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Assessment of salivary gland function after 177Lu-PSMA radioligand therapy: Current concepts in imaging and management

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ABSTRACT

Prostate specific membrane antigen (PSMA) is a transmembrane protein that is highly expressed on prostate epithelial cells and is strongly upregulated in prostate cancer. Radioligand therapy using beta-emitting Lutetium-177 (^{177}Lu)-labeled-PSMA-617, a radiolabeled small molecule, has gained attention as a novel targeted therapy for metastatic prostate cancer, given its high affinity and long tumor retention, and rapid blood pool clearance. In March 2022, the United States Food and Drug administration has granted approval to the targeted ^{177}Lu-PSMA-617 therapy for treatment of patients with PSMA-positive metastatic castration resistant prostate cancer, who have been previously treated with an androgen-receptor pathway inhibitor and taxane-based chemotherapy. Studies have demonstrated the adverse effects of this treatment, mainly encountered due to radiation exposure to non-target tissues. Salivary glands show high PSMA-ligand uptake and receive increased radiation dose secondary to accumulation of ^{177}Lu-PSMA-617. This predisposes the glands to radiation-mediated toxicity. The exact mechanism, scope and severity of radiation-mediated salivary gland toxicity are not well understood, however, the strategies for its prevention and treatment are under evaluation. This review will focus on the current knowledge about salivary gland impairment post ^{177}Lu labeled PSMA-based radioligand therapies, diagnostic methodologies, and imaging with emphasis on salivary gland scintigraphy. The preventive strategies and known treatment options would also be briefly highlighted.

Introduction

Prostate specific membrane antigen (PSMA) is overexpressed in prostate epithelial cells and is a novel target for radioligand therapies to deliver tumoricidal doses of ionizing radiation to prostate cancer cells. However, undesired amount of radiation is also delivered to healthy non-target tissues or organs that show high PSMA expression such as salivary glands, lacrimal glands, and kidneys. Among the major salivary glands, maximum concentration of PSMA-ligand is seen in parotid and submandibular glands, while relatively low concentration is seen in sublingual glands [1] (**Fig. 1**). Preclinical studies have shown low to moderate intensity heterogeneous PSMA staining in salivary glands on immunohistochemistry, in addition to low uptake of radiolabeled anti-PSMA antibodies, both of which are incongruent with the high uptake seen on diagnostic PSMA-targeted PET/CT scans [2]. While the exact mechanism of intense PSMA-ligand uptake in salivary glands remains incompletely understood, it is apparent that there are certain nonspecific mechanisms, possibly the ionic charge of PSMA radioligands that may be contributing towards their increased accumulation in glandular tissues [3, 4].

Different molecular mechanisms have been suggested to play a role in different phases of radiation-induced salivary gland damage, more extensively studied in head and neck cancer patients treated with external beam radiation therapy, than to PSMA radioligand therapy. Radiation exposure to the salivary glands may cause plasma membrane damage of secretory cells, with disturbance of underlying signal transduction pathways, impaired calcium signaling and/or damage or downregulation of aquaporin-5 (a water channel present on apical membrane of salivary gland acinar cells) [5, 6]. This subsequently leads to loss or impairment of acinar cells that can further progress and cause replacement by connective tissue and fibrosis [6]. It may also be associated with impairment of microvasculature and parasympathetic

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innervation. This causes decreased salivary output, as well as increased viscosity and acidity of saliva (normal pH 6.8–7.2). Radiation induced salivary gland toxicity has also been reported post-radioiodine ablation treatment for thyroid cancer as well as post-radiotherapy for head and neck carcinoma [7, 8]. As expected, the scope of usage of therapeutic PSMA-radioligand therapies such as ^{177}Lu-PSMA-617 and particularly when labeled with alpha-emitters, such as Actinium-225 labeled PSMA-617, can be limited to avoid damage to the glands, thus warranting dose adjustments at the cost of reducing effective tumoricidal effect. Prior studies show that a threshold of 40–50 Gy is sufficient to prevent severe dysfunction of salivary gland tissues and below this threshold, the radiation damage is usually transient and reversible [8–10].

Clinical studies with ^{177}Lu-PSMA radioligand therapy (RLT)

Several dosimetry studies have established that parotid and submandibular glands, in addition to the lacrimal glands and kidneys, receive highest radiation-absorbed dose from ^{177}Lu-PSMA radioligand therapies. Assuming average biodistribution after 4 cycles of therapy at an administered activity of 8 GBq, dose to parotid glands was calculated to be 18.6 Gy and submandibular glands 14.1 Gy [11]. Kabasakal et al. studied the absorbed dose of ^{177}Lu-PSMA-617 in seven patients with progressive prostate cancer and estimated that mean (±SD) radiation dose to parotid glands was 1.17±0.31 mGy per MBq [12]. Kratochwil performed dosimetry analysis in 4 patients with metastatic castration-resistant prostate cancer and revealed a mean (±SD) parotid dose of 1.28±0.40, and submandibular 1.48±0.37 Gy/GBq [13]. Similar results were shown in other studies as well [14–17]. The deterioration in parotid glands has been found to be more common, compared to submandibular glands [18–20]. Based on evidence obtained from diagnostic positron-emission tomography scans, it is postulated that the absorbed dose in salivary glands declines with greater disease burden, increased body mass and a larger body surface area. This is probably explained by the tumor-sink effect [11].

Several studies have reported the outcomes and adverse effects of ^{177}Lu-PSMA RLT in patients with advanced prostate cancer. **Table 1** details the relevant findings from major studies, focusing on side effects related to salivary gland function. The symptoms of salivary gland toxicity with ^{177}Lu-PSMA RLT were reported to be mild and transient, mostly based on clinical assessment, though the rates of developing symptoms such as dryness of mouth and hypogeusia were found to be highly variable, ranging between 20 and 60% [13, 21-29]. Only few studies with small patient cohort used scintigraphy for objective

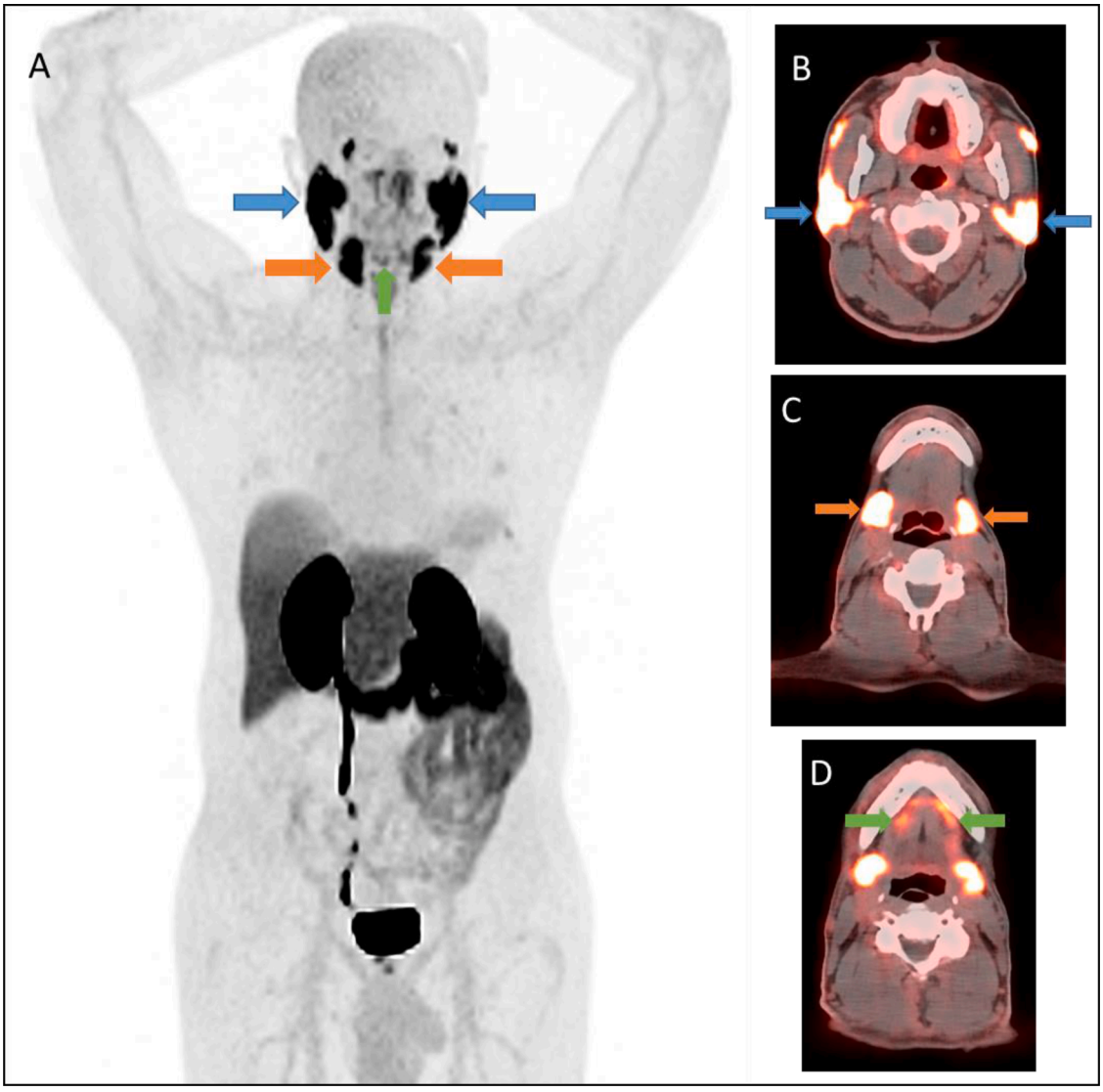

Fig. 1. Concentration of PSMA-ligand in major salivary glands. (A) Maximum-intensity projection image of 18F-Piflufolastat PET/CT, with (B, blue arrows) Fused PET/CT images at the level of parotid glands, (C, orange arrows) at the level of submandibular glands, and (D, green arrows) at the level of sublingual glands.

Table 1
Overview of salivary gland toxicity across several studies.

Authors, year and type of study	Radiopharmaceutical, dose	Number of patients	Salivary gland scintigraphy performed	Preventive technique	Percentage who developed salivary gland dysfunction, when	Severity
Ahmadzadehfar et al. [19], 2016, prospective	^{177}Lu-DKFZ-617 PSMA, mean 5.6 GBq (range 4.1 – 6.1 GBq)	10 hormone- and chemo-refractory PCa – only 1 cycle	Yes – baseline on treatment day and 8 weeks after therapy	Ice packs over parotid and submandibular glands from 30 min prior to and up to 4 h after administration	20% (2 patients), hypoguesia and dry lips in the first 2 weeks after treatment	No significant change in uptake and clearance of ^{99m}Tc from salivary glands
Ahmadzadehfar et al. [20], 2016, prospective	^{177}Lu-DKFZ-617 PSMA, mean dose per cycle 6.0 GBq (range 4.1 – 7.1 GBq)	24 hormone and chemo-refractory PCa – 1 cycle in 2 and 2 cycles in 22 patients	No	Ice packs over parotid and submandibular glands from 30 min prior to and up to 4 h after administration	8.7% (4 patients), dry lips/mouth and hypoguesia in the first 4–8 weeks after treatment	NA
Baum et al. [14], 2016, prospective	^{177}Lu-DOTAGA-(l-y)fk(Sub-Kue)(^{177}Lu-PSMA), median dose per cycle 5.67 GBq (range 3.6 – 8.7 GBq)	56 progressive mCRPC – 1 cycle for 16, 2 cycles for 15, 3 cycles for 17, 4 cycles for 6, and 5 cycles for 2 patients	No, Structured questionnaire used	Intravenous hydration using 1.6 L of 5% Lysine HCl and 10% L-arginine HCl mainly for renal protection	3.5% (2 patients) Mild symptoms of dry mouth after 3rd and 4th cycles with spontaneous resolution within 3 months	NA
Heck et al. [21], 2016, prospective	^{177}Lu-DOTAGA-(l-y)fk(Sub-Kue)(^{177}Lu-PSMA),	22 progressive mCRPC - 2 cycles for 8, 3 cycles for 6, 4 cycles for 6, and 6 cycles for 2 patients	No	Cooling of salivary glands, saliva production stimulated by lemon drops, Intravenous hydration with amino acid solution mainly for renal protection	37% (7 patients), transient in first few days after treatment	NA
Kratochwil et al. [11], 2016, prospective	^{177}Lu-PSMA-617, range 4–6 GBq	30 progressive mCRPC - 1 cycle for 12, 2 cycles for 7, 3 cycles for 11 patients	No	Intravenous hydration using 2 L of 0.9% saline; flow 333 ml/h starting 30 min before treatment.	6.6% (2 patients) with dry mouth after 3rd cycle – prescribed saliva gels/ spray. Mild xerostomia without relevant loss in quality of life was occasionally reported after 1st and 2nd cycle.	NA
Rahbar et al. [22], 2016, prospective	^{177}Lu-PSMA-617, mean dose range 5.92±0.44 GBq – 5.86±0.73 GBq	28 progressive mCRPC – 1 cycle in 6 and 2 cycles in 22 patients	No	Cooling pads over parotid and submandibular glands from 30 min prior to and up to 4 h after administration. Intravenous administration of 1000 ml of Ringers solution post treatment	14% (4 patients) mild xerostomia in 3 patients after 1st cycle and in 1 patient after 2nd cycle	NA
Rahbar et al. [23], 2017, multicenter retrospective	^{177}Lu-PSMA-617, range 2–8 GBq	145 progressive mCRPC patients in 12 therapy centers – 1–4 cycles	No	Cooling pads over parotid and submandibular glands from 30 min prior to and up to 4 h after administration (11/12 centers)	8% (11 patients) with mild to moderate xerostomia	NA
Yadav et al. [26], 2019, prospective	^{177}Lu-PSMA-617, range 3.7–8 GBq	90 progressive mCRPC patients, 1–7 cycles	No	No intervention	11% (10 patients with transient dry mouth)	
Wollenweber et al. [27], 2021, retrospective	^{177}Lu-PSMA-617, 7.361 ±0.293 GBq	27 progressive mCRPC patients, 3 cycles	Yes, baseline prior to 1st treatment and 1 month after 3rd treatment cycle and structured questionnaire used	Cold packs over parotid and submandibular glands from 30 min prior to and up to 6 h after administration. Before and after ^{177}Lu-PSMA-617, 1000 ml of 0.9% saline infusion at 300 ml/h over 30 min	37% (7 patients with dry mouth, 4 weeks after 3rd cycle)	No significant change in uptake and clearance of ^{99m}Tc from salivary glands
Hofman et al. [24], 2021, TheraP - multicenter randomized Phase-2 trial	^{177}Lu-PSMA-617, range 6.0–8.5 GBq	98 progressive mCRPC patients in 11 therapy centers – 3–6 cycles	No	No intervention for salivary glands. 1.5 L oral hydration encouraged on the day of treatment.	60% (59 patients) with mild Grade 1 to moderate Grade 2 dry mouth), 12% (12 patients with Grade 1–2 dysgeusia)	NA
Sartor et al. [25], 2021, Vision-multicenter randomized Phase-3 trial	^{177}Lu-PSMA-617, 7.4 GBq	~554 progressive mCRPC, 4–6 cycles	No	None reported	38% patients with dry mouth	NA

assessment of salivary gland function (8–12 weeks after treatment) that showed no significant change from baseline [21, 29]. The incidence of salivary gland toxicity was often reported to be below 37% when prevention techniques such as good hydration and/or external cooling were used to prevent salivary gland damage (**Table 1**) [22, 23, 29].

Diagnosis and measurement of salivary gland impairment

Salivary secretions are subdivided into three types: mucous, serous and seromucous. Mucous secretions are viscous due to presence of complex carbohydrates attached to mucins that result in the lubricating

effect of saliva. Serous secretions produced by parotid glands are more watery due to absence of mucin. Submandibular glands contain mixed seromucous secretory units. Saliva plays a vital role in preparation of food for swallowing, taste modulation, and the initial digestion by salivary amylase and maltase. Salivary gland toxicity typically manifests as xerostomia, i.e., dryness of the oral cavity, that results from salivary gland malfunction such as in Sjogren's syndrome. Most relevant problems that affect the quality of life in patients with xerostomia are change in taste (predominance of bitter and salty taste), burning sensation in tongue and/or lips, difficulty in mastication and swallowing (frequent consumption of fluids during meals), in addition to sleep and speech difficulties. Decreased salivary function can cause oral bacterial overgrowth and exacerbate tooth decay and periodontal disease. Clinical signs that are often helpful in diagnosing xerostomia in patients include, sticking of intraoral mirror to the buccal mucosa or tongue, frothy saliva, no pooling of saliva in the floor of the mouth, loss of papillae on tongue dorsum, glassy appearance of oral mucosa (especially the palate) and dental caries (more than two teeth) [30]. Several structured questionnaires have been developed to aid in identifying patients with xerostomia [31, 32]. **Table 2** describes few examples of commonly used questionnaire, positive answers to which have been correlated with low salivary flow rates [33]. These are however subjective methods of assessment and often show poor reproducibility.

Based on the common terminology criteria for adverse events, there are three grades of severity defined for dry mouth like symptoms. These include (i) *Grade 1* - symptomatic without significant dietary alteration (e.g., dry or thick saliva); unstimulated saliva flow >0.2 ml/min, (ii) *Grade 2* - moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min, and (iii) *Grade 3* - inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min [34]. Two grades of severity have been defined for dysgeusia are *Grade 1* - altered taste but no change in diet, and *Grade 2* - altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste [34].

The normal secretion rate of saliva is 0.25–0.35 ml/min that can increase upon stimulation to 1.0–3.0 ml/min [35, 36]. A diagnosis of hyposalivation is made when the stimulated salivary flow rate is ≤0.5–0.7 ml/min and the unstimulated flow rate is ≤0.1 ml/min [37]. There are different methods that can be used to measure salivary output and flow rates, but these can be challenging to perform. For instance, (i) in the draining method, patients are asked to drain saliva from the lower lip into a graduated container for 15 min, (ii) another method, where pre-weighed cotton rolls are placed at the orifice of the ducts of major salivary glands and re-weighed after collection time, (iii) spitting method and, (iv) suction method [38, 39]. The results obtained by these different methods may not be necessarily comparable, probably attributable to difference in techniques and duration, variability in nature and length of application of stimulants. In addition, there are certain neglected factors that affect salivary output such as diurnal variation in salivary output, effects of hydration and posture, and evaporation when breathing through the open mouth [40, 41].

Table 2
Structured questionnaire to assess low salivary function.

Authors	Questions/Statements	Response
Fox et al. [31]	(Q1) Does the amount of saliva in your mouth seem to be too little? (Q2) Do you have any difficulty swallowing? (Q3) Does your mouth feel dry when eating a small meal? (Q4) Do you sip liquids to aid in swallowing dry food?	Yes/No
Thomson et al. [29]	(S1) My mouth feels dry. (S2) I have difficulty in eating dry foods (S3) I get up at night to drink. (S4) My mouth feels dry when eating a meal. (S5) I sip liquids to aid in swallowing. (S6) I suck sweets and cough lollies to relive dry mouth. (S7) I have difficulties swallowing certain foods. (S8) The skin of my face feels dry. (S9) My eyes feel dry. (S10) My lips feel dry. (S11) The inside of my nose feels dry.	Never = score 1 Hardly ever = score 2 Occasionally = score 3 Fairly often = score 4 Very often = score 5

Imaging assessment of salivary glands

Several imaging modalities can be used for morphologic assessment of salivary glands such as ultrasound, plain radiography, magnetic resonance (MR) imaging, computed tomography, and digital subtraction sialography (DSS). These are especially helpful in evaluation of sialectasis, sialolithiasis and tumors [42]. DSS is an invasive technique of retrograde application of contrast, usually iohexol, after cannulation of the duct and introduction of a catheter or sialographic cannula. It has been utilized for investigating the ductal system of major salivary glands in patients with Sjögren's syndrome, however, it is operator dependent and is limited by subjective interpretation. Associated potential complications may include ductal trauma, activation of clinically dormant infection, and adverse reaction to contrast agent [42]. Ultrasound may be used to evaluate inflammatory conditions qualitatively by measuring the echotexture and blood flow to the parotid glands, but only limited studies have evaluated its role in determining changes after radioligand therapy [43]. Acute sialadenitis that usually occurs within a week of radiation exposure, is associated with edema and diffuse glandular enlargement. While chronic changes occur over months and the salivary glands become increasingly hyperechoic on USG as they are replaced by fat and fibrosis. MR sialography uses patient's own saliva as contrast agent and can be performed in patients with acute sialadenitis. However, there are several shortcomings including poor spatial resolution compared to radiographic sialography, need for sufficient salivary output, long acquisition time, cost and limited use in patients with claustrophobia, pacemaker or implanted metals [42]. The role of these modalities is limited in functional evaluation of salivary glands, and none of them can provide objective or quantitative assessment, specifically in the post radiation setting.

Functional imaging using radiopharmaceuticals can be used for diagnosing salivary gland impairment. Salivary gland scintigraphy described in detail below has been found to be a promising tool. Only limited evidence exists regarding the use of PSMA targeted positron emission tomography (PET/CT) in assessing salivary gland toxicity, visually or quantitatively [44].

Assessment of salivary gland function using ^{99m}Tc-pertechnetate ($^{99m}TcO_4^-$) salivary gland scintigraphy

This is a noninvasive low-cost technique, useful for quantitative assessment of function and salivary flow of parotid and submandibular glands. Sublingual glands are not visualized and cannot be assessed. Quantitative assessment has been found to be of clinical significance in evaluation of inflammatory conditions such as Sjogren's syndrome or mixed connective tissue disorders and has also been used to assess the objective decline in parenchymal function after radioiodine treatment in patients with thyroid cancer [18–20]. Unlike other imaging techniques, scintigraphy can also identify cases with glandular dysfunction secondary to neurotransmission blockade. Scintigraphy utilizes standard lemon stimulation technique for evaluation of salivary flow. Several criteria have been described in literature for quantification of gland function and excretion.

Prior to the procedure, confirmation is obtained that the patient has no citrus allergy or intolerance to lemon. Patients are encouraged to fast for at least 1 hour to avoid dietary interference and stop thyroid-

blocking agents such as iodide or perchlorate for 48 h. The latter is important as the uptake of ^{99m}Tc-pertechnetate anions in salivary glands is handled in a manner analogous to radioiodine [45]. Concurrent use of loop diuretics such as furosemide and bumetanide should be carefully evaluated since the glandular uptake of ^{99m}Tc-pertechnetate anions is partly driven by Na+/K+/Cl- co-transporter localized in the basolateral membrane of the acinar (fluid secreting) cells [46]. Scintigraphy is performed with the patient lying supine in Water's position (chin and nose touching collimator face), followed by intravenous injection of approximately 370–555 MBq (10–15 mCi) of ^{99m}Tc-pertechnetate. Dynamic blood flow study is performed immediately after injection for 5 s/frame for 1–2 min, followed by sequential images of 2 min/frame for up to 20 min on a large field-of-view gamma camera equipped with low-energy high-resolution parallel hole collimator and 15% energy window around the 140 keV photopeak of ^{99m}Tc. Images are stored in 128×128 matrix. The second dynamic study is performed for 2 min/-frame for another 20 min and patient is orally administrated with 5–10 ml of lemon juice ± mixed with water, using a straw, syringe or dropper. In ideal conditions, the patients should be unaware of the lemon stimulation until the time of administration, to prohibit psychologic stimulation of the glands. Post lemon administration, the patient is encouraged to squish, hold and distribute the lemon juice around his mouth before swallowing, without moving the head to achieve maximum stimulus on salivary gland excretion. Alternatively, a single longer dynamic acquisition may also be used, incorporating both the prestimulus and post stimulus phase [45].

Both qualitative and quantitative assessments are important in scan interpretation. A region of interest (ROI) drawn over each salivary gland (left and right parotid, left and right submandibular glands) and background (left or right temporal brain region) can help in generation of time activity curves. Normal glands show early and prompt uptake with fast-rising time-activity curve followed by a slow-rising component to nearly a plateau within 6–10 min post injection. Post-lemon stimulation, there is a sharp decline of activity in the gland with subsequent slow build up (**Fig. 2**). Qualitative assessment is usually performed in comparison to background thyroid gland uptake. Salivary gland uptake is considered normal when visually similar to thyroid uptake, in the absence of any underlying thyroid pathology [47]. Uptake is abnormal if the intensity is reduced, often seen in early glandular dysfunction, or severely reduced with complete absence of radioactivity in the salivary glands [47, 48]. Normal excretion is qualitatively defined as visual drop in the gland activity post stimulation, intensity similar to background activity at nadir.

In patients with history of thyroid cancer and radioiodine ablation, qualitative assessment is usually done by visual assessment of degree of ^{99m}Tc-pertechnetate uptake in salivary glands compared to background. Some articles describe a three-point scoring system where, uptake scores 0, 1 and 2 are respectively defined as severe (no uptake, similar to background), mild-to-moderate (reduced uptake but greater than background), and no dysfuntion (normal uptake) [49]. In the absence of reference background, normal uptake is difficult to define and quite subjective. Often there is asymmetry noted in the uptake patterns of bilateral parotid and submandibular glands which helps in relative assessment of function [20, 50]. Due to the limitations of visual assessment being observer-dependent and limited capacity to discriminate between borderline results, semiquantitative analysis has been proposed. Abnormality is indicated if the criteria are met with either visual or semiquantitative analysis. Several studies have described different criteria for classification and interpretation of salivary gland function [48, 51].

There are two components for semi-quantitative assessment, i.e., the gland uptake or extraction capacity and excretion from the gland into the oral cavity. The gland extraction of radioactivity from the circulation can be measured by calculating uptake rate parameter obtained from the initial slope of time activity curve, expressed as count rate per second (cps/s), with average normal value of 0.10±0.09 cps/s for all salivary glands, calculated by Loutfi et al. in 21 healthy volunteers [51]. Using circular ROI with either right or left temporal brain region as reference background, uptake ratio (UR) of salivary glands was calculated i.e. UR=(maximum uptake-background uptake)/background uptake. Decreased uptake was defined as uptake ratio <2.28 for parotid gland and <1.60 for submandibular glands [47]. The normal uptake (U) percentage in each salivary glands reflecting the parenchymal function can be estimated as Uptake% = [(count of gland*calibration factor)/activity

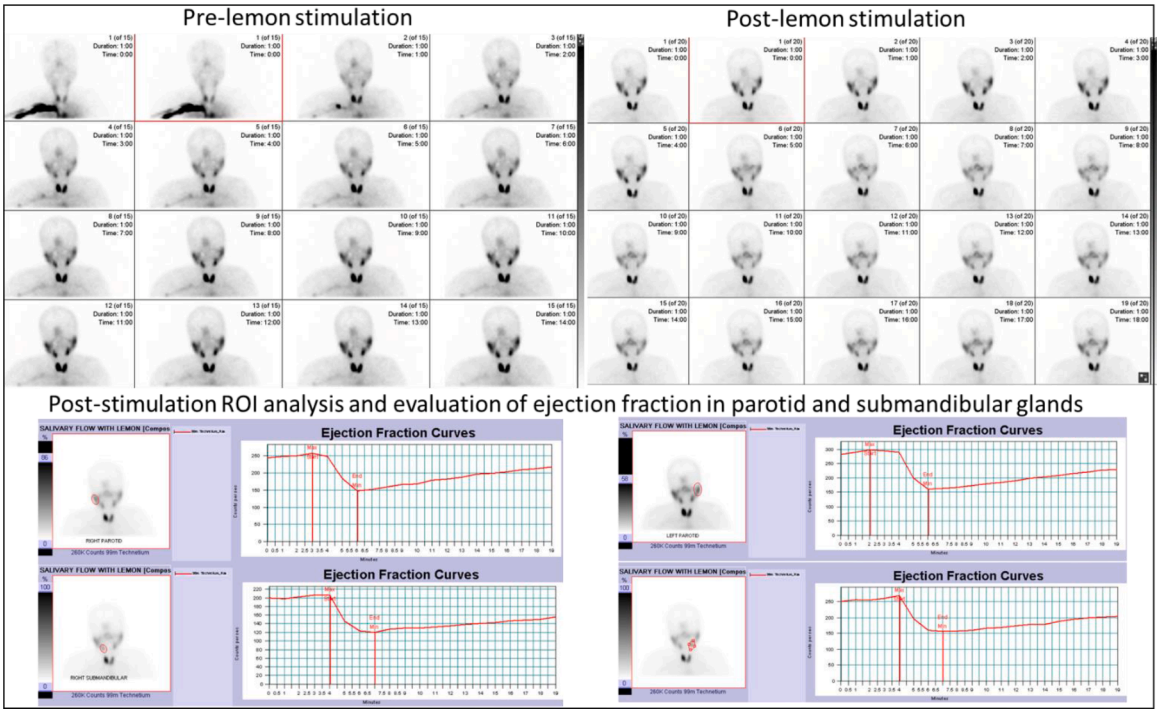

Fig. 2. Salivary gland scintigraphy using ^{99m}Tc-pertechnetate ($^{99m}TcO_4^-$).

injected]*100. Normal uptake% for parotid glands was estimated to be 0.45%±0.14 and for submandibular glands 0.39%±0.12, by Klutman et al. by averaging 12–14 min counts post-injection ($U_{12–14}$), with background ROI located over the brain [52].

Given that the radiation induced salivary gland toxicity also affects the secretory or excretory function, the quantitative assessment of washout rate is another parameter that has been found to be beneficial. In patients with equivocal findings on visual analysis, quantification of washout can enable the diagnosis of mild damage. Ejection fraction (EF) is calculated post lemon stimulation, as $EF = [(U_{max} - U_{min})/ U_{max}]*100$; with normal value estimated to be approximately 50% (49.5%±10.6) for parotid and 40% (39.1%±9.2) for submandibular glands [52]. Garcia-Gonzalez et al. calculated the normal EF of 56% for parotid and 39% for submandibular glands in 83 non-Sjogren's syndrome patients [53]. Similar results were also seen in another study with normal volunteers, with mean ejection fraction of 56.5%±8.9 in salivary glands [54]. A 4-grade scoring system was devised for assessment of patients with Sjogren's syndrome, with grades 0, 1, 2 and 3 respectively defined as normal (>50% excretion rate), mild dysfunction (excretion rate 40–50%), moderate dysfunction (excretion rate 25–40%) and severe dysfunction (<25% excretion rate) [54]. There is dearth of literature on assessing the clinical impact of the scoring system on predicting the outcomes of patients. Fewer articles have evaluated the washout rate in thyroid cancer patients post-radioiodine ablation and have used variable scoring systems, such as relative comparison of the gland function or use of a three-point scoring system, where 0, 1 and 2 are respectively defined as severe dysfunction (100% retention), mild to moderate dysfunction (10–100% retention) and normal (<10% retention post lemon juice stimulation) [49, 55].

Due to lack of published data regarding the use of salivary gland scintigraphy in assessment of toxicity secondary to PSMA-targeting radioligand therapies, no definite conclusions can be drawn regarding the cut off values for quantitative parameters. However, ample evidence is available to support that salivary gland scintigraphy is a suitable imaging modality for evaluating gland impairment.

Prevention of salivary gland toxicity

For protection of salivary glands and reduction of undesirable radiation exposure, the focus is (i) either to reduce the accumulation of radioligand in the glands, (ii) or to accelerate the clearance of radioactivity from the glands. External cooling using icepacks is hypothesized to cause vasoconstriction, reduce blood flow, and decrease PSMA accumulation in salivary glands. The frozen icepacks are applied on both cheeks starting 30 min prior to treatment, up to 4 h post administration of ^{177}Lu-PSMA-617, with frequent interval replacement of fresh icepacks. A study by van Kalmthout et al. showed relatively mild although significant difference in the SUV max and SUV peak values of ^{68}Ga-PSMA between left and right parotid gland in 24 patients when unilateral icepack was used, applied 30 min prior to radiotracer injection up to the termination of the scan [56]. The absolute reduction in SUV max and SUV peak was 14.52 and 13.45%, respectively. However, no significant difference was seen in ^{68}Ga-PSMA uptake in 20 patients with bilateral icepacks, compared to the control group [56]. Several studies have previously used external cooling methodology to reduce salivary side effects, while assessing efficacy and toxicity of ^{177}Lu-PSMA therapy in metastatic prostate cancer, as described in Table 1 [13, 21-23]. Limited evidence suggests refraining from gustatory stimulation with food during the administration and early biodistribution phase of radionuclide therapy with PSMA-ligands to reduce accumulation within the glands [44]. Use of botulinum toxin to suppress the salivary gland metabolism may be a method for reducing off-target toxicity in PSMA radioligand therapy and warrants further studies. Anecdotal evidence in a 63-years-old man showed that 45 days post-USG guided intraparenchymal parotid injection of 80 units of botulinum toxin A reduced the parotid SUVmean on ^{68}Ga-PSMA PET/CT by 64%, compared to baseline [57]. Few studies have evaluated role of monosodium glutamate, oral administration of folic polyglutamate tablets and addition of cold PSMA ligand PSMA-11 to the standard ^{177}Lu-PSMA-617 dose in reducing salivary gland uptake of ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617 respectively, in preclinical animal models [58–60].

The common methods utilized to accelerate clearance of radioactivity from salivary glands include lemon juice and Vitamin C administration. A prospective study by Yu et al. enrolled 31 patients who underwent dynamic PET/CT imaging with ^{68}Ga-PSMA-11, of which 11 received oral Vitamin C, 30 min after starting the dynamic acquisition. A significant decrease in the SUVmean values of the parotid and submandibular glands was noted in patients who received Vitamin C, compared to the control group [61]. The study demonstrated that there is increased radiation clearance and decreased accumulation in the salivary glands, in association with oral Vitamin C administration. However, the reduction of radioactivity was transient since the Vitamin C stimulation occurred only 30 min from the start of imaging process, rather than a continuous stimulation. The radioactivity continued to accumulate in the salivary glands after the effect of Vitamin C disappeared.

Treatment of salivary gland toxicity

Basic remedies for the treatment of xerostomia include proper hydration, increasing humidity at nighttime using a humidifier or decreasing indoor heat, avoidance of irritating dentifrices and crunchy hard-foods, and use of sugar-free chewing gums/candies. FDA approved sialagogues, such as pilocarpine and cevimeline, have shown efficacy in all stages of hyposalivation. Pilocarpine (Salagen™) is typically administered at a dose of 5 mg, while Cevimeline (Evoxac™) at a dose of 30 mg, three times a day before meals for at least 3 months [62]. These drugs are cholinergic parasympathomimetics that bind to muscarinic-M3 receptors and can cause pharmacologic smooth muscle contraction in humans and stimulation of various exocrine glands. The most common side effect of these drugs is sweating. Other less common side effects may include cutaneous vasodilation, nausea, diarrhea, bronchoconstriction, hypotension, bradycardia, increased urinary frequency and vision problems. Both drugs are relatively contraindicated in patients with uncontrolled asthma or COPD, and in patients using beta-adrenergic blockers, and should be used with caution in patients with active gastric ulcers or uncontrolled hypertension. Pilocarpine is also contraindicated in patients with narrow-angle glaucoma and iritis [63]. Salivary substitutes and mouthwash have no proven effect but may help temporarily relieve the symptoms. Mucin containing lozenges have been found to be beneficial in providing longer moistening of oral cavity and overall improvement in oral function [64]. In patients with refractory xerostomia secondary to radioiodine treatment, there is suggested role of ductal obstruction as well that may cause prolongation of symptoms. Canzi et al. analyzed data from eight studies to assess the impact of sialendoscopy intervention on outcomes of 122 patients suffering from radioiodine induced sialadenitis. They noted that the intervention helped in resolving duct stenosis and mucus plugs that led to complete or partial resolution of symptoms in approximately 89% of patients [65]. The other treatment options that are currently under investigation include intraglandular gene therapy, down-regulation of key regulators of DNA damage-induced apoptosis (antisense therapy), and stem cell therapy [66].

Conclusion

PSMA-radioligand therapies such as ^{177}Lu-PSMA-617 is associated with radiation dose to major salivary glands that may lead to xerostomia. The overall incidence of xerostomia is quite variable among studies. Dose reduction techniques such as hydration can help reduce salivary gland radiation dose and toxicity, while external cooling has shown limited role with temporary effects. Several other preventive

strategies to reduce radiation-induced salivary gland damage are currently under investigation. Salivary gland scintigraphy is a noninvasive highly reproducible low-cost technique, useful for objective and quantitative assessment of salivary flow/function of parotid and submandibular glands and can help detect early changes in post-radiation setting. Prospective studies using salivary gland scintigraphy in patients receiving radioligand therapy would provide objective assessment for follow up of functional gland impairment.

Conflicts of interest

There are no relevant conflicts of interest.

CRediT authorship contribution statement

Sonia Mahajan: Conceptualization, Investigation, Methodology, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Validation. **Ravinder K. Grewal:** Conceptualization, Data curation, Supervision, Writing – review & editing. **Kent P. Friedman:** Investigation, Methodology, Data curation, Writing – review & editing. **Heiko Schöder:** Conceptualization, Data curation, Supervision, Writing – review & editing, Validation. **Neeta Pandit-Taskar:** Conceptualization, Data curation, Supervision, Writing – review & editing, Validation.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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