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ORIGINAL ARTICLE

Initial clinical experience performing sialendoscopy for salivary gland protection in patients undergoing ^{225}Ac-PSMA-617 RLT

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Abstract

Purpose The main side effect of prostate-specific membrane antigen targeting alpha therapy (PSMA TAT) is dry mouth syndrome. Inflammation of the salivary glands and consequent reduced salivary function have been reported in patients after radioiodine therapy. The beneficial effects of sialendoscopy on radiation-induced inflammation in tissue are well known. Thus sialendoscopy with dilatation, saline irrigation and steroid injections (prednisolone) was performed before and after ^{225}Ac-PSMA-617 TAT to reduce inflammatory effects in the salivary glands and to improve or prevent xerostomia.

Methods Eleven men with metastatic castration-resistant prostate cancer (mean age 68.5 years, range 58–80 years) underwent sialendoscopy, dilatation, saline irrigation and steroid injection of both submandibular and both parotid glands before or after every cycle of ^{225}Ac-PSMA-617 TAT. Sialendoscopy and steroid injection were performed by a senior ENT physician. Quality of life was evaluated using two health-related quality of life (HRQOL) questionnaires, the Xerostomia Questionnaire (XQ) and the Xerostomia Inventory (XI) before and 3 months after the intervention.

Results In all 11 patients both parotid and both submandibular glands were affected by radiation sialadenitis and sialendoscopy was performed. The patients experienced no complications after sialendoscopy, and showed a significant improvement in HRQOL as measured using the XQ and XI. After sialendoscopy the XQ score decreased significantly from 77.7 ± 13.6 to 42.7 ± 14.8 ($p = 0.003$) and the XI score decreased from 44.5 ± 6.9 to 25.8 ± 12.8 ($p = 0.003$). Due to the limited number of patients we only report tendencies.

Conclusion Sialendoscopy with dilatation, saline irrigation and steroid injection had beneficial effects on salivary gland function and HRQOL in patients undergoing ^{225}Ac-PSMA-617 RLT. However, even with sialadenoscopic support after multiple cycles of TAT, salivary gland function was reduced and xerostomia was present. Therefore, not only inflammation but also the direct effect of radiation is a putative cause of dry mouth. Further research is necessary to determine the main side effects of PSMA TAT.

Keywords PSMA-617 · Ac-225 · TAT · Xerostomia · PSMA-RLT

Introduction

PSMA-617 is a low molecular weight ligand of prostate-specific membrane antigen (PSMA) which is used for targeting prostate cancer, but also shows some physiological binding to the salivary and lacrimal glands [1, 2]. Recently published prospective phase 2 data suggest a high occurrence of 80% of grade 1 xerostomia even for ^{177}Lu-PSMA-617 [3]. Targeted alpha therapy (TAT) was introduced as an experimental treatment in patients with metastasized castration-resistant prostate cancer (mCRPC) in whom all approved therapies had been exhausted and who were not eligible for ^{177}Lu-PSMA radioligand therapy (RLT) [4, 5]. Especially in patients with diffuse type tumour infiltration in the bone marrow,

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^{225}Ac-PSMA-617 TAT seems to be beneficial due to its short range in tissue and lower impact on the red marrow in comparison with beta-emitting nuclides such as ^{177}Lu and ^{90}Y [6]. Unfortunately, a lower level of haematological toxicity may be accompanied by a higher rate of grade 2 xerostomia [5]. Due to the biodistribution and physiological uptake in the salivary glands, dry mouth (xerostomia) is the main side effect of the therapy which depends on the therapeutic nuclide administered (alpha or beta emitter), the administered activity and the number of treatment cycles [4, 7].

It is known that patients receiving radioiodine therapy (RIT) can show xerostomia due to radiation-induced inflammation in the salivary glands [8, 9]. In patients with dry mouth syndrome after RIT, conservative treatment strategies such as frequent sipping of water and saliva substitution might be sufficient [10]. However, depending on the subjective level of distress, sialendoscopy after RIT shows beneficial effects on salivary function and xerostomia symptoms [11, 12]. In our previous experience with ^{225}Ac-PSMA-617, we found that radiation sialadenitis with consequent xerostomia was a major complaint/side effect. We considered that the described beneficial effects of sialendoscopy in patients receiving RIT might be transferable to patients receiving ^{225}Ac-PSMA-617 TAT.

As demonstrated by immunostaining [5] and well in line with the observations with full-length and minibody PSMA antibodies [13, 14] which show no uptake in the salivary glands, only a minimal proportion of salivary gland uptake can be explained by PSMA-specific binding. The mechanism of damage is still unknown. It is considered that radiation-induced inflammation and consequent occlusion of the salivary ducts are responsible for the damage.

In this study we evaluated the effectiveness of sialendoscopy with dilatation, saline irrigation and steroid injection into the submandibular and parotid glands in reducing radiation-induced inflammation and in improving or preventing xerostomia in patients undergoing therapy with ^{225}Ac-PSMA-617.

Materials and methods

Patients

In this single-centre study, patients who had received ^{225}Ac-PSMA-617 salvage therapy for advanced stage mCRPC at the University Hospital Heidelberg between 2015 and 2017 were evaluated. Patients who developed severe xerostomia and high levels of distress that did not respond to conservative treatment were informed about the possibility of treating xerostomia symptoms with a sialendoscopic procedure and were referred to the Ear, Nose and Throat (ENT) Department according to the clinical indication. At the initial consultation in the ENT Department a routine assessment was performed by the same physician (O.C.B.). The assessment included patient interview, clinical examination, sonography and evaluation of health-related quality of life (HRQOL) using the Xerostomia Questionnaire (XQ) and the Xerostomia Inventory (XI) patient-reported outcome measures (PROM) as the standard quality control in all patients, and general information (age, allergies, medication, medical and surgical history). The standard reporting forms and clinical examinations were repeated at the clinical follow-up 3 months after the intervention, and were evaluated as part of an observational study which was approved by the institutional review board (S-085/2018) and conducted according to the principles of the Declaration of Helsinki. All patients provided signed informed consent. Existing clinical data were evaluated retrospectively.

Sialendoscopy procedure

Patients were offered a sialendoscopy procedure if no major contraindications were present (for example, if both parotid and submandibular glands had been resected). All patients underwent sialendoscopy of both parotid and both submandibular glands under local anaesthesia in a standardized manner performed by the same surgeon (O.C.B.). The mucosa of the affected orifice was anaesthetized with lidocaine spray before dilatation with lacrimal probes of different sizes (0 to 0000). Additionally, 2 ml of 2% lidocaine was applied to every duct. Next, the parotid duct and then the submandibular duct were cannulated with a 1.1 mm sialendoscope (Karl Storz, Tuttlingen, Germany) which was further advanced under duct visualization with constant irrigation with isotonic saline solution. Debris and mucous plugs were removed either by irrigation or using forceps. If present, stenotic ducts were dilated with the 1.1 mm and if applicable a 1.6 mm sialendoscope (Karl Storz). At the end of the procedure each gland was additionally flushed with 100 mg of prednisolone under direct visualization. The procedure was carried out without single shot antibiotics.

Scintigraphy of the salivary glands

Salivary gland scintigraphy was performed at baseline and after the intervention to quantify secretory and excretory gland function. Patients were advised to refrain from eating and drinking 6 h before scintigraphy. Brushing of the teeth and chewing gum were not allowed before scintigraphy. After administration of 183 ± 24 MBq ^{99m}Tc-pertechnetate, dynamic imaging of the head and neck region was performed over 30 min. To stimulate excretion of the salivary glands, 10 ml diluted citric acid was administered orally 20 min after injection. Quantitative analysis was performed using time–activity-curves of all four salivary glands. The reference rates for

uptake and excretion of the parotid and submandibular glands were those used by Bohuslavizki et al. [15].

Assessment of therapeutic response

HRQOL was measured before and after the intervention using the the XQ and XI PROMs. The XQ is a disease-specific PROM for xerostomia developed by Eisbruch et al. in 2001 [16, 17] and shows good internal consistency, reliability and sensitivity to changes in xerostomia [18]. The XQ includes questions on eight mouth dryness symptoms which are graded on a Likert scale from zero to ten, with higher scores indicating higher discomfort due to xerostomia. A Likert scale is a psychometric scale commonly used in research involving questionnaires. The cumulative score is transformed to a scale from 0 to 100. The XI PROM is also a disease-specific self-reported questionnaire developed by Thomson et al. in 1999 and includes 11 items [19]. It includes additional questions to the XQ on further aspects of dryness including dry eyes, lips and skin and waking at night because of mouth dryness. Patients rate symptom severity on a scale from one (never) to five (always). To calculate the final score, single scores are added. The best and worst possible scores regarding symptoms of xerostomia in this evaluation were 11 and 55, respectively.

Macroscopic findings during sialendoscopy

Patients were also graded with regard to sialendoscopic findings using an in-house scale (the Bulut scale [20]) that classifies tissue damage using an arbitrary scale from 0 to IV. In grade 0 no endothelial changes or pathology that correlate with the clinical findings of chronic sialadenitis during the sialendoscopy procedure are detectable. In grade I (early stage) prominent vascularity of the endothelium without any mucous plugs, debris or stenosis is present. Grade II is the same as grade I but with mucous plugs or debris. In grade III the endothelium is avascular and appears white with or without mucous plugs and debris, and with or without early or mild duct stenosis. Grade IV is the same as grade III but with severe duct stenosis (>50%).

Statistical analysis

The statistical analysis was performed using the SPSS Statistics, version 22.0.0 (IBM, Armonk, NY, USA). As the number of patients was expected to be less than 20, a descriptive statistical analysis was performed. The significance of differences in the data between before and after the intervention was evaluated using Wilcoxon's signed ranks test for dependent samples. A result was declared statistically significant if the p value was less than 0.05.

Results

Eleven male patients (mean age 68.5 years, range 58–80 years) were selected for the study. In all patients both parotid and both submandibular glands were affected by radiation-induced sialadenitis, and therefore sialendoscopic treatment was administered according to clinical indication. Three patients underwent sialendoscopy after the first cycle of ^{225}Ac-PSMA-617 TAT, three after the second cycle, four after the third cycle and one after the fourth cycle.

The XQ and XI scores before and 3 months after the intervention are summarized in Table 1. The mean time between the two administrations of the HRQOL questionnaires was 98 ± 9.8 days. Patients treated with sialendoscopy showed a significant improvement in HRQOL according to the XQ and XI. After sialendoscopy the XQ score decreased significantly from 77.7 ± 13.6 to 42.7 ± 14.8 ($p = 0.003$) and the XI score decreased from 44.5 ± 6.9 to 25.8 ± 12.8 ($p = 0.003$).

Because of the limited number of patients we are only able to report tendencies. The patients did not experience any complications after sialendoscopy. The XQ and XI scores in relation to the number of ^{225}Ac-PSMA-617 RLT cycles are summarized in Table 2 and Fig. 1. There was a trend towards higher XQ and XI scores in patients who had undergone several RLT cycles. Sialendoscopic findings in patients after one RLT cycle were grade 0 or I, After two RLT cycles patients showed pathological findings (grades III and IV). After three or more RLT cycles all patients showed grade III or IV disease (Fig. 2). There was a trend towards higher salivary duct damage in patients after several RLT cycles.

Scintigraphic findings

Parotid scintigraphy was performed in all patients, Figure 3 shows the scintigraphic findings in a patient who received sialendoscopy after each cycle of ^{225}Ac-PSMA RLT, and for comparison Fig. 4 shows the scintigraphic findings in a patient without sialendoscopy after two cycles of ^{225}Ac-PSMA RLT. Regions of interest were defined to enable quantitative evaluation of the four major salivary glands. Sialendoscopy showed a decrease in nuclide accumulation, especially in the parotid glands after PSMA TAT. As shown in Table 3, there were changes in parotid and the submandibular gland function, especially excretory function of the submandibular glands, over time. Figure 3 shows the course of secretory and excretory function during PSMA TAT in a patient treated with ^{177}Lu-PSMA-617 RLT. The first salivary gland scintigraphy after the first cycle showed that the function of the left parotid gland (Fig. 3, upper row, green line) was already reduced, and the other glands showed normal function. After the second cycle, the secretory and excretory functions of both parotid glands were reduced, and the submandibular glands showed normal function. After the third cycle, the secretory and excretory

Table 1 Health-related quality of life questionnaire scores before and 3 months after sialendoscopy

Questionnaire	Score (mean ± standard deviation)	*p* value
Xerostomia Questionnaire		
Before sialendoscopy	77.7 ± 13.6	0.003
After sialendoscopy	42.7 ± 14.0	
Xerostomia Inventory		
Before sialendoscopy	44.5 ± 6.9	0.003
After sialendoscopy	25.8 ± 12.8	

functions of all four glands were reduced. In comparison with patients without sialendoscopy, our impression was that changes in salivary gland function were postponed by one cycle. After three or more cycles of PSMA TAT, salivary gland function was reduced regardless of sialendoscopy. Because of the limited number of patients after different cycles, we did not perform a statistical analysis and can only report tendencies.

Discussion

In this study we evaluated the effectiveness of sialendoscopy, dilatation, saline irrigation and steroid injection of the submandibular and parotid glands in reducing radiation-induced inflammation and in improving or preventing xerostomia in patients undergoing therapy with ^{225}Ac-PSMA-617.

Due to physiological tracer uptake in the salivary glands, xerostomia is a well known side effect of PSMA TAT [4]. Due to the tumour sink effect, it is less common during the first treatment cycle in patients with a high tumour burden [21, 22], and typically appears after the second or third cycle of PSMA TAT. It has been reported that even patients with a favourable response may discontinue PSMA TAT because of the reduction in quality of life related to dry mouth syndrome and dysgeusia [4]. As summarized recently [23], xerostomia has also been reported to occur as a side effect of beta emitter-based ^{131}I-MIP1095 PSMA therapy [24, 25], but due to more refined dosimetry is only a minor issue for ^{177}Lu-PSMA-617 [22]. However, in a prospective phase 2 trial, 80% of patients

Table 2 Health-related quality of life questionnaire scores before and 3 months after sialendoscopy in relation to the number of radioligandtreatment cycles

	Number of patients	Score (mean ± standard deviation)
Sialendoscopy after the first treatment cycle		
Xerostomia Questionnaire		
Before sialendoscopy	3	59.6 ± 9.3
After sialendoscopy	3	28 ± 3.7
Xerostomia Inventory		
Before sialendoscopy	3	36 ± 4.4
After sialendoscopy	3	22.7 ± 2.5
Sialendoscopy after the second treatment cycle		
Xerostomia Questionnaire		
Before sialendoscopy	3	77.2 ± 1.8
After sialendoscopy	3	46.8 ± 4.8
Xerostomia Inventory		
Before sialendoscopy	3	43.7 ± 3.2
After sialendoscopy	3	32 ± 3
Sialendoscopy after the third treatment cycle		
Xerostomia Questionnaire		
Before sialendoscopy	4	88.2 ± 4.8
After sialendoscopy	4	46.8 ± 17.4
Xerostomia Inventory		
Before sialendoscopy	4	50.8 ± 3.8
After sialendoscopy	4	33.3 ± 2.8
Sialendoscopy after the fourth treatment cycle		
Xerostomia Questionnaire		
Before sialendoscopy	1	91.2
After sialendoscopy	1	57.6
Xerostomia Inventory		
Before sialendoscopy	1	47
After sialendoscopy	1	27

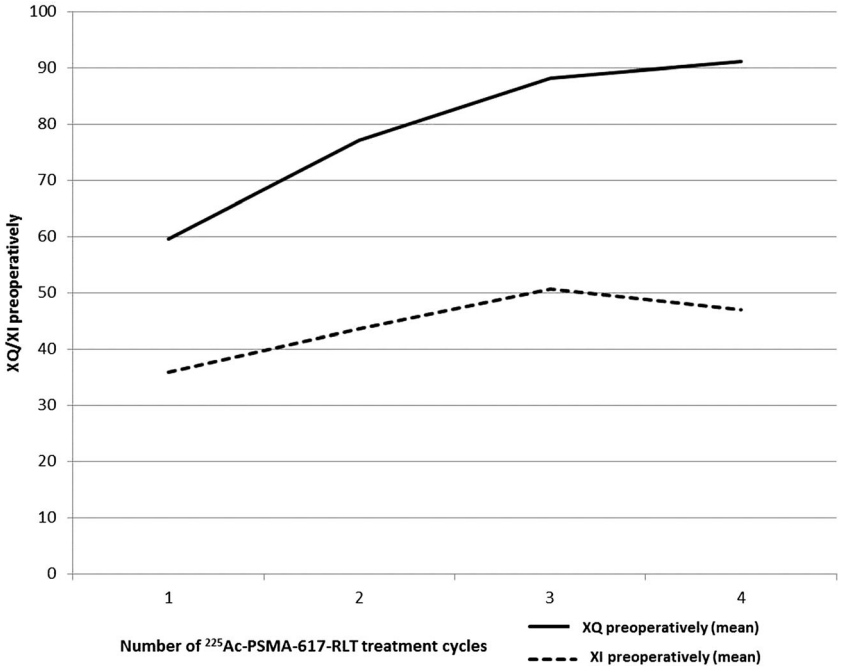

Fig. 1 Xerostomia Questionnaire (XQ) and Xerostomia Inventory (XI) questionnaire scores in relation to the number of ^{225}Ac-PSMA-617 RLT cycles. Higher scores indicate higher discomfort due to xerostomia. There was a trend towards higher XQ and XI scores in patients after several treatment cycles

reported grade 1 xerostomia even with ^{177}Lu-PSMA-617 RLT [3]. Ice-pack cooling of the salivary glands to reduce blood perfusion and consequently nuclide uptake in the salivary glands has also been reported not to be beneficial [26].

The evaluation of disease-specific quality of life questionnaires showed that patients who received sialendoscopy benefited from this minimally invasive intervention. The combination of irrigation with saline, dilatation with the sialendoscope and intraductal steroid administration was well tolerated and helped delay xerostomia. However, both sialendoscopy and parotid scintigraphy showed parenchymal destruction over time (Fig. 2) and loss of salivary gland function (Fig. 3) that depended on the number of treatment cycles. After four cycles of TAT, all patients had dry mouth syndrome. Therefore, the assumption that only radiation-induced sialadenitis and consequent xerostomia occurs after repeated

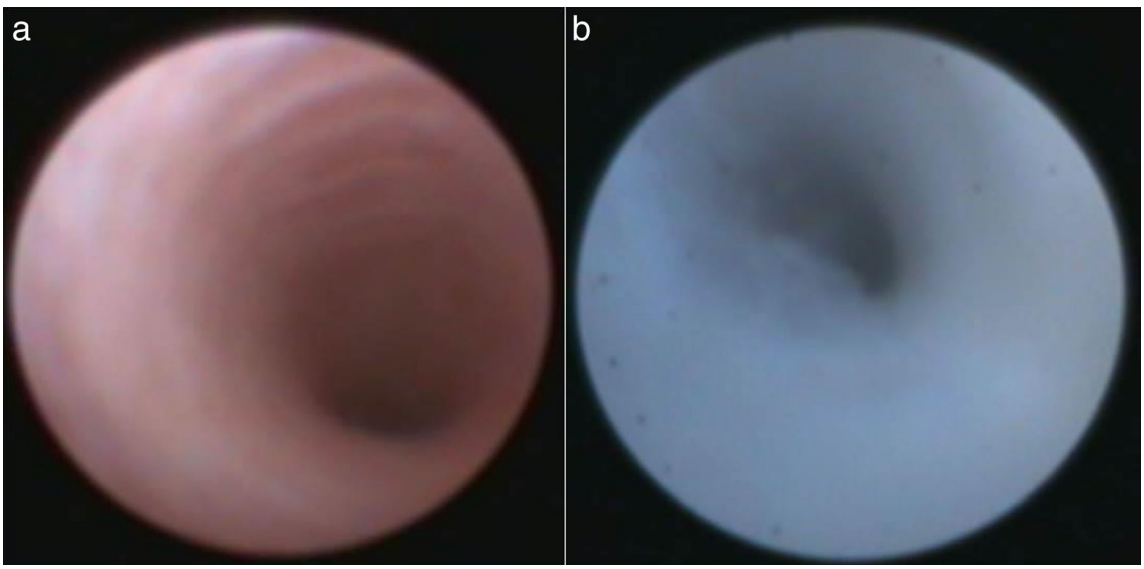

Fig. 2 Intraoperative imaging and scoring of the parotid duct according to the Bulut scale [20]. **a** Parotid duct endothelium without pathology, and with normal configuration and endothelial vascularization. **b** Left parotid duct after the third cycle ^{225}Ac-PSMA-617 TAT shows severe changes in the endothelium and signs of grade III radiation-induced sialadenitis. In grade III disease the endothelium appears avascular with mucous plugs and mild duct stenosis

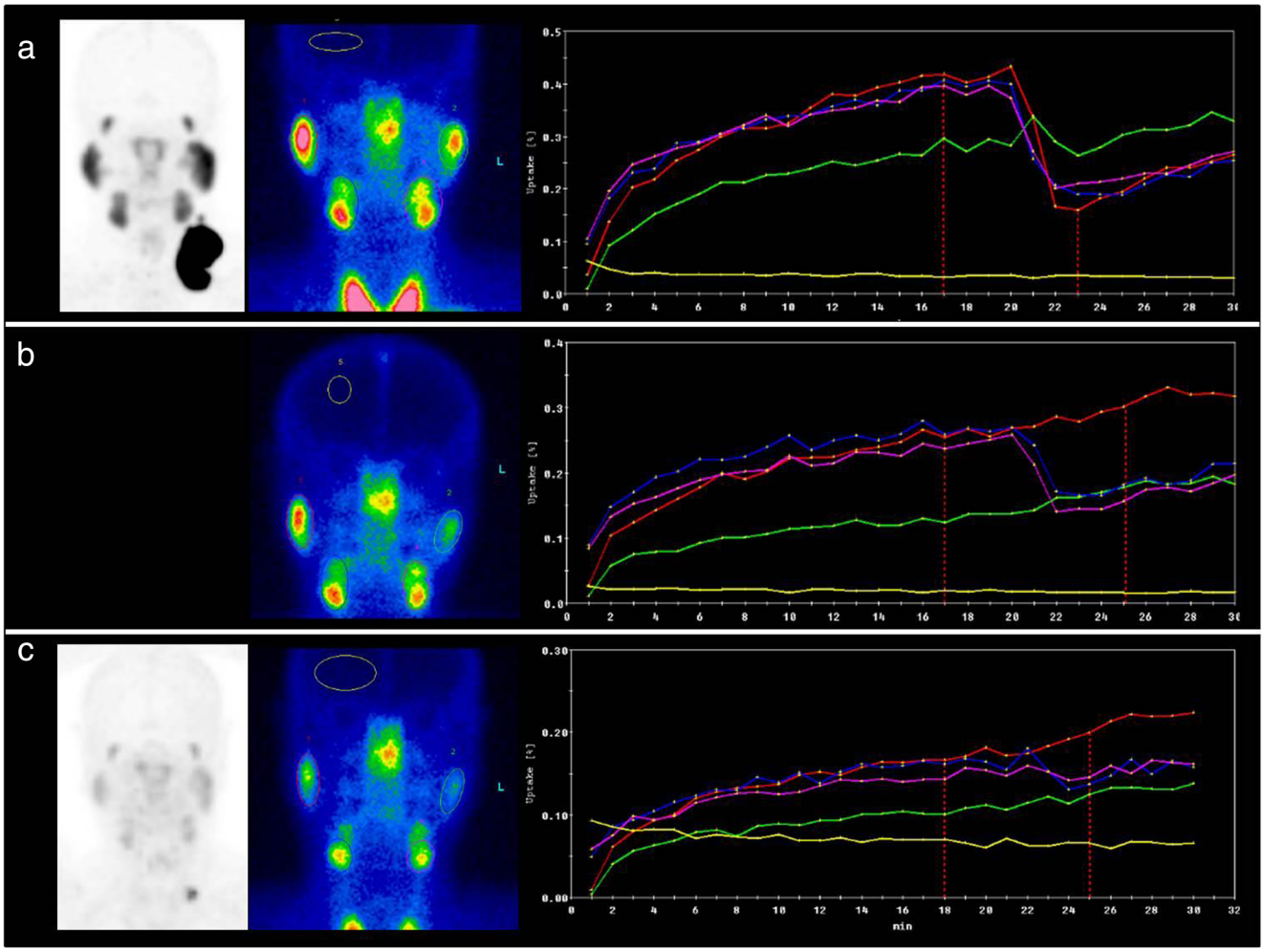

Fig. 3 Parotid scintigraphy after each cycle of PSMA TAT in a patient who received sialendoscopy. **a** After the first cycle. **b** After the second cycle, the secretory and excretory function of both parotid glands is reduced, and the submandibular glands show normal function. **c** After the third cycle, the secretory and excretory function of all four glands is reduced. *Red lines* right parotid gland, *green lines* left parotid gland, *blue lines* left submandibular gland, *purple lines* right submandibular gland, *yellow lines* background. The left red vertical dotted lines visualize the time point of application of citric acid, the right red vertical dotted lines visualize the time point of measurement of the excretory function. *Left* PSMA PET/CT maximum intensity projection images of the salivary glands, *middle* ^{99m}Tc-pertechnetate images and ROI definition, *right* time course of tracer uptake

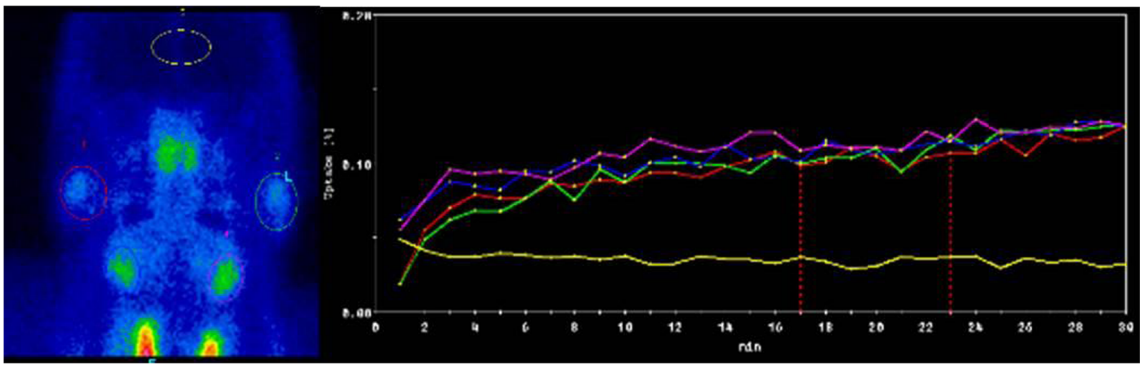

Fig. 4 Parotid scintigraphy after two cycles of TAT in a patient who did not receive sialendoscopy. The patient received three cycles of ^{177}Lu-PSMA-617 RLT (cumulative activity 16 GBq ^{177}Lu) before the two cycles of TAT. *Red line* right parotid gland, *green line* left parotid gland, *blue line* left submandibular gland, *purple line* right submandibular gland, *yellow line* background. The left red vertical dotted lines visualizes the time point of application of citric acid, the right red vertical dotted lines visualize the time point of measurement of excretory function

Table 3 Changes in secretory and excretory function of the parotid and submandibular glands after ^{225}Ac-PSMA-617 TAT. The reference limits are those used by Bohuslavizki et al. [15]

	Secretory phase		Excretory phase	
	Parotid glands	Submandibular glands	Parotid glands	Submandibular glands
Lower limit of the reference range of Umax [%]	0.17	0.15	28.3	20.7
Initial imaging	0.21 ± 0.08	0.25 ± 0.11	34.8 ± 31.7	32.2 ± 18.2
After one or more cycles	0.09 ± 0.06	0.10 ± 0.05	−2.03 ± 9.63	6.80 ± 11.05

Umax[%] implies the maximum uptake in percent of the intraveniously applicated radionuclide in the specific salivary gland

TAT must be reconsidered. We consider that a direct effect of radiation on the parenchyma of the salivary glands may have a greater impact on salivary gland function. This seems to be confirmed by the macroscopic findings during sialendoscopy, as the endothelium showed avascularity with the presence of stenosis.

The technique of sialendoscopy was recently introduced for the treatment of radiation-induced xerostomia. For example, De Luca et al. investigated its use after RIT [27], and it was further evaluated in a review by Canzi et al. [28]. De Luca et al. [27] found that sialendoscopy is a safe and effective method for the treatment of RIT-induced sialadenitis. These authors examined a total of 30 patients after RIT, measuring the symptoms swelling, pain and xerostomia as markers of treatment response. In patients with xerostomia after RIT, sialendoscopy can be considered an effective and minimally invasive intervention with a sufficient success rate [29]. However, as this is the first analysis evaluating sialendoscopy in patients after ^{225}Ac-PSMA-617 TAT, it remains unclear if the dilatation, irrigation with saline and steroid injection or the treatment combination was the reason for improved HRQOL after the intervention in our cohort.

Although several cycles of PSMA TAT were performed in our patients, the salivary glands still showed residual secretory function. The submandibular glands showed a higher tolerance of radiation than the parotid glands as residual excretory function of the submandibular glands was still present, in contrast to the excretory function of the parotid glands, even after several cycles of TAT. However, salivary function was reduced in general after TAT, as shown in Table 3. A case report in one patient describes the potential beneficial effects of injection of botulinum toxin into the salivary glands 45 days before PSMA PET/CT [7]. However, due to lack of further information about this study (no information as whether the patient had PSMA RLT before injection of botulinum toxin or between the injection and the PET/CT scan), whether botulinum toxin leads to an absolute or relative reduction in uptake in the salivary glands remains unclear, as a rapidly increasing tumour volume might also reduce uptake in the salivary glands [22, 30].

Another approach might be the use of amifostine, as this drug has been used and is approved for salivary gland protection during external beam radiotherapy [31]. Evaluation of the data does not provide support for intravenous use of amifostine [31, 32], especially in regards to the side effect of severe hypotension after intravenous administration. As the effect of radiation-induced inflammation on xerostomia seems not to be as great as expected, we consider that the direct effect of radiation is more important, and thus the topical intraductal administration of amifostine (alone or in combination with prednisone and lidocaine) might reduce the direct effect radiation closer to that of radiation-induced inflammation. However, data in the literature on the direct administration of amifostine are not available and we therefore recommend being cautious.

The experience of xerostomia is subjective. but it can be objectively evaluated with, for example, scintigraphy and HRQOL questionnaires. However, we believe that reduced life expectancy is the more oppressive consideration. In our clinical experience most patients agree to ^{225}Ac-PSMA-617 TAT with the knowledge that a side effect is a decrease in quality of life. Patients need to be informed about the side effect of xerostomia, but this should not have a major influence on the therapeutic strategy. Other systemic antitumoral medications such as taxanes are also associated with a spectrum of side effects [33] including myelosuppression with febrile neutropenia, fatigue, neuropathy, changes in taste and stomatitis [34, 35], but are nevertheless commonly used in the treatment of metastatic diseases. We therefore consider that there is a need for further research into the restoration of salivary gland function, but keeping in mind the advantages of antitumoral effects relative to the side effects. Further prospective studies with larger numbers of patients are needed to evaluate and compare different interventions to protect salivary gland function.

Our analysis had certain limitations, especially associated with the retrospective design of this single-centre observational study. Another shortcoming of this analysis was the relatively short follow-up of 3 months. The relatively small number of 11 patients assessed with sialendoscopy, questionnaires and salivary gland scintigraphy weakens the significance of

the data reported, thus encouraging the initiation of prospective studies, preferably multicentre trials, to increase the number of patients available for statistical evaluation. Prospective analyses in the multi-institutional setting would allow comparison of different interventions that would allow the definition of the best possible algorithms for sialendoscopy.

Conclusion

Sialendoscopy had beneficial effects on salivary gland function and HRQOL in patients undergoing ^{225}Ac-PSMA-617 TAT. However, after multiple cycles of TAT, reduced salivary gland function became chronic. Hence, xerostomia symptoms might be caused not only by radiation-induced inflammation but also by the direct effect of radiation. However, dry mouth is a very subjective experience and the reduced life expectancy is the more oppressive consideration. Therefore, the side effect of xerostomia should not have a major influence on the therapeutic strategy. Further prospective studies with larger numbers of patients are needed to evaluate and compare different interventions to protect salivary gland function.

Compliance with ethical standards

Conflict of interest U.H. is the holder of the patent for PSMA-617.

H.R., F.G., P.F. and C.K. are stock holders of Endocyte Inc., West Lafayette, IN, USA.

The other authors declare no conflict of interest.

Ethical approval All procedures performed in this retrospective evaluation involving human participants were in accordance with the ethical standards of the institutional research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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