, respectively.

Patient 5 (Figure 5) demonstrated similar uptake to patient 4, but with the normal uptake in the right parotid and left submandibular gland and lack of uptake in the other major glands. This is attributed to 2 ^{131}I -treatments, and for the right submandibular gland most likely also to EBRT with an average dose to a tumor in the right neck of 66 Gy.

Discussion

A weakness of this study is the lack of PSMA PET/CT scans prior to ^{131}I -therapy. Given that the uptake of PSMA in salivary glands is well-documented, it is reasonable to assume that these patients had normal physiological uptake in all their glands prior to ^{131}I -therapy, and that the substantial reduction exhibited is most likely the result of radiation damage. The most striking result is the high inpatient variation of damage to different glands, including strong and unexpected asymmetry in paired parotid and submandibular glands. This asymmetry has been briefly reported before and is discussed below. To our knowledge, this is the first

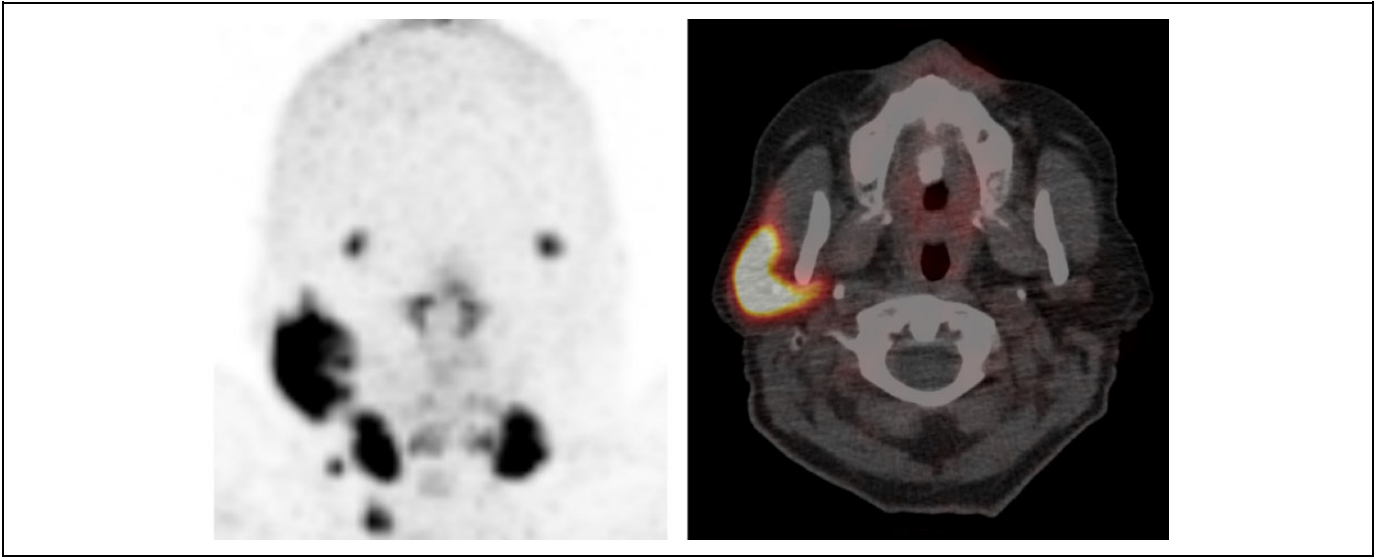


Figure 2. Images from patient 2.

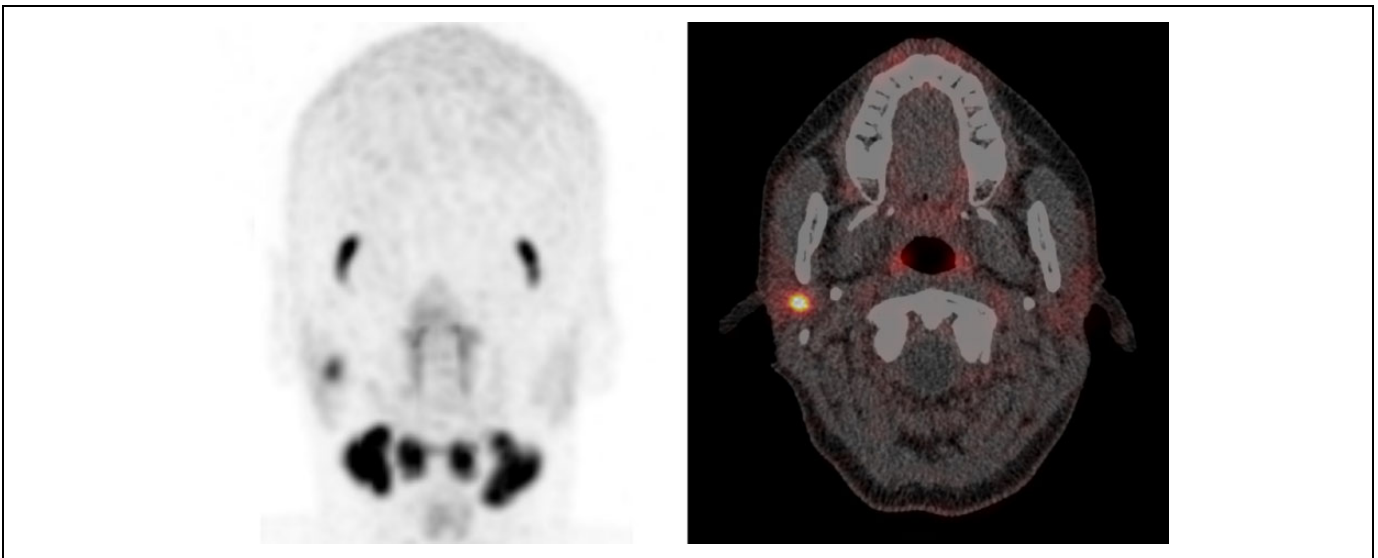


Figure 3. Images from patient 3.

report of objective noninvasive evaluation of acinar gland cells in salivary glands after ^{131}I -therapy, using PSMA PET/CT. This new information can contribute to better understanding of differences between the administered ^{131}I -activity and clinical complaints and to the development of new hypotheses on underlying causes and protective strategies.

Dose–Effect Relation

Our results demonstrate that PSMA PET/CT can detect significant damage and can reveal variations thereof between individual salivary glands. The effective dose from ^{131}I to parotid and submandibular glands has been reported in the range of 0.2 to 0.7 mGy/MBq, or on average about 3.7 Gy for 7400 MBq. Thus, the

estimated dose to the salivary glands in several of the presented patients is well below generally accepted dose constraints in EBRT (eg, 26 Gy in 2 Gy fractions). The fact that objective damage can be demonstrated, and many patients who received ^{131}I -therapy complain of xerostomia despite the relatively low estimated delivered doses, indicates that these constraints may not be suitable for ^{131}I -therapy. The PSMA PET/CT may be useful to determine better dose–effect relations for salivary glands; however, its quantification is beyond the scope of this study given the low number of patients.

Comparison With Other Techniques

Several other techniques have been applied to evaluate salivary glands toxicity before and after ^{131}I -therapy, most notably

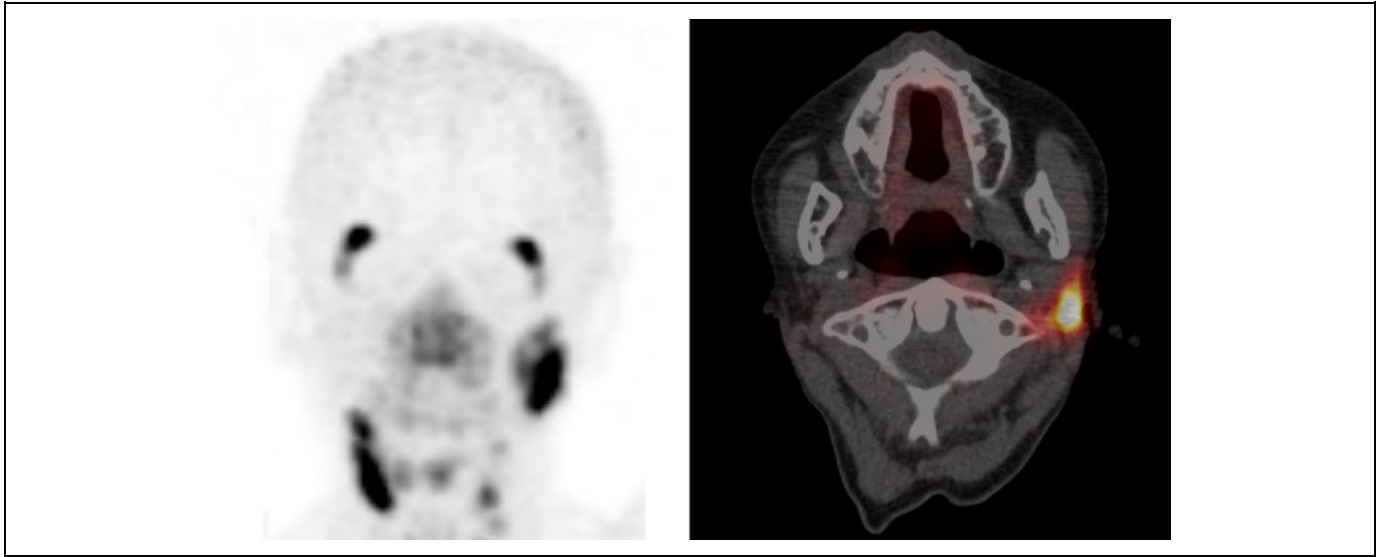


Figure 4. Images from patient 4.

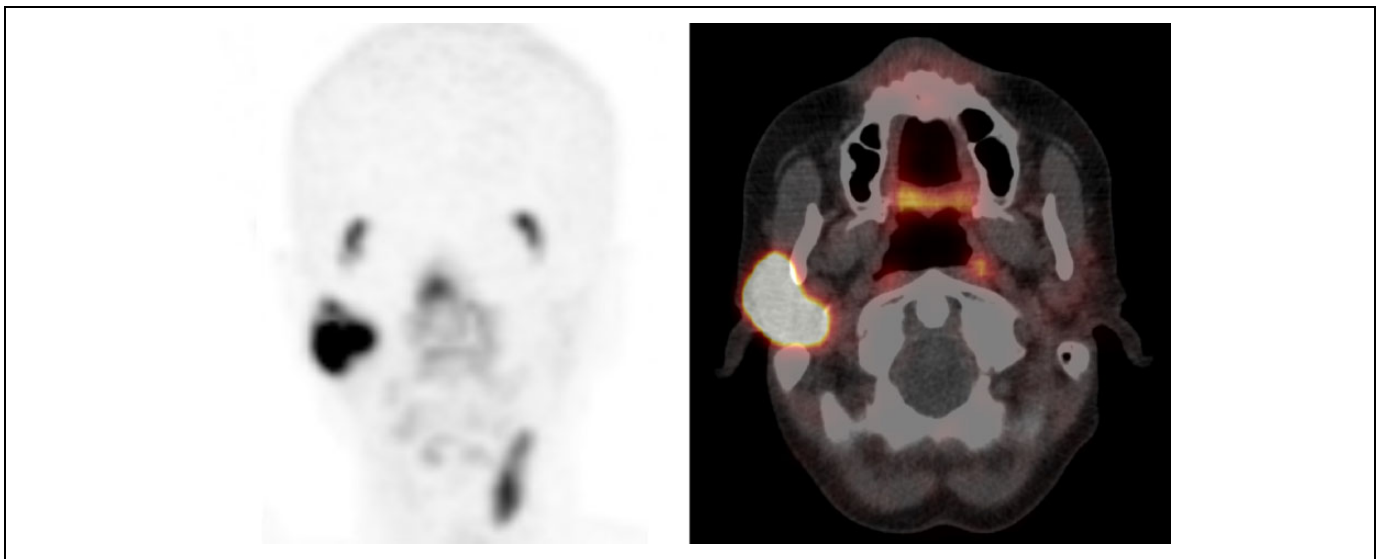


Figure 5. Images from patient 5.

[^{99m}Tc]pertechnetate scintigraphy.^{3,5,6,9,15} However, when compared with PSMA PET/CT, these scans suffer from low spatial resolution and planar views with overprojection. Moreover, the activity of the salivary glands on these scans may vary significantly with stimulation, clearance, blockages, and local perfusion, which makes it a less objective measure than PSMA PET/CT. Other imaging instruments have primarily been applied to evaluate the effects of other treatment modalities. Ultrasound of salivary gland characteristics is operator-dependent and correlates weakly with symptoms and outcome treatment for Sjögren syndrome.¹⁶ Magnetic resonance sialography was shown to correlate with damage after EBRT, but was limited to ductal effects.¹⁷

Many studies also make use of sialometry, measuring whole and glandular saliva flow rates.^{2,18,19} However, the studies which investigated ^{131}I -related toxicity were subject to variability in salivary flow rate as a result of hyper/hypothyroidism, which may influence their accuracy. Other factors such as stress, hydration, and medication also affect salivary flow rates. A study² found a decrease in salivary flow rates post ^{131}I -therapy, but the uptake of ^{131}I in the salivary glands on diagnostic scans did not correlate with the decrease in flow rates post treatment. Thus, if we wish to understand the relationship between toxicity and dose distribution of ^{131}I , the noninvasive, objective, quantitative, and 3-dimensional instrument PSMA PET/CT is considered a promising modality.

Asymmetry in Toxicity

Assuming the anatomical and physiological symmetry of left and right salivary glands is of the same type, it would follow that the distribution of ^{131}I in the left and right glands would be symmetrical, but this goes against the results observed in this study.

Objective asymmetric loss of salivary gland function due to ^{131}I -therapy has been documented and visualized before.^{4,20} One study⁶ demonstrated the reduction in saliva volume production due to ^{131}I -therapy and showed that in general the parotid glands were affected more than the submandibular glands. They also found that the left parotid gland was more affected by radiation damage than the right in 14 of the 19 patients. Another study³ that featured more than 200 ^{131}I -therapy patients with pre and post treatment scintigraphy scans found that 47.4% of all patients had some amount of decrease in uptake, and that severe reduction in uptake by the parotid glands was more frequent than in submandibular glands. Of these, 38.6% had worsening in 1 gland, 49.5% had worsening in 2 glands, 6.9% in 3 glands and 5% in all 4 glands. They also found that 50.6% of patients had reduction in uptake for both parotid glands and 21.4% for both submandibular glands; however, no overall bias in damage to left or right could be statistically determined.

Several have explained³⁻⁵ that the higher incidence of damage to the parotid gland from ^{131}I could be due to higher concentrations of radiosensitive serous acinar cells, whereas the mucinous tissue of the submandibular glands may provide a “radioprotective” effect. The difference in commonly applied dose constraints for EBRT also hints at this difference in radiosensitivity (eg, 26 Gy for parotid vs 39 Gy for submandibular glands).

Since in this study sufficient time has elapsed to allow for any recovery of glandular tissue,¹⁴ the normal uptake of some of the glands in Table 2 can be explained. However, the complete loss of function of different types of glands on one side but not both is not likely to be explained completely by the discussed radiosensitivity alone. Therefore, we postulate that asymmetric loss of salivary gland function is likely due to physiological differences in delivery (perfusion) or retention (excretion rates) of ^{131}I among these glands. Glands that currently appear damaged were likely more perfused or excreted less ^{131}I , leading to a higher delivered radiation dose in the gland. A gland exhibiting inherently higher retention is exposed to more radiation from a ^{131}I -treatment, which can consequently cause narrowing or obstruction in its duct and sialadenitis.^{4,20,21,22} This can lead to increased retention/lowered excretion in a subsequent ^{131}I -treatment, causing more extensive radiation damage. This cumulative effect could result in some glands losing complete function after multiple ^{131}I -treatments, while other glands may be unaffected, possibly explaining the inpatient and interpatient variation exhibited by these 5 patients. This concept warrants further scientific research with the aim to reduce ^{131}I -induced toxicity in salivary glands.

Strategies to Reduce Toxicity

Many studies have established the connection between ^{131}I -therapy and xerostomia, but there is not much evidence that details how this toxicity can be reduced. Stimulating the salivary gland by using sialogogic agents (like lemon candy or pharmaceuticals) has been used to hasten the clearance of the ^{131}I , but the effectiveness of this hasn't been rigorously tested and there are conflicting reports with some suggesting deleterious “rebound effects” due to increased perfusion.^{19,23,24} Our results with highly asymmetric damage to paired glands leads us to hypothesize that differences in perfusion could be a relevant factor, and PSMA PET/CT could be used to test this. It has been proven that blood flow to the scalp can be reduced during chemotherapy to reduce the risk on alopecia, by cooling the region.²⁵ This was recently applied to salivary glands to reduce PSMA uptake. Although the impact was limited,²⁶ given the promising outcomes of radiolabeled PSMA therapies (such as ^{177}Lu , ^{225}Ac , and ^{213}Bi) for prostate cancer, for which xerostomia can also be a significant side effect,²⁷ this further supports PSMA PET/CT as a tool to evaluate strategies for sparing the salivary glands in different types of radionuclide therapies.

In conclusion, salivary gland toxicity from ^{131}I -therapy has unexpectedly high inpatient variation among different gland locations and this can be evaluated with PSMA PET/CT. Possible explanations include variations in perfusion, tracer retention, or radiosensitivity. Further scientific research is needed to elucidate this clinically relevant biological effect, with the aim to develop better protective measures for patients receiving ^{131}I -therapy.


Declaration of Conflicting Interests

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