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PSMA-directed imaging and therapy of salivary gland tumors: a single-center retrospective study

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ABSTRACT

We analyzed the diagnostic performance of prostate specific membrane antigen (PSMA)-PET/CT as well as the dosimetry, efficacy, and safety of ^{177}Lu-PSMA-617-radioligand therapy (PSMA-RLT) in salivary gland malignancies (SGM).

Methods: We identified 28 SGM patients with PSMA-PET/CT from our database. CT and PSMA-PET/CT images were evaluated separately by three blinded readers in joint reading sessions. Pathological findings were grouped into six TNM regions and lesion-based disease extent was classified as no disease (n=1, 4%), unifocal (n=2, 7%), oligometastatic (n=9, 32%), multifocal (n=3, 11%), and disseminated (n=13, 47%).For each region, SUVmax of the lesion with highest uptake was measured and the visual PSMA expression score was evaluated on a per-patient basis using PROMISE criteria. The association between PSMA expression and clinical and histopathological markers was tested using Student's t-test. Five patients underwent PSMA-RLT with intratherapeutic dosimetry. Response assessment was performed using RECIST 1.1, adverse events (AEs) were graded according to CTCAEv5.0 criteria.

Results: Compared to CT, PSMA-PET/CT demonstrated additional metastatic lesions in 11/28 (39%) patients leading to upstaging of TNM and lesion-based disease extent in 3/28 (11%) and 6/28 (21%) patients, respectively. PSMA-PET/CT detected CT-occult local tumor, regional lymph nodes, non-regional lymph nodes and bone metastases in 1 (4%), 4 (14%), 2 (7%) and 4 (14%) patients respectively; no additional lesions were detected in the other pre-defined regions. PSMA expression level was higher than liver in 6 patients (25%). Significantly higher SUVmax was observed in male vs. female patients (15.8 vs. 8.5; p=0.007) and in bone vs. lung lesions (14.2 vs 6.4; p=0.006). PSMA-RLT was discontinued after one cycle in 3/5 patients due to insufficient tumor doses. No CTCAEv5.0 Grade 3 or higher AEs occurred.

Conclusion: In SGM, PSMA-PET/CT demonstrates superior detection rate and led to upstaging in about one third of patients when compared to CT. Male gender and presence of bone metastases were associated with significantly higher PSMA expression. PSMA-RLT was well tolerated but the majority of patients did not have more than one cycle owing to insufficient tumor doses.

Key Words: ^{177}Lu-PSMA; ^{68}Ga-PSMA; PET/CT; theranostics; salivary gland malignancies

INTRODUCTION

Salivary gland malignancies (SGM) are rare head and neck tumors that encompass 24 different histological subtypes, with mucoepidermoid carcinoma and adenoid cystic carcinoma (ACC) being the most frequent ones (*1-3*). SGM most commonly originate from the parotid, submandibular and sublingual glands and are characterized by slow growth and indolent course, but tend to show multiple recurrences and distant metastases (*4*). Although survival outcomes have improved with surgery and postoperative radiotherapy in early and locally advanced stage of the disease, there is no consensus on systemic treatments in recurrent and/or metastatic disease (*5*). No further standard treatment has yet been established for recurrent or metastatic disease. SGM show a high intrinsic resistance to classical cytotoxic drugs. Recently, small phase II trials demonstrated activity of the tyrosine kinase inhibitors lenvatinib or axitinib in ACC (*6,7*). Further, for a subset of patients with specific genetic alteration as NTRK fusions, BRAF mutations or Her2/neu amplifications molecular targeted therapies are available (*8,9*). However, for most patients no molecular targeted therapies are available and those patients are mostly treated with the cytotoxic drugs cisplatin, taxanes, anthracyclins, cyclophosphamide or 5-fluororuacil with only moderate response rate. Taken together, there is a huge unmet medical need to improve the palliative treatment of patients with recurrent or metastatic SGM.

Routine imaging is performed by virtue of magnetic-resonance imaging (MRI) as well as computed tomography (CT) (*10*). Additional ^{18}F-FDG-PET can increase sensitivity, especially with regards to N- or M-stage impacting therapy management in 12.5% of cases (*11*). Furthermore, recent immunohistochemical and PET imaging studies have shown increased prostate specific membrane antigen (PSMA) expression in ACC implying that PSMA-targeted imaging may

improve staging accuracy and ^{177}Lu-PSMA-617-radioligand therapy (PSMA-RLT) can be feasible in a theranostic setup (*12-15*).

The aim of this study is to investigate the diagnostic role of PSMA PET/CT and the safety, feasibility, and efficacy of PSMA-RLT in patients with SGM.

MATERIALS AND METHODS

Eligibility Criteria

Our institutional database was screened for SGM patients undergoing PSMA-PET/CT from May 2015 to October 2021. All patients gave written informed consent to undergo clinical PSMA imaging or therapy. The retrospective analysis of available data was approved by the local institutional review board, the requirement to obtain informed consent was waived (University of Duisburg-Essen, Medical faculty; protocol number: 21-10370-BO).

PSMA PET/CT Image Acquisition

Values are presented as median [interquartile range]. Image acquisition was performed in accordance with the Joint European Association of Nuclear Medicine/ The Society of Nuclear Medicine and Molecular Imaging procedure guidelines: 63 [26] minutes / 98 [21] minutes after the administration of 116 [44.5] MBq ^{68}Ga-PSMA-11 (n=21; 75%) / 281 [97] MBq / ^{18}F-PSMA-1007 (n=7; 25%), respectively (*16*). Images were acquired on a Siemens Biograph mCT (11/28, 39%) or Siemens Biograph Vision 600 (17/28, 61%) PET/CT System (Siemens Healthineers, Erlangen, Germany).

Image Interpretation

CT and PSMA-PET/CT scans were analyzed separately two weeks apart by two blinded nuclear medicine physicians (C.C., M.W.) in joint consensus sessions and an additional board-certified radiologist (C.B.) for the CT reading session. CT scans were read first and for TNM-based analysis, pathological findings were grouped into the following categories: local tumor, regional lymph nodes, non-regional lymph nodes, lung, bone, other regions.

For analysis the lesion-based disease extent, CT and PSMA-PET/CT analysis results were each grouped into the following disease categories: (a) no evidence of disease, (b) unifocal disease (one lesion), (c) oligometastatic disease (2-5 lesions), (d) multifocal disease (6-10 lesions), (e) and disseminated disease (>10 lesions). For PSMA-PET/CT analysis, the maximum standardized uptake value (SUVmax) of the one lesion of each region with highest uptake was measured. The PSMA expression score was assessed visually in accordance with PROMISE criteria on a per-patient level (*17*).

^{177}Lu-PSMA-617 Radioligand Therapy

PSMA-RLT was performed as therapy after exhaustion of established treatment options following the decision of a multidisciplinary tumor board. An overview of patient selection is provided in Figure 1. Key eligibility criteria were adequate bone marrow and kidney function in accordance with the European Association of Nuclear Medicine/ The Society of Nuclear Medicine and Molecular Imaging procedure guidelines for PSMA-RLT (*18*) and a PSMA expression level of at least 2 (*17*). 6.8 ± 1.4 GBq ^{177}Lu-PSMA-617 were administered intravenously each cycle, with a 6-week interval between cycles. Progression-free survival was defined as the interval from treatment start until death or progressive disease according to Response Evaluation Criteria In Solid Tumors 1.1, which was analyzed by two readers (C.C., M.W.) in joint consensus sessions (*19*).

Blood count, creatinine, transaminases, and symptoms were monitored before and under PSMA-RLT and toxicity was graded according to Common Terminology Criteria for Adverse Events (CTCAE v5.0) (*20*).

Dosimetry

Post-therapeutic dosimetry of tumor lesions and kidneys was performed in all patients undergoing PSMA-RLT and calculated according to OLINDA/MIRD recommendations (*21*). SPECT/CT imaging was performed on a SIEMENS Intevo SPECT/CT system using the xQuant reconstruction algorithm, allowing for quantitative ^{177}Lu imaging as previously described (*22*). The chosen imaging schedule was set to include 4 time-points (4, 24, 48 and 120-144 hours) post injection with at least two time-points considered necessary to determine lesion or kidney doses. For logistical reasons, 2 or 3 time-points were acquired for each cycle, respectively.

Statistical Analyses

The statistical analyses were performed using SPSS (IBM SPSS Statistics, Version 27.0. Armonk, NY). Student's t-test was employed to assess differences for SUVmax dependent on gender, location of the primary, and disease site (bone vs. lung).

RESULTS

Patient Characteristics

28 patients (11 men, 39%; 17 women, 61%) were included. Histopathological subtypes were ACC (24/28, 86%), adenocarcinoma (2/28, 7%), acinic cell carcinoma (1/28, 4%) and sebaceous carcinoma (1/28, 4%). The median age was 59 (range, 30-75) years. The clinical indication of PSMA PET/CT was initial staging for 2/28 (7%), restaging for 12/28 (43%) and

evaluation for PSMA-RLT in 14/28 patients (50%). 5/28 patients (18%) underwent PSMA-RLT. Detailed patient characteristics is provided in Table 1.

Five of these patients (3 female, 2 male) received a total of 11 cycles of PSMA-RLT (range, 1-6 cycles). The median age of PSMA-RLT patients was 50 (range: 40-65) years. Demographic and clinical information of the treatment cohort is provided in Table 2.

CT vs PSMA PET/CT Detection Accuracy

CT detected any disease in 25/28 (89%) patients, local tumor in 7/28 (25%) patients, regional lymph nodes in 1/28 (4%) patients, and distant metastases in 22/28 (79%) patients. PSMA-PET was positive in 27/28 (96%) patients and visualized local tumor in 8/28 (29%) patients, regional lymph nodes in 5/28 (18%) patients, and distant metastases in 25/28 (89%) patients (Figure 2). PSMA-PET/CT demonstrated additional metastatic lesions in 11/28 (39%) patients; in 8/28 (29%) patients CT-negative regions were rated positive on PSMA-PET/CT. PSMA-PET/CT detected additional bone metastases in two patients (7%) and non-regional lymph node metastases in one patient (4%) with no disease shown on CT (TNM upstaging). PSMA-PET/CT led to up-shift of lesions-based disease extent in 6/28 (21%) patients (Table 3). Figure 3 shows an exemplary SGM patient, in whom additional bone lesions were detected by PSMA-PET/CT.

In 6/28 (21%) patients ^{18}F-FDG- and PSMA-PET/CT were performed within a 3-month interval without interim progression on morphological imaging. Out of the 6 patients, 2 had higher detection efficacy for PSMA-PET/CT, 2 had higher detection efficacy for ^{18}F-FDG-PET/CT, and 2 had equal detection efficacy for both modalities

PSMA Ligand Uptakes

PSMA expression score was 0 (n=2, 7%), 1 (n=4, 15%), 2 (n=15, 56%), 3 (n=6, 22%), respectively (Figure 4). Male gender (15.8 vs. 8.5; p=0.007) was significantly associated with higher SUVmax (Table 4). The mean SUVmax in tumor sites of patients with a primary in minor salivary glands was 12.8 versus 9.0 in those with a primary located in major salivary glands, without statistical significance (p=0.31). SUVmax was significantly higher in bone vs. lung metastases (14.2 vs 6.4; p=0.006).

PSMA-RLT Absorbed Dose and Efficacy

In total, 5 patients received PSMA-RLT. Dosimetry was performed for kidneys and a total of 13 tumor lesions over 7 therapy cycles. The highest lesion absorbed dose was 0.68 Gy/ GBq (mean: 0.41 Gy/GBq; range, 0.06-0.68 Gy/GBq). The highest lesion uptake ratio after 24 hours was 0.44% (mean: 0.16; range, 0.004-0.44). The mean effective half-life of the lesions was 7.7 minutes (range, 0.32-30.98 minutes). The mean renal absorbed dose was 0.37 Gy/GBq (range, 0.32-0.41 Gy/GBq). Dosimetry results of each cycle are shown in Table 5.

PSMA-RLT was discontinued in 3 patients after one cycle due to visual lesion uptake below liver uptake on the 24 hours post-treatment ^{177}Lu-PSMA scintigraphy. In these 3 patients, systemic treatment was initiated before progression occurred. Progression-free survival was 3 months (n=1) or not reached (n=1, last follow-up: 12 months) after initiation of PSMA-RLT in the two patients remaining with more than one treatment cycle. Of note, the long-term response was observed in the only patient with acinic cell carcinoma, with the remainder suffering from ACC. Supplemental Figure 1 shows a patient example.

PSMA-RLT Adverse Events and Follow-Up

Changes in blood parameters did not meet CTCAEv5.0 criteria for adverse events. Less than serious xerostomia, was reported by both patients undergoing more than one cycle of PSMA-RLT without worsening under treatment.

DISCUSSION

The results of our study indicate a superior detection rate for PSMA-PET/CT in SGM with additional localization of lesions in 11/28 (39%) and TNM upstaging in 3/28 (11%) patients through the detection of CT-occult oligometastatic bone metastases. Therefore, PSMA-PET/CT might be a possible alternative to other hybrid imaging modalities in salivary gland tumors such as ^{18}F-FDG-PET/CT or PET/MRI (*11*,*23*). In addition, PSMA-PET/CT identifies candidates for PSMA-RLT, which was well tolerated and induced tumor response.

PSMA-PET/CT revealed oligometastatic disease in 9/28 (32%) patients (Table 3). Accurate localization of disease supports planning of metastasis-directed therapy. Metastasis-directed therapy of oligometastatic head and neck cancer including SGM has been shown to result in high disease control rates (*24*), which underlines the importance of sensitive imaging to further optimize this treatment option. PSMA-PET/CT revealed multifocal/disseminated disease in 3/9 (33%) patients with CT oligometastastic disease. Detection of multifocal/disseminated disease may thereby more accurately identify patient candidates for systemic therapy not likely to benefit from local treatment alone.

75% of patients have at least one lesion with PSMA uptake equal or higher than liver with significantly higher PSMA expression occurring in male patients and bone lesions (Table 4). Boxtel et al likewise demonstrated high tumor uptake (*13*). Higher PSMA expression in male patients is not supported by current knowledge of PSMA regulation pathways, since high androgen levels

suppress the PSMA encoding gene folate hydrolase 1 potentially leading to a reduction of PSMA expression levels (*25*). This has been demonstrated in prostate cancer patients, where prolonged androgen-deprivation therapy was linked to increases in PSMA expression (*26*). Likewise, the androgen axis can be active in patients with SGM and efficacy and safety of androgen receptor targeted treatment is currently investigated in a prospective single arm clinical trial (NCT04325828). In line, an immunohistochemistry study by Boxtel et al. showed a higher PSMA expression in tumor cells of salivary gland malignancies in females vs. males attributed to lower levels of circulating androgens (*27*). In contrast to immunohistochemistry findings, PSMA-PET/CT allows for the in vivo non-invasive assessment of target PSMA expression of entire lesions and at multiple tumor sites. PSMA-PET/CT indicates that male patients may be more suitable candidates for PSMA-RLT. However, it is worth pointing out that the small sample size is conducive to the occurrence of type 1 errors; therefore, further analyses of larger cohorts are warranted.

In our case series, PSMA-RLT was well tolerated. CTCAE grade 3 or higher events were not noted. There was no treatment limiting xerostomia. In line, side effects of PSMA-RLT were grade 1 to 2 in a study by Nulent et al., and only one patient experienced grade 3 thrombocytopenia (*28*). However, tumor absorbed doses in our patients were unsatisfactory. Although high PSMA expression was noted on both PSMA-PET/CT and early post-treatment SPECT/CT, retention times of PSMA uptake were short resulting in lower absorbed doses than in prostate cancer. A potential explanation is the low detection threshold of PSMA-PET/CT resulting in a high target-to-background signal that may lead to an overestimation of PSMA expression (*29*).

This is the largest study so far to evaluate dosimetry of PSMA-RLT in SGM. Uijen et al reviewed a total of 10 patients and 15 cycles of PSMA-RLT in non-prostate cancer patients, also

including two patients with SGM (*30*). Nulent et al. has demonstrated the first case of ACC treated with PSMA-RLT but treatment response or dosimetry data were not reported (*14*) . Simsek et al. reported one ACC patient treated with PSMA-RLT revealing intense metastatic PSMA uptake on post-treatment imaging performed after 24 hours (*15*). Nulent et al. reported the first cohort study to evaluate the efficacy and safety of PSMA-RLT in SGM (*28*). Six patients with SGM have been treated with PSMA-RLT, which resulted radiological stable disease in two patients after four cycles and clinical response such as pain relief, less dyspnea and less fatigue in four patients after two or four cycles of PSMA-RLT (*28*).

In our study, tumor stabilization over more than one year was only observed for one of five PSMA-RLT patients indicating that further improvement is needed. In the future, RLT may be improved by more stringent patient selection, application of higher activities regimens or introduction of alpha-based RLT. Further research focusing on histopathologic subtypes, specifically on PSMA-RLT in acinic cell carcinoma, may be of interest.

Limitations of this study include its retrospective, single-center design and the small sample size.

CONCLUSION

PSMA-PET/CT demonstrates superior tumor detection and led to upstaging in about one third of SGM patients when compared to CT. Male gender and presence of bone metastases were associated with significantly higher PSMA expression. PSMA-RLT was tolerated well and resulted in disease stabilization in one patient. However, frequent discontinuation after one PSMA-RLT cycle and low tumor absorbed doses indicate that PSMA-RLT for SGM needs further improvement.

DISCLOSURES

Conflicts of Interest

Manuel Weber reports fees from Boston Scientific, Terumo, Eli Lilly, and Advanced Accelerator Applications, outside of the submitted work. Christoph Berliner reports personal fees from Janssen (speakers bureau), ABX (image review) and Roche (image review) outside of the submitted work. Ken Herrmann reports personal fees from Bayer, personal fees and other from Sofie Biosciences, personal fees from SIRTEX, non-financial support from ABX, personal fees from Adacap, personal fees from Curium, personal fees from Endocyte, grants and personal fees from BTG, personal fees from IPSEN, personal fees from Siemens Healthineers, personal fees from GE Healthcare, personal fees from Amgen, personal fees from Novartis, personal fees from ymabs, personal fees from Aktis Oncology, personal fees from Theragnostics, personal fees from Pharma15, outside the submitted work. David Kersting is supported by the Universitätsmedizin Essen Clinician Scientist Academy (UMEA)/German Research Foundation (DFG, Deutsche Forschungsgemeinschaft) and reports research funding from Pfizer outside the submitted work. Benedikt M. Schaarschmidt is supported by a research grant from PharmaCept, outside the submitted work. Wolfgang P. Fendler reports fees from SOFIE Bioscience (research funding), Janssen (consultant, speakers bureau), Calyx (consultant), Bayer (consultant, speakers bureau), and Parexel (image review) outside of the submitted work.

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KEY POINTS

QUESTION: Is PSMA a potential target for theranostic applications in salivary gland malignancies?

PERTINENT FINDINGS: In salivary gland malignancies, PSMA-PET/CT has a higher detection rate than conventional imaging and led to upstaging in about one third of patients. ^{177}Lu-PSMA-617 treatment was tolerable and resulted in disease stabilization in one patient with acinic cell carcinoma.

IMPLICATIONS FOR PATIENT CARE: Preliminary findings demonstrate a superior detection rate for PSMA-PET/CT compared to CT in salivary gland malignancies and a potential role for PSMA-radioligand therapy in a subset of patients. Prospective studies on larger collectives are warranted.

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Figure 1: Consort diagram describing SGM patient selection for PSMA-directed imaging and PSMA-RLT. RLT= radioligand therapy.

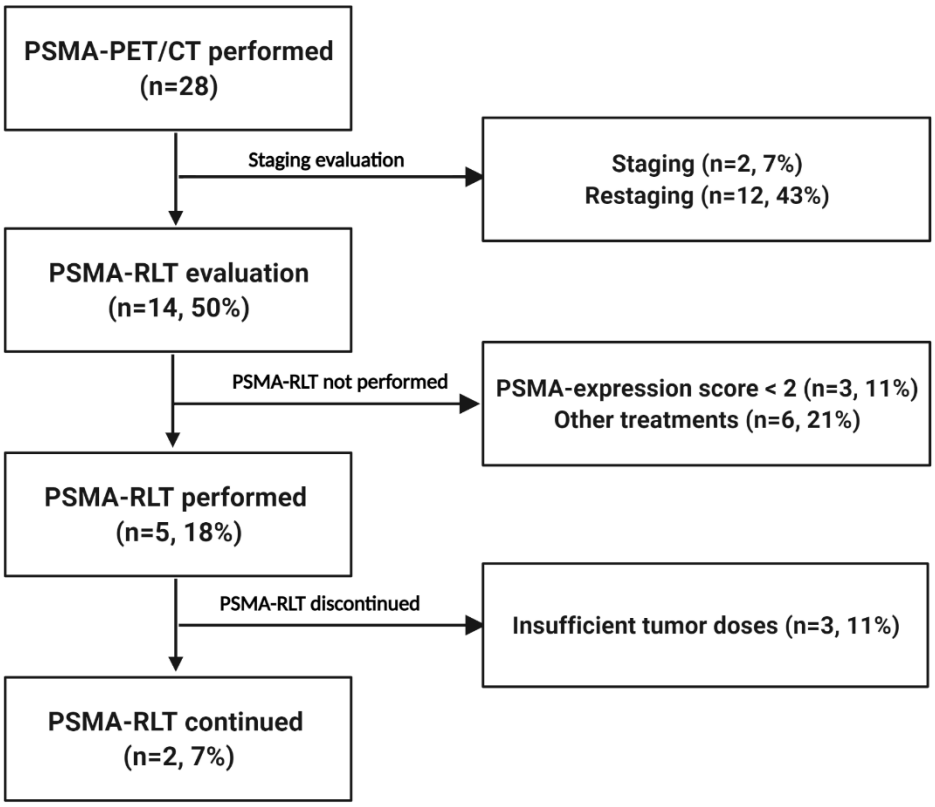


Figure 2: Pie charts demonstrate additional detection of diseased regions by PSMA-PET/CT (orange) when compared to standalone CT (blue). Charts demonstrate percent positive patients among 28 patients, separate for each region.

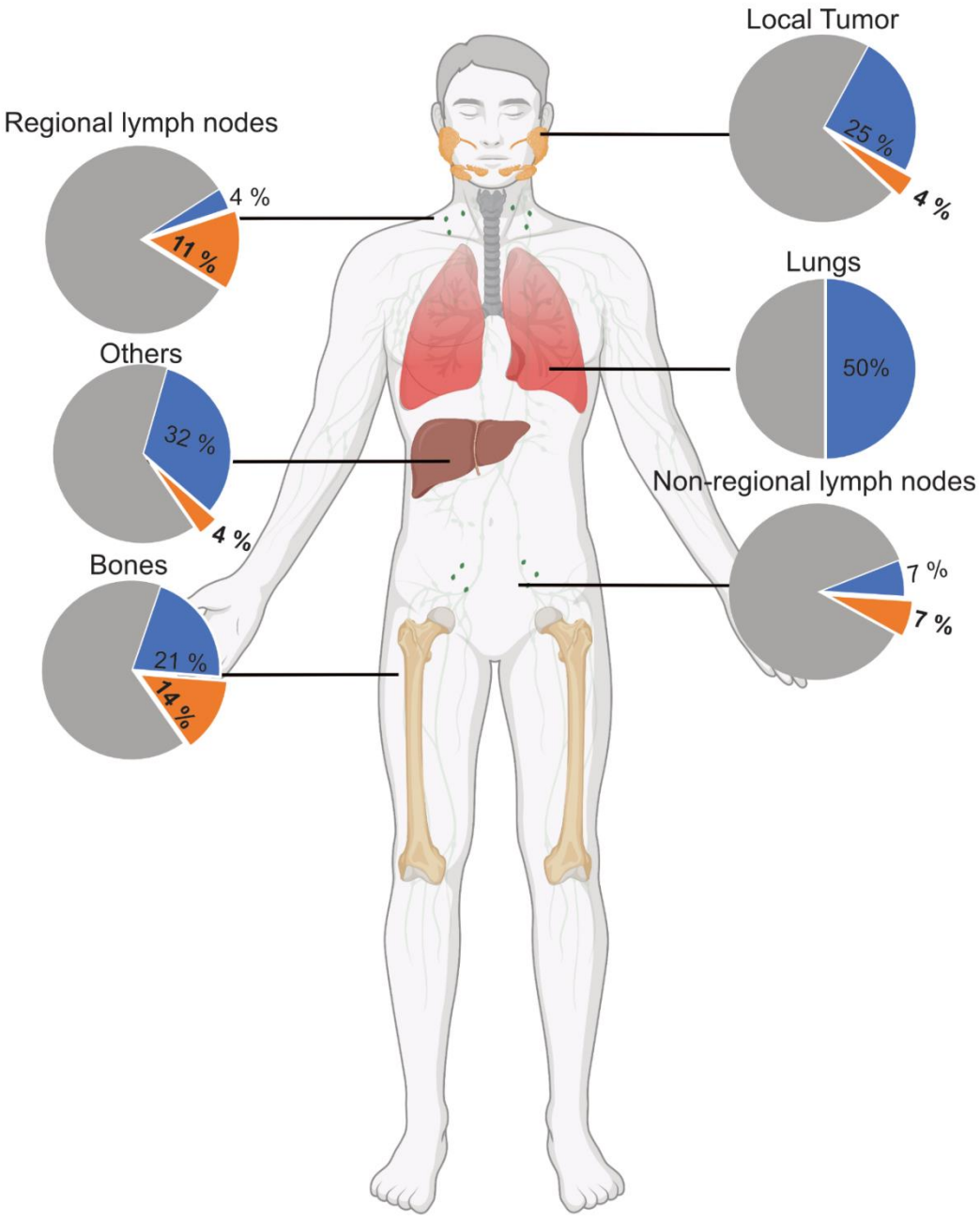


Figure 3: ^{68}Ga-PSMA-PET/CT of a 69-year-old male patient with adenoid-cystic carcinoma of the right submandibular gland after primary resection. Maximum-intensity projection (A) and axial slices (B, C, D, E) of ^{68}Ga-PSMA-PET/CT reveal bone metastases in the 6th left rib (white arrow) and the sacral bone (black arrow) without CT-correlate (F, G) confirmed by follow-up imaging 6 months later.

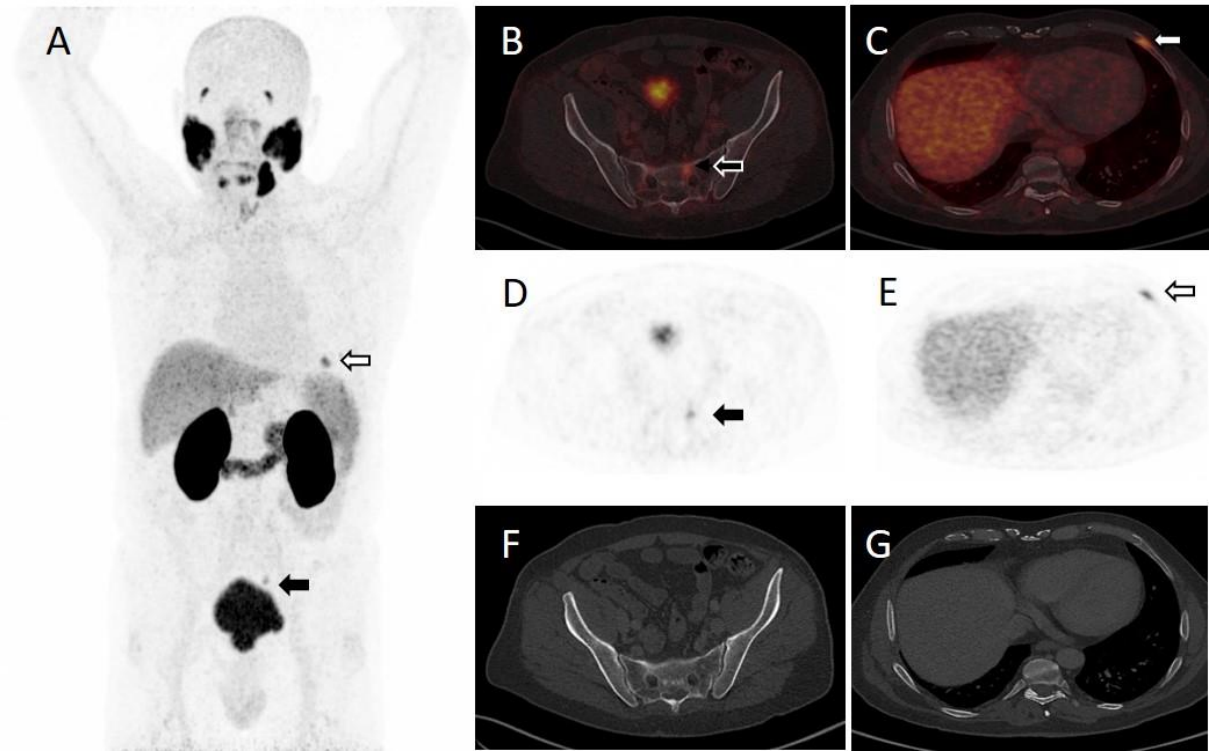


Figure 4: PSMA expression score by PROMISE criteria for n=27 patients. One patient without any detected lesion was excluded.

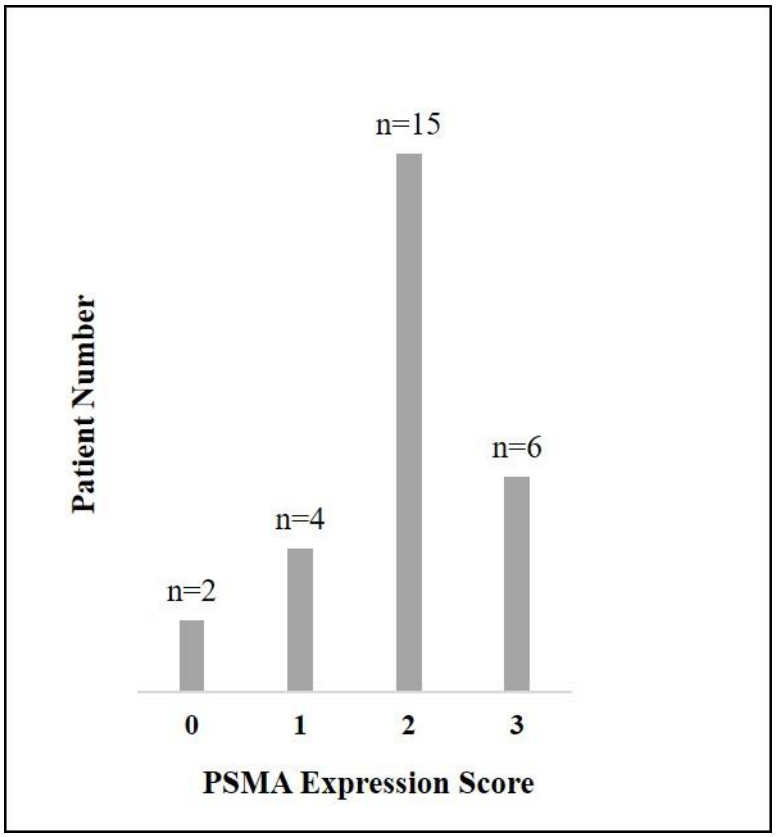


Table 1: Patient characteristics. LN= lymph nodes; RLT= radioligand therapy.

Characteristic	Number of Patients (%)
Gender, n (%)	
Male	11 (39%)
Female	17 (61%)
Age, median (range)	59 (30-75) years
Primary Location, n (%)	
Major Salivary Gland	18 (64%)
Parotid Gland	8 (29%)
Submandibular Gland	7 (25%)
Sublingual Gland	3 (11%)
Minor Salivary Gland	10 (36%)
Clinical Indications, n (%)	
Staging	2 (7%)
Restaging	12 (43%)
Evaluation for RLT	14 (50%)
Previous Treatments, n (%)	
Primary Surgery	25 (89%)
Multiple Surgeries	12 (43%)
Radiotherapy	24 (86%)
Chemotherapy	7 (25%)
Metastasectomy	9 (32%)
Palliative Radiotherapy	6 (21%)
Disease sites at ^{68}Ga-PSMA PET/CT, n (%)	
Local tumor	8 (29%)
Locoregional LN metastases	5 (18%)
Non-locoregional LN metastases	4 (14%)
Lung metastases	14 (50%)
Bone metastases	10 (36%)
Other metastases	10 (36%)

Table 2: Patient characteristics of the PSMA-RLT cohort (*=repeated treatments, † =systemic treatment started immediately after PSMA-RLT). M= male; F= female; ACC= adenoid cystic carcinoma; LN= lymph nodes; TTP= time to progression; RLT= radioligand therapy.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	50	42	40	56	65
Sex	M	F	F	F	M
Histology	ACC	ACC	ACC	ACC	Acinic cell carcinoma
Time from initial diagnosis to RLT	8 years	2 years	4 years	3 years	16 years
Prior treatments	Surgery* Radiotherapy Axitinib Chemotherapy	Surgery Radiotherapy	Surgery Radiotherapy* Metastasectomy	Surgery Radiotherapy	Surgery * Radiotherapy* Denosumab
Primary Location	Paranasal sinus (Minor salivary gland)	Parotid gland	Upper jaw (Minor salivary gland)	Parotid gland	Parotid gland
Metastatic sites	Local Lung	Lung	Bone	Lung Soft tissue	Locoregional LN Bone
PSMA expression score	3	2	3	2	3
RECIST 1.1 response	PD	N/A †	N/A †	SD	SD
TTP after PSMA-RLT	3 months	12 months †	6 months †	Lost to follow-up	12 months

Table 3: Analysis of lesions-based disease extent. Extent shifted towards higher disease burden in 6/28 (21%) patients following PSMA PET. (Oligometastatic disease 2-5 metastasis; multifocal disease, 6-10; disseminated disease ≥11; * = upstaging)

PSMA / CT	No disease n (%)	Unifocal n (%)	Oligometastatic n (%)	Multifocal n (%)	Disseminated n (%)
No disease n (%)	1 (4)	0	1 (4)*	0	1 (4)*
Unifocal n (%)	0	2 (7)	1 (4)*	0	0
Oligometastatic n (%)	0	0	7 (25)	2 (7)*	1 (4)*
Multifocal n (%)	0	0	0	1 (4)	0
Disseminated. n (%)	0	0	0	0	11 (39)

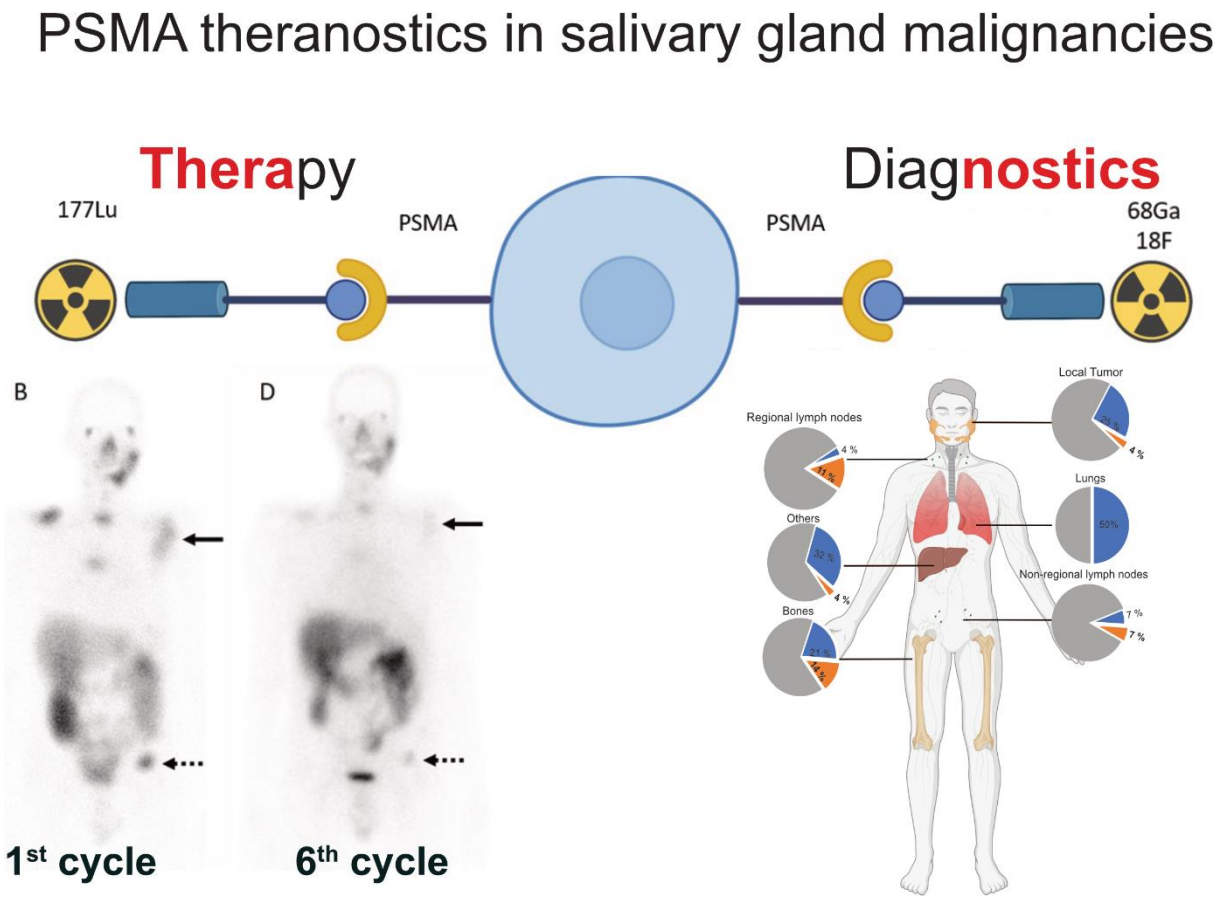
Table 4: Comparison of SUVmax values for gender, primary location at the initial diagnosis, bone metastasis vs lung metastasis and subtypes. Difference was assessed by Student's t-test (*$p<0.05$).

	n (%)	Average SUVmax (SD)	p-value
Total patients	28 (100)	10.7 (7.8)	
Gender			
Male	11 (39)	15.8 (9.8)	0.001*
Female	17 (61)	8.5 (4.9)	
Primary Location at the Primary Diagnosis			
Major Salivary Glands	18 (64)	9 (4.4)	0.308
Minor Salivary Glands	10 (36)	12.8 (8.4)	
Metastasis sites			
Bone	14 (50)	14.2 (10.2)	0.006*
Lung	16 (57)	6.4 (4.2)	
Other	7 (25)	8.8 (2.8)	
Subtype			
ACC	24 (86)	10.1 (5.9)	0.352
Others	4 (14)	14.2 (16)	

Table 5: Results of individual patient dosimetry. Pt= Patient; L1= Lesion 1; AD= Absorbed dose; L2= Lesion 2; SUV^{M}= SUVmax; SUV^{m}= SUVmean.

Pt No	Cycle No	Activity	L1	L1 AD (Gy/GBq)	SUV^{M}	SUV^{m}	L2	L2 AD (Gy/GBq)	SUV^{M}	SUV^{m}	Renal AD (Gy/GBq)
1	1	7.6	Lung	0.06	11.9	6.1	Recurrent	0.42	22.9	14.6	0.35
1	2	7.5	Lung	0.08	11.9	6.1	Recurrent	0.23	22.9	14.6	0.32
2	1	7.5	Lung	0.26	9	5					
3	1	6.1	Bone	0.68	11.2	7.7	Bone	0.22	16.4	10.4	0.38
4	1	5.8	Lung	0.42	7.2	4	Lung	0.65	13.7	7	
5	1	6.1	Bone	0.41	27.1	14.9	Bone	0.49	30	17.4	0.39
5	2	7.5	Bone	0.17	27.1	14.9	Bone	0.25	30	17.4	0.34

Graphical abstract



Supplemental Figure 1: 65-year-old patient (patient 5 in Table 2) with acinic cell carcinoma. Previously, complete remission was achieved by surgery and radiotherapy of the primary, lymph node metastases, and locoregional recurrence. On routine re-staging, bone scintigraphy revealed new bone metastases. The patient demonstrated progressive disease under conventional radiotherapy and PSMA RLT was evaluated. Maximum-intensity projection of ^{68}Ga-PSMA-PET/CT (A) revealed disseminated bone metastases in the ribs, vertebrae, pelvis (dashed arrow) and scapulae (solid arrow) with high target PSMA-expression. PSMA-RLT was initiated and high tumoral PSMA-expression was confirmed by post-treatment scintigraphy (B) 24 hours after the administration of 6.1 GBq ^{177}Lu-PSMA. Absorbed doses were 0.41 and 0.49 Gy/GBq, respectively, for two tumor lesions and 0.39 Gy/GBq for the kidneys. Follow-up ^{68}Ga-PSMA PET/CT (C) after 4 cycles demonstrated decreased PSMA expression (SUVmax: 36 to 14.5). Treatment was continued with additional two cycles of PSMA-RLT. Post-treatment scintigraphy of 6th cycle (D) showed decreased PSMA expression of metastatic lesions. ^{18}F-PSMA PET/CT (E) after 6 cycles of PSMA-RLT demonstrated stable disease.