Salivary gland toxicity after PSMA-targeting radioligand therapy (PRLT) in patients with advanced prostate cancer:

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A single-center systematic investigation

Dissertation

zur Erlangung des akademischen Grades

doctor medicinae

vorgelegt dem Rat der Medizinischen Fakultät

der Friedrich-Schiller-Universität Jena

von Thomas Langbein

geboren am 02.09.1986 in Mühlhausen

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Tag der öffentlichen Verteidigung: 31.08.2021

Vorsitzende der Promotionskommission für klinische Fächer II:

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“Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.”

Marie Curie

Content

Acronyms

3D-CRT	three-dimensional conformal radiotherapy
Ac-225	Actinium-225
ADT	androgen deprivation therapy
ALT	Alanine transaminase
AST	Aspartate transaminase
BCR	biochemical recurrence
Bi-213	Bismuth-213
CI	confidence interval
Cl	chloride
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DGN	German Society of Nuclear Medicine
DTC	differentiated thyroid cancer
EANM	European Association of Nuclear Medicine
EBRT	external beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EF	excretion fraction
EORTC	European Organization for Research and Treatment of Cancer
F-18-FDG	Fluorine-18 fluorodeoxyglucose
FDA	Food and Drug Administration
Ga-68	Gallium-68
Gll	Glandulae
GMP	good manufacturing practice
HNC	head and neck cancers
I-131	Iodine-131
IMRT	intensity-modulated radiation therapy
In-111	Indium-111
JRC	Joint Research Centre
K	potassium
LET	linear energy transfer
Lu-177	Lutetium-177
mCRPC	metastatic, castration-resistant prostate cancer
MDP	methylene diphosphonate
MIP	maximum intensity projection
MIRD	medical internal radiation dose
MV	metabolic volume
Na	sodium
$NaClO_4$	sodium perchlorate
OS	overall survival
PC	prostate cancer
PET	Positron emission tomography
PET/CT	Positron emission tomography/ Computed tomography
PET/MRI	Positron emission tomography/ Magnetic resonance imaging
PFS	progression-free survival
pg	parotid gland
PRLT/RLT	(PSMA-targeted) Radioligand Therapy
PROM	patient-reported outcome measures
PSA	prostate specific antigen
PSMA	Prostate-specific membrane antigen
Ra-223	Radium-223
RECIST	Response evaluation criteria in solid tumors
RIT	radioiodine therapy
ROI	regions of interest
RP	radical prostatectomy
RT	radiation therapy
s.p.	status post
SG	salivary gland
SGS	salivary gland scintigraphy
smg	submandibular gland
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SPECT/CT	single-photon-emission computed tomography / Computed tomography
SUV	standardized uptake value
SUVmax	maximum standardized uptake value
sXI	shortened Xerostomia Inventory
Tc-99m	Technetium-99m
TER	tubular extraction rate
TSH	thyroid-stimulating hormone
Umax	maximum tracer uptake
VOI	volume of interest
ZBB	Zentralklinik Bad Berka, Germany

Abstract

PSMA targeting radioligand therapy is a novel and promising treatment option in mCRPC patients, that still have to face a poor prognosis, despite several available therapies. Numerous studies have shown encouraging response rates of PRLT with an overall low toxicity profile. This pioneering work was able to pave the way to a recent large, international, phase-III trial. However, an intense off-target uptake of the radiopharmaceuticals with considerable organ doses to the salivary glands can be observed with varying published rates of xerostomia. Mild to moderate mouth dryness in 5 % up to 87 % of the cases have been reported. For Ac-225-labeled PSMA radioligand therapy xerostomia became even the dose-limiting toxicity. Variations of the reported salivary gland toxicity rates might be explained by differences in the patient characteristics on one side as well as by methodological differences of data acquisition. Objective of this study was a systematic, standardized short and long-term follow up investigation of a larger single-center population of advanced prostate cancer patients after PRLT by using patient reported outcome measures as well as clinical examination and objective assessment based on salivary gland scintigraphy and PSMA-PET/CT parameters.

Data of 3 patient groups with advanced prostate cancer were retrospectively analyzed that had undergone either Lu-177 PSMA RLT or a combination of Ac-225 and Lu-177 PSMA (Tandem-PRLT) at Zentralklinik Bad Berka, Germany. In group I, 91 mCRPC patients were included, which had received 2 cycles of Lu-177 PSMA PRLT with a cumulative activity of 14.3 GBq. Baseline data before the first PRLT cycle were obtained, including an enoral clinical examination, a standardized questionnaire (shortened Xerostomia Inventory), salivary gland scintigraphy using Tc-99m pertechnetate with both qualitative and quantitative assessment (maximum uptake Umax, excretion fraction EF) as well as the SUVmax and the metabolic volume of the SGs in the pre-therapeutic Ga-68 PSMA-11-PET/CT. Possible risk factors for xerostomia (e.g., pretreatments, medication) were documented. Follow up data of all mentioned parameters were acquired in the same way post-therapeutically. In group II, 40 patients with advanced PC were analyzed, who had undergone 2-9 cycles of PRLT (mean cumulative activity up to 61.8 GBq) with a median follow-up of 24 months. Follow-up data were obtained similar to group I (clinical examination, questionnaires, dynamic SGS and Ga-68 PSMA PET/CT parameters). Patient group III consisted of 18 end-stage PC patients selected for Tandem-PRLT with available follow-up data at 2 months after treatment. 2.0 – 7.0 MBq of Ac-225 and 3.0 - 7.2 GBq of Lu-177 PSMA had been administered for treatment. Subjective and objective salivary gland hypofunction was assessed similar to group I and II.

Overall, only very mild to moderate xerostomia occurred after Lu-177 PSMA RLT. In short-term follow-up after 2 cycles of PRLT, 24 % of the patients reported grade 1 mouth dryness, while in long-term follow-up after up to 61.8 GBq of Lu-177 PSMA xerostomia grade 1-2 was reported in 40 % of the patients. In accordance with this sXI scores rose only slightly, but significantly from 7 to 8 in short-term and to 9.2 in long-term follow-up. A highly significant correlation between the follow-up sXI score and post-therapeutic xerostomia was detectable. No predefined clinical signs of chronic hyposalivation were observed in any patient after PRLT. SGS parameters revealed no significant changes both qualitatively and quantitatively after Lu-177 PSMA RLT; however, the occurrence of even mild xerostomia after treatment showed a significant correlation to the SGS parameter of the parotid glands. While no changes of the SUVmax of the SGs were found, a highly significant decline of the metabolic volume both in short and long-term follow-up was observed. The analysis of possible factors of salivary gland toxicity after PRLT showed no influence of patient age, previous treatments (including taxane-based chemotherapy) or the cumulative administered activity of Lu-177 PSMA. While the tumor burden, visually assessed on the baseline PSMA-PET/CT, had a significant effect on the biodistribution of the PSMA radioligand (as could be expected), no influence on both subjective and objective signs of salivary gland hypofunction were found.

After Tandem-PRLT a more distinct increase of mouth dryness could be observed: 12 of 18 patients reported xerostomia grade 1-2, and an increase of the sXI from 9.5 – 14.0 was present. Those findings were in line with a significant reduction of the EF on the SGS of all salivary glands and a decrease of the MV on PSMA PET/CT, especially of the parotid glands. On the other hand, Umax values on the SGS did not show any decline, no severe xerostomia was observed and no patient discontinued treatment (as it has been reported previously for Ac-225 PSMA monotherapy).

While salivary gland toxicity after Lu-177 PSMA appears to have minor clinical relevance compared to the effects from EBRT in patients with head and neck malignancies or high-dose radioiodine therapy in patients with DTC, even after one cycle of Tandem-PRLT a significant subjective and objective SG impairment can be observed. A standardized protocol including a validated questionnaire, an easy-to-perform salivary gland scintigraphy as well as PSMA-PET/CT parameters were able to objectify and quantify salivary gland dysfunction and might be helpful for future clinical research on this topic. Effective preventive strategies of SG uptake of PSMA radioligands remain still an urgent clinical need, especially concerning subsequent alpha-PRLT cycles or when using PSMA RLT in earlier stages of prostate cancer in the future.

Zusammenfassung

Die PSMA-vermittelte Radioligandentherapie (PRLT) ist eine relativ neue und vielversprechende Behandlungsmöglichkeit beim metastasierten, kastrationsresistenten Prostatakarzinom (mCRPC), für das trotz mehrerer verfügbarer Therapieoptionen immer noch eine schlechte Prognose besteht. In zahlreichen Einzelstudien („single center studies“) konnten exzellente Ansprechraten mit einem sehr niedrigen Nebenwirkungsprofil nach PRLT dokumentiert werden, was zur Initiierung einer großen, internationalen Phase-III-Studie führte. Jedoch wird eine intensive Anreicherung der Radiopharmaka mit beträchtlichen Organdosen in den Speicheldrüsen beobachtet, wobei die veröffentlichten Daten hinsichtlich einer posttherapeutischen Xerostomie deutlich variieren. Eine leichte bis mäßige Mundtrockenheit wurde in 5 % bis zu 87 % der Fälle nach Lu-177 PSMA beschrieben, während bei der Therapie mit Ac-225-markierten PSMA-Liganden eine schwere Xerostomie sogar dosislimitierend ist. Diese unterschiedlichen Raten an Speicheldrüsentoxizität können einerseits durch differente Patientenkollektive erklärt werden, sie sind jedoch auch auf methodische Unterschiede bei der Datenerfassung zurückzuführen. Ziel dieser Arbeit war daher eine systematische, standardisierte Untersuchung und Dokumentation von kurzfristigen und langfristigen Auswirkungen der PRLT auf die Speicheldrüsenfunktion bei Patienten mit fortgeschrittenem Prostatakarzinom. Hierzu erfolgte eine monozentrische Analyse von Patientensymptomen, als auch von objektiven diagnostischen Parametern.

Es wurden retrospektiv Daten von 3 definierten Patientengruppen untersucht, bei denen entweder eine Lu-177-PSMA RLT oder eine Kombination aus Ac-225 und Lu-177 PSMA (Tandem-PRLT) in der Zentralklinik Bad Berka durchgeführt wurde. In Gruppe I wurden 91 mCRPC-Patienten aufgenommen, die 2 Zyklen Lu-177-PSMA-RLT mit einer durchschnittlichen kumulativen Aktivität von 14,3 GBq erhalten hatten. Ausgangsdaten vor der ersten PRLT wurden erfasst, darunter eine enorale klinische Untersuchung, ein validierter Fragebogen, eine quantitative Speicheldrüsenszintigraphie (Bestimmung des maximalen Uptakes Umax und der Exkretionsfraktion EF) sowie SUVmax und das metabolische Volumen (MV) der Speicheldrüsen im prätherapeutischen Ga-68 PSMA-11-PET/CT. Mögliche Risikofaktoren für eine Xerostomie (z.B. Vortherapien, Medikamente) wurden ebenfalls dokumentiert. Alle Parameter im Follow-up wurden in gleicher Weise erfasst. In Gruppe II wurden 40 Patienten mit fortgeschrittenem PC analysiert, die 2-9 Zyklen PRLT (bis zu 61,8 GBq kumulative Aktivität) erhalten hatten mit einem medianen Follow-up von 24 Monaten. Die prä- und posttherapeutischen Daten wurden in gleicher Weise wie für Gruppe I erhoben (klinische Untersuchung, Fragebögen, dynamische SGS- und Ga-68-PSMA-PET/CT-

Parameter). Patientengruppe III bestand aus 18 mCRPC Patienten, die für eine Tandem-PRLT ausgewählt wurden und bei denen Follow-up Daten 2 Monate nach Therapie vorlagen. Es wurden 2,0 - 7,0 MBq Ac-225 und 3,0 - 7,2 GBq Lu-177 PSMA appliziert. Die subjektive und objektive Funktionsminderung der Speicheldrüsen wurde analog zu Gruppe I und II bestimmt.

Insgesamt wurde nach Lu-177 PSMA RLT eine nur sehr leichte bis moderate Mundtrockenheit beobachtet. Nach 2 Zyklen PRLT berichteten 24 % der Patienten von einer Xerostomie Grad 1, während im Langzeit-Follow-up nach bis zu 61,8 GBq Lu-177 PSMA bei 40 % der Patienten eine Xerostomie Grad 1-2 auftrat. Konsistent dazu stiegen die sXI-Werte nur geringfügig, jedoch signifikant von 7 auf 8 im kurzfristigen Verlauf und auf 9,2 im Langzeit-Follow-up. Es konnte eine hochsignifikante Korrelation zwischen dem sXI-Score im Follow-up und der posttherapeutischen Xerostomie nachgewiesen werden. Kein Patient zeigte enorale Manifestationen einer chronischen Hyposalivation nach der PRLT. Die SGS-Parameter zeigten nach der Therapie mit Lu-177 PSMA keine wesentlichen qualitativen und quantitativen Veränderungen, jedoch konnte eine signifikante Korrelation zwischen dem Auftreten einer selbst leichten Xerostomie und den SGS-Parametern der Parotiden gefunden werden. Während die SUVmax keine Veränderungen zeigten, wurde eine hochsignifikante Abnahme des metabolischen Volumens sowohl im Kurz- als auch im Langzeit-Follow-up beobachtet. Das Patientenalter, erfasste Vortherapien oder die kumulativ verabreichte Aktivität von Lu-177 PSMA hatten keinen Einfluss auf die Speicheldrüsentoxizität nach PRLT. Während die Tumorlast, basierend auf dem Ausgangs- PSMA-PET/CT, einen zu erwartenden Einfluss auf die Biodistribution der PSMA-Radioliganden hatte, war kein Effekt auf subjektive oderobjektive Parameter der Speicheldrüsenunterfunktion nachweisbar.

Nach Tandem-PRLT zeigte sich eine deutlich höhere Rate an Mundtrockenheit: 12/18 Patienten litten unter einer Xerostomie Grad 1-2 mit einem Anstieg des sXI scores von 9,5 - 14,0. Hiermit korrelierte eine signifikante Reduktion der EF bei der SGS aller Speicheldrüsen und eine Abnahme des MV, insbesondere der Parotiden. Die Umax-Werte der SGS zeigten andererseits keine Abnahme, es wurde auch keine schwere Xerostomie beobachtet und kein Patient brach die Behandlung ab (wie es andernorts zuvor für die Ac-225-PSMA-Monotherapie berichtet worden war).

Während die Speicheldrüsentoxizität nach Lu-177 PSMA klinisch eine eher geringe Relevanz hat, kann selbst nach einem Zyklus Tandem-PRLT eine signifikante Speicheldrüsenschädigung beobachtet werden. Das beschriebene Untersuchungsprotokoll hilft diese Beeinträchtigung zu objektivieren und zu quantifizieren, effektive präventive Strategien sind jedoch weiterhin dringend notwendig.

1. Introduction

1.1 Prostate Cancer

With almost 60 000 new cases per year, prostate cancer (PC) represents by far the most common type of malignancy in men in Germany (Robert Koch-Institut und Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. 2019). About 26 % of all cases of cancer in male patients are caused by PC (Deutsche Krebsgesellschaft et al. 2018). The average age of onset is estimated at 71 years. A mortality rate of approximately 11.3 % has been published (about 14 000 deaths per year) making it the second most lethal type of cancer in males (Barnes et al. 2016). In 2014 about half a million men were living with PC diagnosed up to 10 years ago, so that a further increase in both incidence and prevalence can be expected due to demographic developments.

On a global scale, with approximately 1 276 000 new diagnoses and 359 000 deaths in 2018, PC is currently the second most common type of cancer in men worldwide (Figure 1). Those numbers are expected to grow to almost 2.3 million new cases and 740 000 deaths by 2040 because of the increase of age and population (Ferlay et al. 2018). In particular, the portion of early stages is increasing, which is most probably due to screening using the prostate specific antigen (PSA) in serum. About 40% of the male population in western, industrialized countries bear the risk of developing prostate cancer during their lifetime, but only 10% will develop symptoms and 3% will die from it (Bott et al. 2003).

In case of localized PC - besides active surveillance in low-risk tumors - radical prostatectomy (RP) with additional lymphadenectomy or, alternatively, definitive radiation therapy (RT) - today almost entirely performed as intensity-modulated radiation therapy (IMRT) (Pfister et al. 2014, Viani et al. 2016) - is applied as primary treatment. However, there is a risk of a “biochemical” recurrence (BCR) in about one third of the patients, in two thirds of them within 2-3 years, in the remaining 30 % after more than 5 years, in some cases even up to 10 years after primary treatment (Fornara 2006). In high-risk prostate cancer patients a risk of BCR of 55 to 70 % after 3-5 years is estimated (D'Amico et al. 1998).

In 16 % of the patients metastases are detected within 10 years (Loeb et al. 2010). In a large meta-analysis of 1471 men with PC in the US, 520 cases of BCR after RP occurred within one year, patients with an early recurrence had a statistically increased risk of distant metastases (33.1 vs. 18.1%) (Sundi et al. 2014). Epidemiological data from 767 550 US-American patients between 2004 and 2013 showed a primary metastatic disease in approx. 3 % of the cases at the time of diagnosis (Weiner et al. 2016).

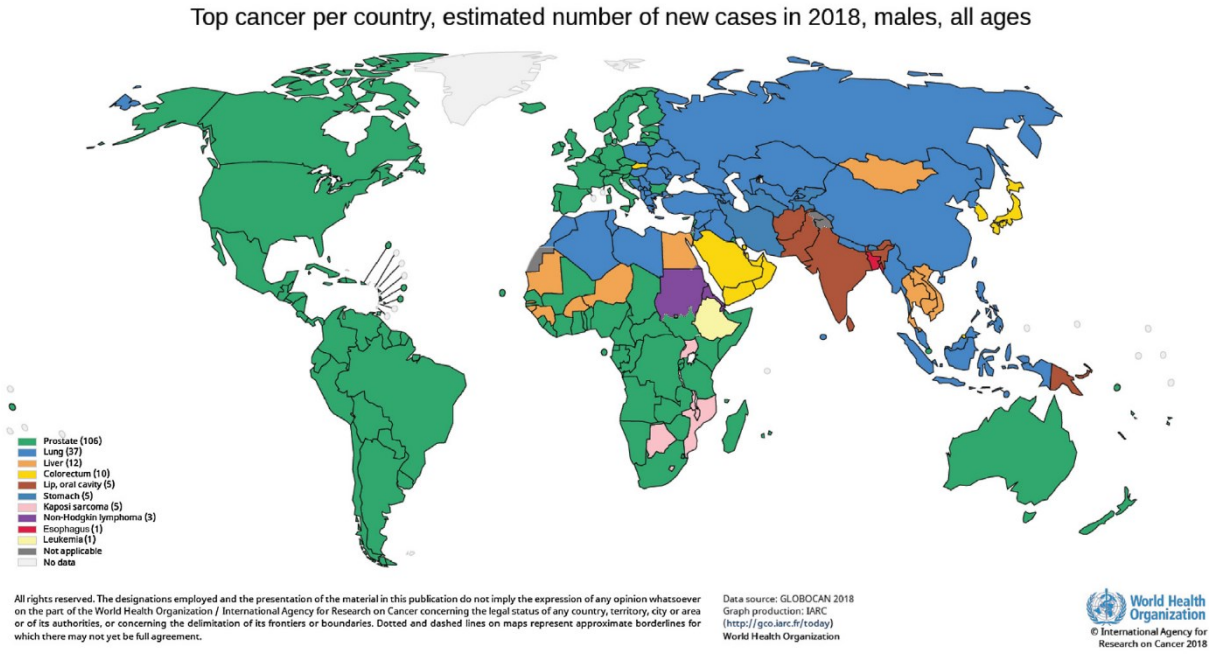


Figure 1 World map showing the most common type of cancer in males for each country based on estimated incidences in 2018 by the World Health Organization. Prostate cancer (green) presents the second most common type of cancer in men worldwide. *Adapted from (Culp et al. 2020)*

1.1.1 Treatment of advanced Prostate Cancer – Status quo

Currently, patients are stratified into different risk groups for biochemical recurrence based on the combination of serum PSA value, the Gleason score, and the clinical stage (Mottet et al. 2017). In the stage of serological recurrence after salvage surgery or salvage radiotherapy as well as in the presence of distant metastases, androgen deprivation therapy (ADT) by means of pharmaceutical or surgical castration is still the therapy of choice. However, after some time resistance to castration often develops, with a significant re-increase of the PSA-level despite ADT (Loblaw et al. 2004) (Figure 2).

Patients with metastatic, castration-resistant prostate cancer (mCRPC) have to face an unfavorable prognosis despite available systemic therapies (Halabi et al. 2008). Next-generation anti-hormonal therapies such as abiraterone or enzalutamide showed excellent clinical trial data in early stages of the disease, but in mCRPC patients, survival benefits of only a few months had been achieved compared to the control groups (de Bono et al. 2011, Scher et al. 2012). According to the current German S3 guideline, first-line treatment of symptomatic mCRPC patients remains chemotherapy with docetaxel (Deutsche Krebsgesellschaft et al. 2018). The survival benefit, however, is stated with a few weeks to months in average (Seruga und Tannock 2011).

Second-line chemotherapy with cabazitaxel demonstrated treatment response in docetaxel-resistant prostate cancer patients with a longer progression-free survival (PFS) and overall survival (OS) compared to patients who received mitoxantrone plus prednisone (de Bono et al. 2010). However, side effects were frequently observed (e.g. febrile neutropenia, neutropenic infection, diarrhea, and hematuria). Autologous cellular immunotherapy with Sipuleucel-T received FDA approval in 2010 for treatment of asymptomatic or minimally symptomatic mCRPC patients. Compared to the placebo arm no differences in time to progression were detected, but a superior OS was found (25.9 versus 21.4 months) (Small et al. 2006).

While beta emitting radioisotopes like Samarium-153 and Strontium-89 have long been used for symptomatic palliation in advanced metastatic prostate cancer, the alpha emitter Radium-223 locally irradiates osteoblastic prostate cancer metastases by binding as a calcium mimetic. The ALSYMPCA trial showed an OS benefit compared to placebo (14.9 vs. 11.3 months) in docetaxel-resistant or –ineligible patients (Parker et al. 2013). Although initially presenting a remarkable low toxicity profile, higher rates of death or bone fractures were observed in combination with abiraterone during the follow-up phase.

Poly(ADP–ribose) polymerase (PARP) inhibitors have been investigated for years in breast and ovarian cancer. In a phase II trial, olaparib has shown significant response rates in heavily pretreated mCRPC patients, in which a high portion of somatic alterations in DNA damage repair genes has been assumed (Mateo et al. 2015, Pritchard et al. 2016). Therefore, a breakthrough designation for olaparib in mCRPC patients has been recently granted by the FDA. The immune checkpoint inhibitor pembrolizumab did show some antitumor activity in a current phase II-trial in docetaxel-refractory mCRPC patients (Antonarakis et al. 2020).

According to the German S3 guideline, "in patients in good general condition, after exhausting all recommended therapy options (...) a therapy attempt with Lutetium-177-PSMA based on the recommendation of an interdisciplinary tumor board..." is indicated in case of further disease progression (Deutsche Krebsgesellschaft et al. 2018).

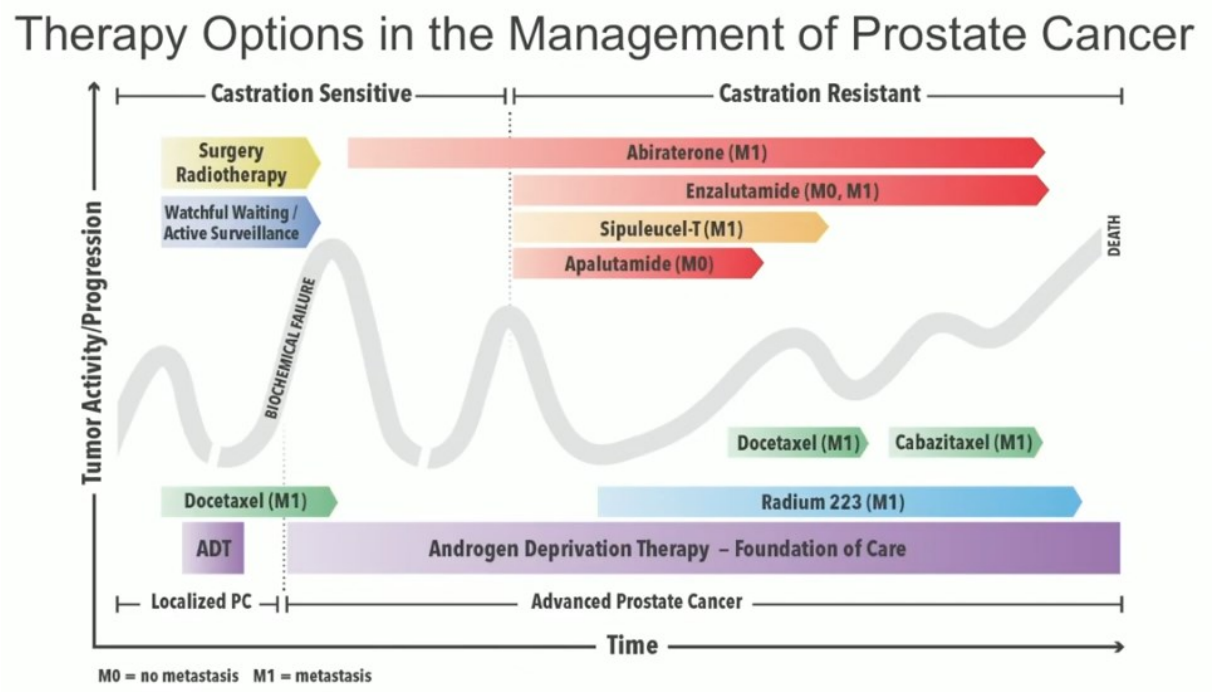


Figure 2 Course of disease of prostate cancer. Adapted from *Figg WD et al., Drug Management of Prostate Cancer. 2010. Springer, New York*

1.1.2 PSMA-directed Radioligand therapy (PRLT)

1.1.2.1 PSMA as a molecular target

The Prostate-specific Membrane Antigen (PSMA) is a transmembrane protein (750 amino acids, 84 kDa) that shows a distinct overexpression on prostate cancer cells (Silver et al. 1997, Mannweiler et al. 2009) (Figure 3). This expression increases with the degree of dedifferentiation - the Gleason score - as well as with metastatic spread and castration resistance and is characterized by a continuous cell internalization of the radioligands (Bostwick et al. 1998, Bander et al. 2003) (Figure 4).

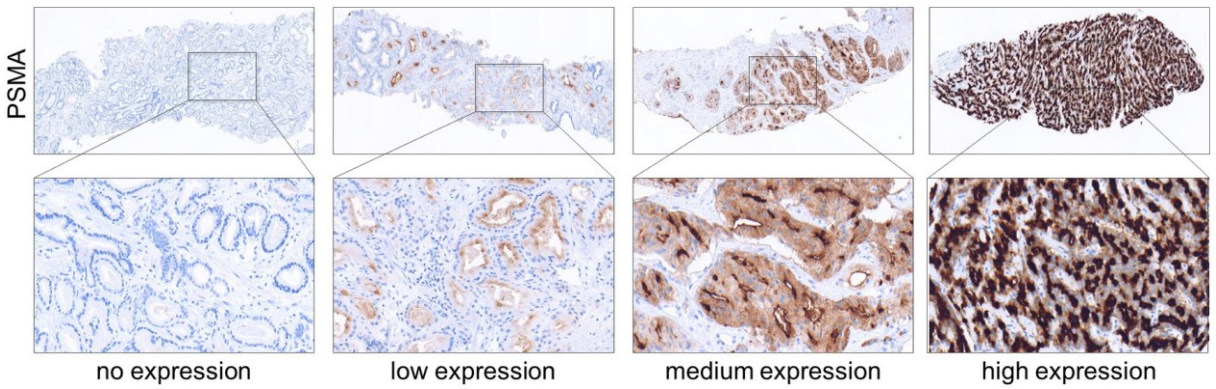


Figure 3 Immunohistochemical stainings of different grades of prostate cancer obtained from needle biopsies, upper line 4x magnification, lower line 40x magnification. *From (Hupe et al. 2018).* PSMA expression is prostate cancer specific and increases with tumor grade.

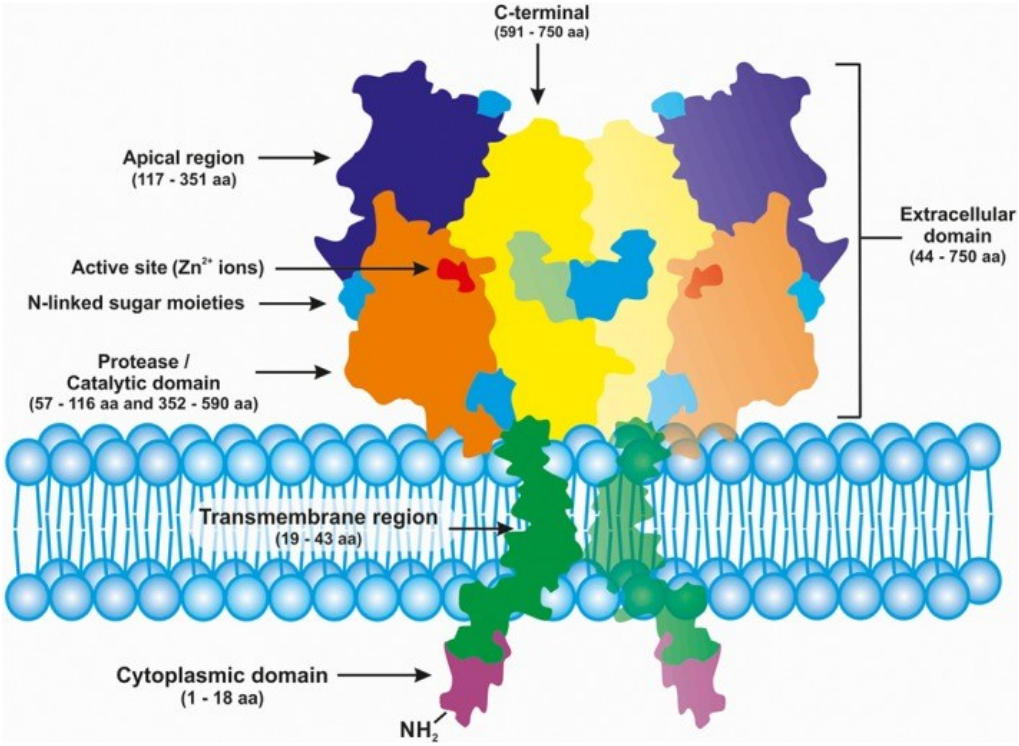


Figure 4 Molecular scheme of PSMA: a continually internalized cell surface enzyme, also named glutamate carboxypeptidase II (GCP-II) or folate hydrolase (FOLH1) because of its respective enzymatic activity. *From (Evans et al. 2016).*

Contrary to its name, physiological PSMA expression has been demonstrated in other organs (e.g. in the proximal renal tubule, duodenum and parotid glands (Silver et al. 1997)), in other tumor entities (e.g. in renal cell carcinoma (Ahn et al. 2019), hepatocellular carcinoma (Sasikumar et al. 2016), primary lung cancer (Shetty et al. 2016) or follicular lymphoma (Kanthan et al. 2016) and in the neovasculature of various malignancies (Haffner et al. 2009). The exact reason for overexpression of this folate hydrolase I or glutamate carboxypeptidase II on dedifferentiated prostate carcinoma cells is still not entirely understood.

Early clinical studies (Bander et al. 2005, Afshar-Oromieh et al. 2013) showed that this molecular target is ideally suited for ‘Theranostics’ (diagnosis and therapy in the context of personalized medicine (Baum et al. 2017, Herrmann et al. 2017) of prostate carcinoma. Theranostics in this context means specific, molecular imaging and therapy with similar radiopharmaceuticals, such as the imaging of recurrent and advanced prostate cancer by PSMA-targeting PET/CT or PET/MRI (Han et al. 2018) in combination with radioligand therapies explained below.

The first compound used for PSMA-targeting PET imaging was developed by the research group at Johns Hopkins University publishing results on the use of 11C-MeCys-C(O)-Glu or 11C-(S)-2-[3-((R)-1-carboxy-2-methylsulfanyl-ethyl)-ureido]-pentanedioic acid (11C-

MCG), an asymmetric urea and potent inhibitor of GCP II, in mice and in a baboon in 2002 (Pomper et al. 2002). In early clinical studies, anti-PSMA antibodies such as 7E11-C5 (ProstaScint®) or J591 were used for that purpose (Bander et al. 2003), but due to a long biological half-life and low tumor penetration, they had rather little clinical success.

In 2012, first data from the German Cancer Research Center in Heidelberg on the use of urea-based PSMA inhibitors (PSMA-11 or HBED-CC-PSMA) labeled with the radioisotope Gallium-68, a positron emitter for PET diagnostics, were published (Eder et al. 2012, Afshar-Oromieh et al. 2013). Due to their high binding affinity in combination with fast cell internalization and plasma clearance, these ligands show a more favorable tumor to background ratio (Maurer et al. 2016) and therefore are part of the most comprehensively investigated PSMA ligands so far.

In a prospective, multi-center study of 635 prostate cancer patients with biochemical recurrence after prostatectomy, primary local radiation or both, high values for detection rates (75% in the entire cohort, 97% with a PSA value ≥ 5.0 ng/mL) and positive predictive values (PPV 84% - 92%), as well as investigator independence and absence of side effects of Ga-68-PSMA-PET/CT have been described (Fendler et al. 2019). A meta-analysis of 5113 prostate cancer patients with biochemical recurrence after definitive therapy from 43 studies reported an overall detection rate of 70.2% (93.9% with a PSA value ≥ 2.0 ng/mL) (Tan et al. 2019).

For primary staging and exact localization of prostate carcinoma, Eiber et al. demonstrated superiority of PET imaging over multiparametric magnetic resonance imaging (mpMRI) in 53 patients with histologically confirmed prostate cancer (sensitivity of 92% vs. 66%) (Eiber et al. 2016), while hybrid imaging using Ga-68-PSMA HBED-CC PET/MRI increased the detection rate to 98%. In histologically confirmed tumor localization, PET diagnostics showed a higher accuracy due to high uptake differences between malignant and benign prostate tissue samples. A correlation between the quantitative PET parameters - the standardized uptake value (SUV) - and the Gleason score or PSA value could not be detected.

Also, in preoperative lymph node staging a superiority of PSMA-PET/CT over the diagnostic standard using CT alone could be demonstrated. Sensitivity of 84 % vs. 65 % and specificity of 82 % vs. 76 % were found (Herlemann et al. 2016). Compared to planar bone scintigraphy with Tc-99m-MDP for the diagnosis of osseous metastasis, Pyka et al. reported a significantly higher sensitivity of Ga-68 PSMA PET/CT (Pyka et al. 2016). In another recently published prospective, multicenter study the diagnostic efficacy of Ga-68 PSMA PET/CT in primary staging of 302 men with high-risk prostate cancer was compared to CT and bone scan in a two-armed, randomized trial. A significant superior accuracy was observed for PSMA

PET/CT vs. conventional imaging (92% vs. 65%; p<0·0001) indicating that PSMA PET/CT might be a suitable replacement for conventional imaging (Hofman et al. 2020).

1.1.2.2 Lu-177 PSMA

The concept of Theranostics includes diagnostics and therapy within the framework of personalized medicine. In nuclear medicine, the principle is to define molecular targets for certain types of tumors to be able to select the optimal radioligand for diagnostics and therapy (Baum und Kulkarni 2012). This principle basically dates back to the first radioiodine therapies carried out in the 1940s (Hertz und Roberts 1946).

Due to its advantageous physical properties – a half-life of 6.7 days, a high local energy transfer (Emax 0.49 MeV) and short penetration range in tumor tissue of approx. 2 mm - the beta emitter Lutetium-177 (Lu-117) is today widely used in radionuclide therapy with numerous radiopharmaceuticals. Based on the co-existing gamma emission, there is an additional benefit from the possibility of obtaining planar scintigraphy as well as 3-dimensional SPECT/CT images, both for qualitative assessment of tracer distribution and for patient-individual dosimetry studies, whereby both the tumor dose and relevant organ doses can be quantitatively calculated

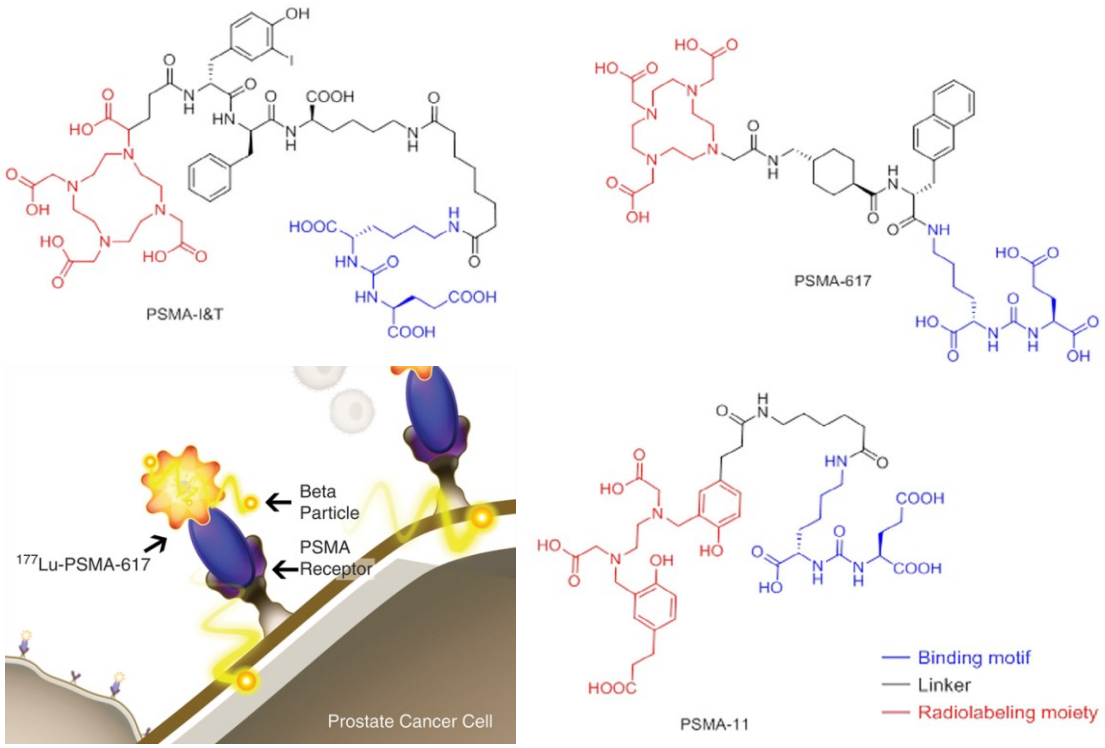


Figure 5 Chemical structure of PSMA-targeting compounds and the basic molecular mechanism of PSMA-directed Radioligand therapy. *Adapted from (Lutje et al. 2017) and Endocyte©/Novartis©*

The first PSMA-directed endoradiotherapies, however, were applied using the ligand MIP-1095 labeled with I-131 in 28 mCRPC patients performed by the Heidelberg group at the German Cancer Research Center in 2011-2013 (Zechmann et al. 2014). Despite doses delivered to the tumor lesion of over 300 Gy, this radionuclide therapy was soon left because of relative high rates of acute side effects, mainly salivary gland toxicity.

In April 2013, the research group at Zentralklinik Bad Berka, Germany (hereinafter referred to as "ZBB") has administered the first Lu-177 labeled PSMA-targeting radioligand therapy worldwide using the ligand PSMA-TUM-1 (DOTAGA-FFK(Sub-KuE)) developed at the Technical University Munich (Baum et al. 2016).

Initial results of the first 56 mCRPC patients treated at ZBB showed remarkable response rates in this heavily pretreated patient population. A PSA decline > 50% was achieved in 59 % of the cases, the median PFS was 13.7 months. In the first preliminary analysis a low rate of side effects has been observed. Except of transient, mild xerostomia in a few cases and a minimal hematotoxicity, no organ toxicity and no other relevant side effects were reported, especially no significant nephrotoxicity (Baum et al. 2016). An extended analysis of 224 patients treated at ZBB showed a PSA decline by ≥50% in 54 % of the patients (Kulkarni et al. 2018b). Noteworthy, even a complete remission of disease according to molecular imaging criteria was observed in 10 cases (4.5 %). A median OS of 27 months and a median PFS of 11.5 months were achieved. Several other promising publications on the application of Lu-177-PSMA-I&T or -617 (Figure 5) in mCRPC patients from other German centers were published with PSA response rates between 38 and 60% (Table 1).

Authors, Year	**Center**	**No. of patietns**	**PSA-decline > 50 % (% of patients)**	**PFS (months)**	**OS (months)**
Baum et al., 2016	Bad Berka	56	59	13.7	nr
Kulkarni et al., 2016	Bad Berka	119	58	10.7	n/a
Kratochwil et al., 2016	Heidelberg	30	43	n/a	n/a
Ahmadzadefar et al., 2016	Bonn	24	60	n/a	n/a
Rahbar et al, 2017	German Multicenter trial	145	45		
Fendler et al., 2017	LMU Munich	15	60		
Heck et al., 2019	TU Munich	100	38	4.1	12.9
Seifert et al., 2020	Münster	78	35-54	9.5 - 12.3	11.3 - 12.7

Table 1 Retrospective data on efficacy of Lu-177 PSMA RLT from different centers in Germany since 2016. *Adapted from (Farolfi et al. 2019)*

Since 2013, in over 200 mCRPC patients treated with Lu-177 PSMA at ZBB receiving up to 12 cycles of PRLT no significant nephrotoxicity in long-term follow-up has been observed (Kulkarni et al. 2018b). Even in 16 patients with a single functioning kidney that underwent PRLT with Lu-177 PSMA no indication of an additive renal toxicity was detected during a mean follow-up period of about 2 years. No CTCAE grade 3 or 4 nephrotoxicity was observed, no significant change of the tubular extraction rate (TER) detected by Tc-99m–MAG3 renal scintigraphy was reported (Zhang et al. 2019).

A retrospective investigation on treatment efficacy of Lu-177 PSMA in 83 mCRPC patients pretreated with taxane-based chemotherapy compared to 84 patients without previous chemotherapy showed a distinct inferior median OS of 10.7 months vs. 27.1 months. Median radiographic PFS was reported with 6.0 months for pretreated patients and 8.8 month for chemotherapy naïve patients. Lu-177 PSMA RLT showed only minimal adverse effects in both patient groups (Barber et al. 2019).

Hofman et al. published the first prospective Lu-177 PSMA single-center phase 2 study in 2018 (Figure 6). In this single-arm trial of 30 mCRPC patients that had undergone at least one line of chemotherapy (docetaxel or cabazitaxel) and one line of 2nd generation ADT (abiraterone or enzalutamide) prior to PRLT, a PSA decline of ≥50% in 57% of the patients occurred. The most common reported side effect was grade 1 mouth dryness according to CTCAE in 26/30 (87%) patients. Furthermore, grade 3 or 4 thrombocytopenia occurred in 4/30 patients and low grade transient nausea and fatigue in some cases was observed (Hofman et al. 2018).

This high-impact results have paved the way for an international, phase-3 trial (VISION trial), in which Lu-177 PSMA competes against standard-of care in terms of OS and PFS in overall 750 participants with mCRPC after at least one regime of chemotherapy and secondary hormonal manipulation (Rahbar et al. 2019). The enrollment was reported as completed in December 2019; first results of the interim analysis are expected to be published later in 2020.

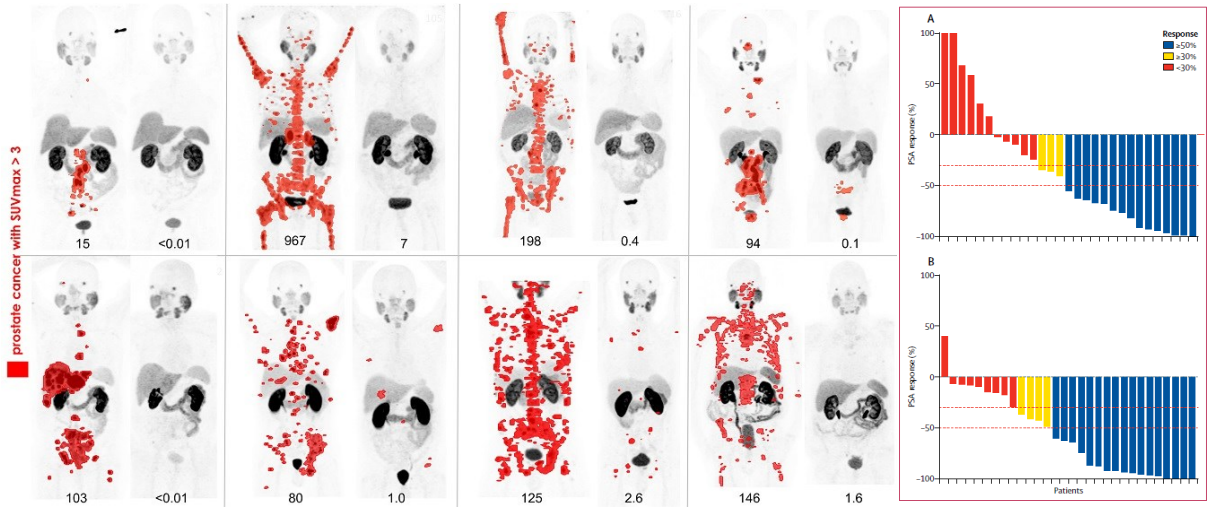


Figure 6 **Left:** Ga-68 PSMA-11 PET maximum intensity projection (MIP) images at baseline and 3 months after RLT with Lu-177 PSMA-617 in 8 patients and a PSA decline ≥ 98 % in a setting of a prospective phase II study. *Society of Nuclear Medicine and Molecular Imaging (SNMMI) Image of the year 2018.* **Right:** (A): PSA response after 12 weeks and (B) best PSA response from baseline. *From (Hofman et al. 2018).*

1.1.2.3 Ac-225 PSMA

Although radioligand therapy using Lu-177 PSMA is able to deliver high doses to the tumor, approximately one fourth to one third of the patients remain refractory to the treatment (progression of the disease). Furthermore, patients with disseminated bone and bone marrow involvement - which occurs commonly in end-stage prostate cancer - exhibit a higher rate of hematological impairment. Alpha-emitting radioisotopes like Actinium-225 or Bismuth-213 are characterized by a shorter range and a higher linear energy transfer when compared to beta-emitters, leading to a higher biological effectiveness due to an increased fraction of DNA double strand breaks (Figure 7). Therefore, they offer promising treatment options in mCRPC patients even after resistance to Lu-177 PSMA.

Based on these assumptions, the research group at the DKFZ in Heidelberg, Germany introduced Ac-225 PSMA RLT in 2016 to increase the efficacy of PSMA-targeted radioligand therapy with dramatic initial treatment responses in 2 heavily pretreated patients. One of the patients had shown disease progression after 2 cycles of Lu-177-PSMA prior to the Ac-225 PSMA RLT. In both far advanced cases, PSA values declined to a non-detectable level, a corresponding complete response on PSMA PET/CT was observed (Kratochwil et al. 2016a).

Apart from clinical relevant xerostomia, no other notable side effects were observed. In the following publications Kratochwil et al. suggested an empirically established fixed-dose regimen of 100 kBq/kg of body weight for Ac-225 PSMA-617 in a larger cohort of patients

(Kratochwil et al. 2017) and found remarkable antitumor activities as durable as other therapies for castration-resistant prostate cancer with a median tumor control of 9 months (Kratochwil et al. 2018). On the downside, xerostomia was reported to be significantly more severe than for Lu-177 labeled PSMA ligands and became the dose-limiting toxicity. Among the initial 40 patients treated with Ac-225 PSMA at 2-monthly intervals 4 patients had to discontinue treatment despite an initial response due to severe xerostomia.

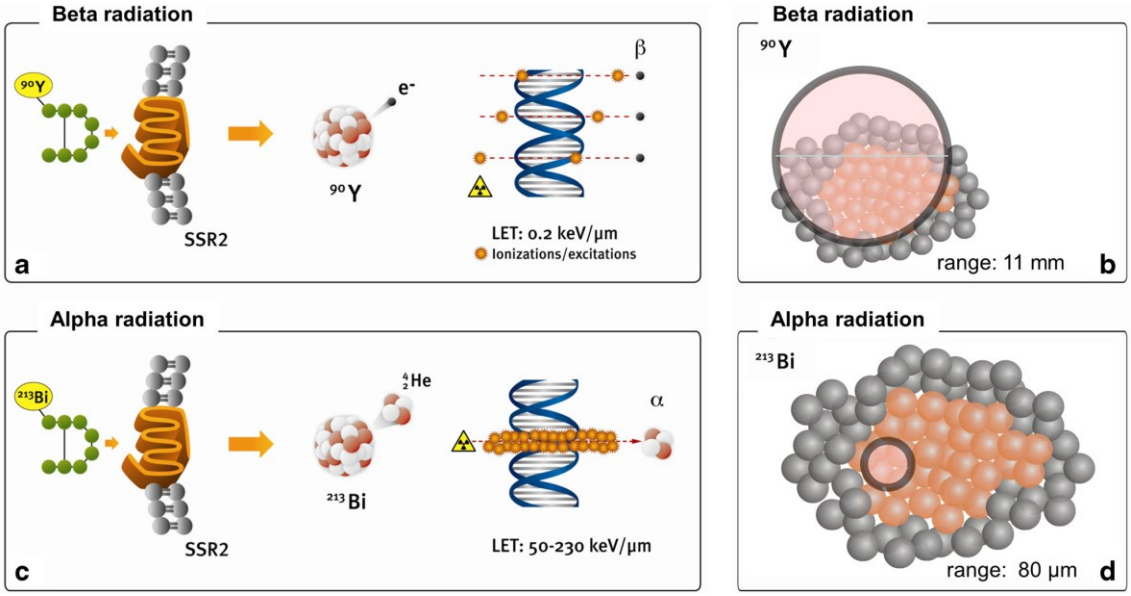


Figure 7 Physical properties of alpha vs. beta radiation. **a,c:** While alpha emitters cause mainly double-strand DNA breaks due to a much higher linear energy transfer (LET), beta radiation induces predominantly repairable single-strand DNA damage. **b,d:** Difference in tissue range of alpha and beta radiation. Less cross-fire radiation exposure to surrounding cells compared to beta emitters is delivered by alpha emitters with only about two or three cell diameters range (50 – 100 µm) *From (Kratochwil et al. 2014).*

Data from 73 mCRPC patients treated with Ac-225 PSMA-617 in South Africa showed similar promising results (Sathekge et al. 2019b). The patients in this cohort tended to be less heavily pretreated: only 37 % of the participants had undergone previous chemotherapy before Ac-225 PSMA RLT and only 1 % of the patients had received 2nd generation ADT; 14 % of the cases were treated with Lu-177 PSMA prior to Ac-225 PSMA. An even better clinical outcome was demonstrated with 70% of patients showing a PSA decline ≥ 50%, in 29% of the patients a complete response on Ga-68 PSMA-PET/CT was found. A median PFS of 15.2 months and a median OS of 18 months was achieved. Xerostomia grade I-II was observed in 85% of patients, however, no grade III and no treatment discontinuation due to mouth dryness was reported. The

remarkable therapeutic efficacy and reduced toxicity to the salivary glands were partly discussed by the authors with an applied de-escalation concept of the administered Ac-225 PSMA in subsequent treatment cycles.

Since the beginning of 2018, Ac-225 PSMA RLT was also available at ZBB for treatment of end-stage mCRPC patients who were failing (or non-suitable) for Lu-177 PSMA RLT alone. Initially, Ac-225 PSMA RLT has been applied as monotherapy, leading to comparable high rates of salivary gland toxicity as well (Langbein et al. 2018) despite very promising response rates. Therefore, soon the concept of Tandem-PRLT was introduced, which stands for the same-day co-administration of Lu-177 and lower activities of Ac-225 labeled PSMA (compared e.g., to the Heidelberg data) (Kulkarni et al. 2019).

The outcome of the first 30 end stage mCRPC patients treated at ZBB with this Tandem-PRLT regime demonstrated equally convincing results. A decline in PSA by ≥50% was seen in 10/30 cases. A nearly complete remission seen on Ga-68 PSMA PET/CT was found in 3 patients. Median OS was reported with 33 weeks, median PFS with 21 weeks. In the preliminary analysis there was no severe xerostomia and no discontinuation of treatment observed. A detailed investigation of salivary gland toxicity of the Tandem-PRLT approach is an integral part of this study (patient group III, section 3.1.4 and 4.3) and will be therefore discussed later.

In a recently published, single center, retrospective analysis of 20 mCRPC patients receiving one cycle of Tandem PRLT with Ac-225 – and Lu-177 PSMA with comparable treatment activities this encouraging results could be confirmed (Khreish et al. 2020). 13/20 (65%) patients showed a PSA-response ≥50% while only mild xerostomia was reported.

1.2 Salivary glands

1.2.1 Anatomy/ physiology/ Xerostomia

The human saliva is produced by three pairs of exocrine major glands - the parotid glands, the submandibular glands and the sublingual glands (Glandulae parotideae, Gll. submandibulares and Gll. sublinguales) situated extraoral. In addition, there are several hundred solitary, minor salivary glands (SG) distributed in the mouth and throat mucosa (labial and buccal gland, glossopalatine gland, and palatine and lingual glands) (Figure 8, (Probst et al. 2008)).

The parotid gland, located in the retromandibular fossa is the largest among the 3 major SGs, weighs about 15- 30 g and produces predominantly serous saliva. The secret reaches the oral cavity via the parotid duct, also known as Stensen's duct, located opposite of the upper second molar tooth. Accessory parotid gland tissue may be found anteriorly over the masseter muscle. The facial nerve divides the parotid gland into a superficial and deep lobe (Nanci 2012).

The submandibular glands are the second largest SGs and can be found in the submandibular triangle and weigh about 7-16 g. Their seromucous saliva is secreted into the gingiva-buccal vestibule via the submandibular gland duct, also known as Wharton's duct, that opens on the floor of the mouth, on the summit of the so called caruncula sublingualis, lateral to the lingual frenulum. Above the mylohyoid and medial to the sublingual fossa of the mandible the sublingual glands are located and weigh about 3-4 g. Their mucosal saliva secretes with or near the submandibular duct (Kumar 2011).

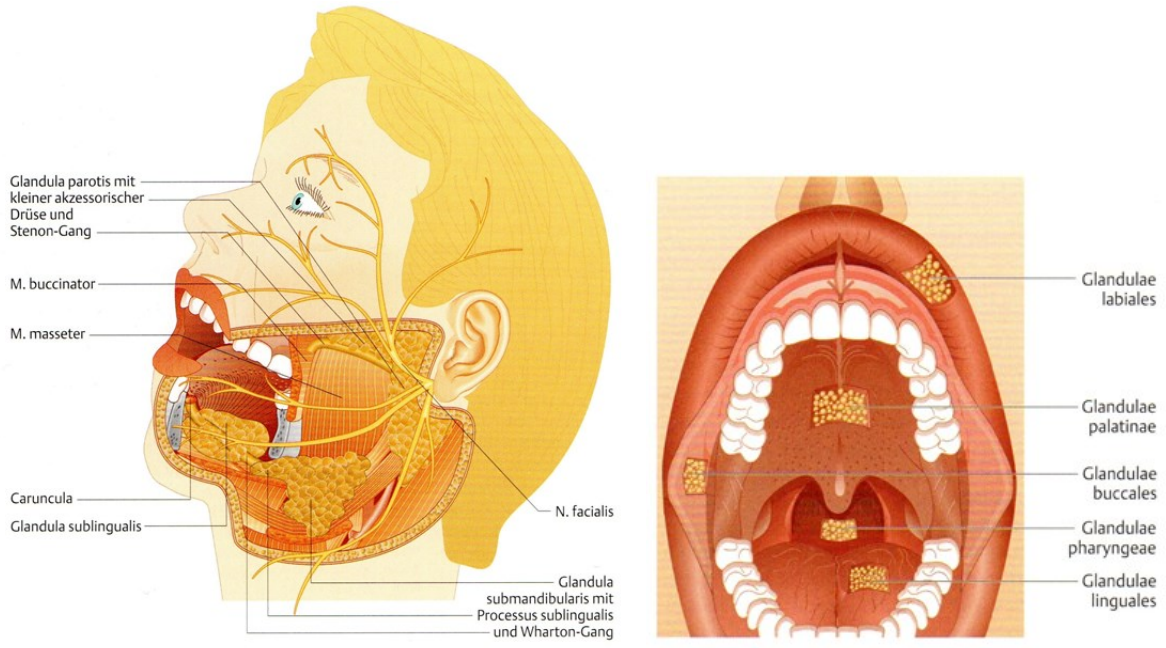


Figure 8 **Right:** Major salivary glands, **Left:** minor salivary glands. *From (Probst et al. 2008)*

All salivary glands consist histologically of the same basic terminal structure – the acini – as the functional unit which is connected by a duct system. The epithelial secretory cells of the acinus produce the primary saliva which is either classified as serous, mucous or mixed seromucous and are surrounded by myoepithelial cells. These contractile cells are able to accelerate the initial flow of saliva from the acini (Nanci 2012).

The duct system contains the intercalated duct, where macromolecule components, i.e., lysozyme and lactoferrin, are stored and contribute to the saliva. The distal following striated ducts receive the primary saliva from the intercalated ducts which constitute the largest portion of the duct system. The combination of infoldings and mitochondria cause the striations seen in the light microscope. Here, active transport and electrolyte reabsorption especially of sodium and chloride and secretion of potassium and bicarbonate takes place (Lawrence B. Berk 2005). Also, glycoproteins like kallikrein and epidermal growth factor are secreted. In the following interlobular excretory ducts smaller ducts join to large ducts, eventually forming a main duct leading to the oral opening.

Under physiological conditions the oral cavity is kept moist by a film of saliva, which constantly coats its inner surfaces. Therefore, the salivary glands have to constantly secrete a certain minimum amount of saliva. On average, a total of approximately 800 to 1500 ml of saliva are being produced per day, whereby many internal and external factors can influence this rate (Lawrence B. Berk 2005). Causes for hyper- or hyposalivation are listed in Table 2. Hyposalivation is defined as a rate of 0.1–0.25 ml/min unstimulated or 0.5–1 ml/min stimulated saliva secretion while an unstimulated secretion rate > 1 ml/min or stimulated rate > 3.5 ml/min is considered as hypersalivation. A rate below unstimulated 0.1 ml/min is called xerostomia which corresponds to the clinical symptom of mouth dryness. In combination with the sensation of dryness of other mucous membranes, such as the conjunctiva it is called sicca syndrome. A complete loss of salivation is defined as asialia (Turner 2016).

Data from epidemiological studies indicate that about one in four adults show signs of reduced salivary flow. The prevalence is over 30% in individuals over 65 years of age (Tanasiewicz et al. 2016). Also, there is a certain circadian rhythm observable in the secretion rates with its nadir during sleeping hours. The secretion is regulated by the vegetative nervous system. Activation of the parasympathetic nervous system stimulates the salivary production of the Gll. parotideae, activation of the sympathetic nervous system rather stimulates the Gll. submandibulares.

Main components of saliva are water with a proportion of about 99.5 %, keeping it fluid and protects the oral mucosa from drying out like a lubricant. Muzines make the chyme able to

glide along the oral cavity, throat and esophagus. In addition, saliva contains enzymes for digestion (e.g. alpha-amylase) and immune defense substances (e.g. lysozyme, lactoferrin, secretory IgA) with antibacterial, antiviral and antifungal activity. Further functions of saliva are the neutralization of acids via specific buffer systems and the ability to remineralize. It dissolves substances to be carried to taste buds. By being saturated with calcium and phosphate ions it supports maturation of teeth to increase surface hardness, decreases permeability, and increase resistance of enamel to caries. Tissue repair of the oral mucosa is supported by proteins present in saliva (Miranda-Rius et al. 2015).

Causes for hyposalivation	Causes for hypersalivation
Acute or chronic inflammation of the SGs	Acute inflammation of the SGs und the oral mucosa
Dehydration	nutritional irritants, acids
Systemic diseases: Sjogren's syndrome, Diabetes mellitus, viral infections like mumps (parotitis epidemica)	Intoxication (mercury, arsenic, lead)
anxiety, mental stress, depression	Nausea, pregnancy
Tumors of the salivary glands, sialolithiasis	
radiation of head and neck; radioactive iodine therapy	
Medication, e.g., anticholinergics (atropine, scopolamine, glycopyrronium bromide), alpha-receptor-blocker (phentolamine), beta-receptor-blocker (propranolol), anti-histamines, antihypertensive drugs (clonidine, reserpine), psycho-pharmaceuticals (antidepressants, neuroleptica, tranquilizer)	Medication, e.g., parasympathomimetic drugs (pilocarpine, muscarine, nicotine), Iodine, bromide, fluoride, curare, theophylline, caffeine

Table 2 Influences on salivation

	resting saliva	stimulated saliva
source	predominantly by the submandibular glands, sublingual glands and the minor SGs	predominantly by the parotid glands
consistency	More mucous	More serous
Content	Mucines, less enzymes	More enzymes, less mucines
pH	5.7-7.1	7.0 – 7.8
Normal secretion rate	0.3 – 0.4 ml/min	1-3 ml/min

Table 3 resting saliva compared to stimulated saliva characteristics

During the clinical examination of the salivary glands the following aspects should be considered: Systemic diseases, especially metabolic diseases, which can affect the function of the salivary glands (diabetes mellitus, other endocrinopathies), relevant medication (Table 2), previous diseases, procedures or therapies in the region of the salivary glands or the oral cavity (e.g., percutaneous irradiation, radioiodine therapy, section 1.2.3).

During inspection, the outer contour of the glandular region should be assessed. Enoral the excretory ducts (Wharton and Stenson duct) are to be observed as well as the salivation both spontaneous and after massaging the glands. Consistency, color and turbidity of the saliva are also relevant. With a focus on xerostomia certain pathognomonic signs of dry mouth were previously reported (Table 4) (Das und Challacombe 2016), which led to the development of a clinical scoring system – "The Challacombe Scale of Clinical Oral Dryness", described in detail below (Challacombe 2011) (3.3.1).

Mild	Severe
• Frothing of saliva.	• Depapillation or erythema of the dorsum of the tongue.
• Mild depapillation of the sides	• Fissuring of the dorsum of tongue.
of the tongue.	• Atrophic mucosa.
• Thickening of the saliva.	• Residual food debris.
• Dry lips.	• Cervical caries.

Table 4 Clinical signs of mouth dryness

In case of persistent xerostomia some basic principles should be applied such as optimal oral hygiene and intensive fluoridation to minimize the risk of caries. In case of difficulties with food intake frequent drinking of small portions of water is recommended. Established causal therapy options are still not available. The basal salivation between meals can be improved e.g. by chewing gum, also, artificial saliva in the form of sprays can be used. Pharmacologically, residual saliva production can be increased by parasympathomimetics such as pilocarpine (Miranda-Rius et al. 2015, Davies und Thompson 2015).

In a recent study, therapy-refractory xerostomia in thyroid cancer patients after radioiodine-induced sialadenitis was treated with sialendoscopic interventions which resulted in 89% of the patients with partial or complete remission of symptoms (Canzi et al. 2017). This approach has been translated to patients suffering from xerostomia after Ac-225 PSMA radioligand therapy, where in an early clinical study patients showed a significant improvement of their complaints (Rathke et al. 2019). Another recent salvage approach is targeting the regeneration of the SGs. In a clinical trial of head and neck cancer patients after external

radiotherapy, ultrasound-guided transplantation of adipose tissue–derived mesenchymal stem cells to the submandibular glands showed an increase in salivary flow of 50% four months after the intervention (Gronhoj et al. 2018).

1.2.2 Assessment of the salivary glands function

There are various subjective and objective methods to investigate the function of the salivary glands. The most commonly used ones are to interrogate patients about their complaints of mouth dryness based on common toxicity criteria (CTCAE). For a more refined assessment numerous clinically validated questionnaires have been introduced (Fox et al. 1987, Pai et al. 2001, Eisbruch et al. 2003, van der Putten et al. 2011). Among them the "Xerostomia Inventory", a multi-item questionnaire, that has been used to quantify xerostomia and demonstrated a correlation with resting saliva flow rates and a standard dry-mouth question responses (Thomson et al. 1999).

An objective investigation includes, in addition to the clinical examination, the measurement of resting or stimulated salivary flow rates by e.g., collecting patient's saliva by constantly drain saliva into a graduated container for 15 minutes (draining method) or by using pre-weighed cotton rolls held in the mouth for a defined time. Other possibilities are the spitting or the suction method (Villa et al. 2015). Morphologic evaluation of the salivary glands can be conducted by using ultrasound, MRI or CT, or more invasively by using conventional/CT sialography or sialendoscopy (Cung et al. 2017). However, a reliable functional assessment of the SGs appears only possible to a limited extent with these methods.

Scintigraphy of the salivary glands (SGS) using Tc-99m-Pertechnetate has already been introduced for this purpose in 1965 (Börner et al. 1965). The transport of iodine by a Na+/K+-ATPase-dependent Na-K-Cl cotransporter into the salivary gland cells is similarly used by Tc-99m-pertechnetate, which is accumulating and subsequently washed out in the SGs. This phenomenon can be used to investigate perfusion, concentration and secretion of all major salivary glands simultaneously and non-invasively (Kohn et al. 1992).

In head-and-neck cancer patients after external radiotherapy SGS showed a significant correlation of the uptake 1 year after radiotherapy and the mean dose delivered to the parotid gland (Roesink et al. 2004). For the early detection of Sjögren's syndrome in 71 patients SGS demonstrated a sensitivity of 87% and specificity of 93% and was considered the method of choice for this purpose (Markusse et al. 1992). Especially in the context of sialadenitis after radioiodine therapy SGS showed a high sensitivity for functional impairment already in early stages (Bohuslavizki et al. 1997, Solans et al. 2001).

1.2.3 Postactinic sialadenitis after percutaneous irradiation and radioiodine therapy

Mouth dryness remains still one of the most common side effects of radiotherapy in patients with head and neck cancers (HNC) (Dirix et al. 2006). A substantial reduction in quality of life has been reported with HNC patients suffering from oral discomfort or pain, difficulties to speak, chew or swallow and having increased dental caries or oral infections after EBRT. Consecutively, those complaints can lead to a relevant weight loss due to the reduced food intake. In a long-term study after conventional two-dimensional radiation therapy 64 % of the HNC patients reported a moderate to severe degree of xerostomia (Wijers et al. 2002).

EBRT continues to play a central role for the treatment of HNC since 74% of the patients receive either definitive or adjuvant radiotherapy (Delaney et al. 2006). New technologies like three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiation therapy (IMRT) were introduced to lower the above-mentioned side effects. Nowadays, IMRT is considered as standard of care for RT in HNC and shows significant improvements of the toxicity profile without compromising the efficacy (Lee et al. 2006, Fang et al. 2008, Nutting et al. 2011). In a meta-analysis of 33 studies of HNC patients treated with either conventional 2D/3D-RT or IMRT, late xerostomia was reported in 12%–82% and 2.3%–69% of the cases, respectively (Kouloulias et al. 2013).

Despite intensive research the cellular and molecular mechanisms underlying the loss of salivary gland function after radiotherapy are still not entirely understood (Grundmann et al. 2009). Typically, radiosensitivity of cells are observed in tissues with higher proliferation rates while salivary glands proliferate slowly and are consisting of highly differentiated cells. In the acute phase, e.g., the first week of radiotherapy, a 50-60% loss of salivary flow can be observed with a loss of acinar cells and glandular shrinkage (Henson et al. 1999, Dirix et al. 2006) (Figure 9).

Preclinical data suggest a multifactorial process initiated by DNA damage to various tissue components within the gland, including the parenchymal acinar cells, endothelium, stem/progenitor cells and also parasympathetic innervation (van Luijk et al. 2015, Lombaert et al. 2008, Konings et al. 2005, Guo et al. 2014). Furthermore, apoptosis, occurring within the first days after irradiation, has been proposed as a potential cause of the loss of both acinar cells and glandular innervation (Knox et al. 2013, Avila et al. 2009). Excessive DNA damage leading to a cellular senescence was found to be a fundamental mechanism of radiation-induced salivary hypofunction in a mouse model (Marmary et al. 2016). Also the later salivary gland damage

has been suggested to be based on radiation-induced loss of acinar cells, together with impaired parasympathetic innervation and injury to vascular structures (Cotrim et al. 2007).

The maximum cumulative dose to the parotid gland that allows recovery of salivary gland function was published as 24-26 Gy (Eisbruch et al. 1999, Li et al. 2007). In patients whose salivary glands received lower doses of radiation (< 25 Gy), a recovery of salivary function within 12-24 months could be observed (Braam et al. 2006, Dirix et al. 2006). Salivary gland scintigraphy combined with single-photon-emission computed tomography (SPECT) was used to assess the parotid gland function after conformal radiotherapy. 22.5 Gy was found to be the mean dose resulting in a 50% loss of salivary excretion fraction. Furthermore, a significant loss of function was observed as well in the caudal part of the spared parotid glands, where mean doses of 10- 15 Gy had been delivered (Bussels et al. 2004). The maximum tolerable cumulative dose to the submandibular glands has been published at around 39 Gy, suggesting that these glands may be less radiosensitive than the parotid glands (Murdoch-Kinch et al. 2008).

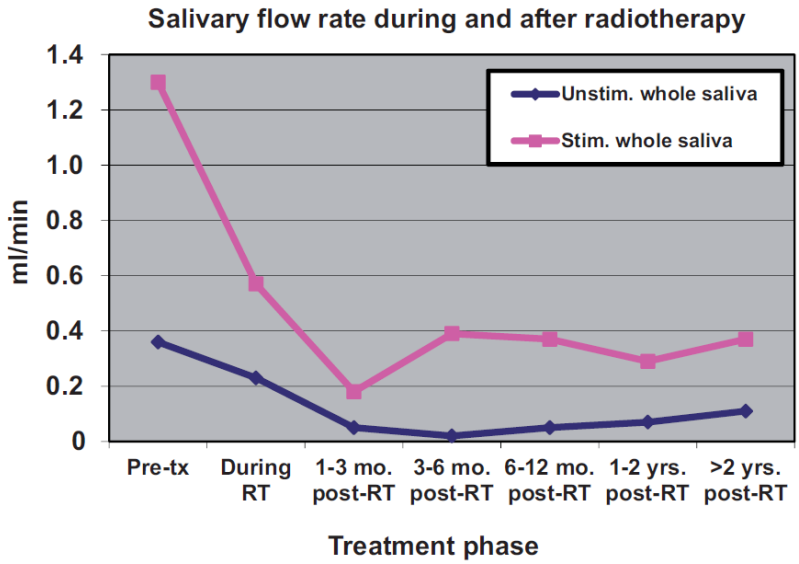


Figure 9 Unstimulated and stimulated saliva flow rate changes during and after head and neck radiotherapy. Tx = treatment, RT = radiotherapy, Mo. = months, Yrs. = years, Unstim. = unstimulated, Stim. = stimulated. *From (Jensen et al. 2019).*

Sialadenitis is also known to be a common side effect of radioiodine therapy (RIT) (Van Nostrand 2011, Mandel und Mandel 2003). The occurrence of persistent xerostomia (in 16-54% of the patients) and abnormal salivary gland scintigraphy (in 37%-72% of the patients) vary among several studies (Clement et al. 2015). Solans et al investigated patients after radioiodine therapy for different thyroid neoplasms or hyperthyroidism with a cumulative

radioactivity of 925 MBq up to 18.5 GBq by using a standardized questionnaire to determine subjective oral dryness and salivary gland scintigraphy to objectify salivary gland dysfunction (Solans et al. 2001). 32.9% of the patients reported xerostomia in the first year of follow-up, which was still present in 15.2% of cases 3 years after the last dose of radioiodine. A reduced salivary gland function on SGS was found in 50.6% cases in the first year and persisted in 13.9% of cases to the second year of follow-up.

A cumulative activity of more than 5.55 GBq I-131 was found to cause more likely xerostomia and associated complications (Jeong et al. 2013). In patients with differentiated thyroid cancer (DTC) that received cumulatively 3.7 to 5.5 GBq of I-131, a reduction in the stimulated saliva flow rate was noted in 34% of patients and a high radioactivity was associated with a ≥50% drop in saliva flow rates in 10% of the patients (Klein Hesselink et al. 2016).

1.2.4 Uptake of radiopharmaceuticals in the salivary glands

The uptake mechanism of I-131 to the salivary glands acinar cells is known to be comparable to the Na+/K+/Cl cotransport system in the thyroid gland which is also used for Tc-99m-pertechnetate in SGS (Helman et al. 1987). For this reason, sodium perchlorate ($NaClO_4$) is able to block both the uptake of Tc-99m-pertechnetate and radioiodine to the thyroid and the salivary glands (Soldin et al. 2001). While the predominant portion of the administered I-131 accumulates in the SG parenchyma, up to 24% of the radioactivity is secreted through the saliva, and causes constriction of salivary ducts with salivary retention and symptoms of obstruction (Mandel und Mandel 2003).

There is much less known about the uptake of other radiopharmaceuticals to the salivary glands, however, in many radiopharmaceutical studies and in clinical routine salivary gland uptake by various radiotracer has been observed. For example, a significant physiologic salivary gland uptake of F-18-fluorocholine in prostate cancer patients was reported (Schillaci et al. 2010). Also a mild to moderate F-18 fluorodeoxyglucose (FDG) uptake into the salivary glands can be observed (Hadiprodjo et al. 2012). Furthermore, a mild physiologic background accumulation of both radiolabeled somatostatin-receptor-targeting antagonists (like DOTA-JR11 or -OPS201) and agonists (like DOTATATE or DOTATOC) can be detected in patients with neuroendocrine tumors (Fani et al. 2017, Kunikowska et al. 2012). For all mentioned radiopharmaceuticals, in contrast to radioiodine, no molecular uptake mechanism has been found yet, therefore a predominantly non-specific uptake is commonly considered.

In recent years, the salivary gland uptake of PSMA-targeting radiopharmaceuticals became more and more of interest for clinical and preclinical research (Taieb et al. 2018),

mainly due to the rapid increase of administered radioligand therapies with Lu-177 and Ac-225 PSMA in mCPRC patients and their respective side effect profiles (Hofman et al. 2018, Heck et al. 2019, Kratochwil et al. 2018). As mentioned above, especially the high prevalence of severe xerostomia after Ac-225 PSMA created an urgent unmet clinical need (Langbein et al. 2018). Nevertheless, still little is known about the exact molecular background of the uptake and it remains controversial whether it is based on a specific or non-specific mechanism.

Early publications stated a physiologic PSMA expression in the salivary and lacrimal glands, however, at much lower levels than in prostate cancer tissue (Israeli et al. 1994, Troyer et al. 1995). Therefore, the uptake of PSMA-radioligands could be considered as specific, however, further publications contradicted with no relevant PSMA expression in salivary glands based on immunohistochemical investigations (Silver et al. 1997, Chang et al. 1999). In 2017 Kratochwil et al. described the PSMA protein on immunochemistry staining to appear "in focal hot spots of acinar cells preferably along their luminal border but not homogeneously dispersed within the parenchyma…" (Kratochwil et al. 2017). Another study showed that PSMA-specific radioimmunoconjugates, like In-111 J591 and Lu-177 J591 did not demonstrate significant uptake to the salivary glands (Pandit-Taskar et al. 2008), supporting the non-specific hypothesis of accumulation.

In a preclinical setting on pig salivary gland tissue the uptake of Lu-177 PSMA was investigated using autoradiography (Tonnesmann et al. 2019). The uptake of the radiotracer was found to be partly PSMA-specific, with a high non-specific uptake fraction. The authors therefore advocated a combination of both specific and non-specific uptake mechanisms. Another recent study in human submandibular gland tissue showed only focal expression of PSMA in immunohistochemistry limited to the intercalated ducts, while, in contrast, a high Ga-68 PSMA uptake in the SGs on PET scans was observed. These findings lead to the conclusion that the high PSMA radioligand accumulation in the salivary glands are not the result of a PSMA-mediated uptake (Rupp et al. 2019).

2 Purpose of this study

At the time of preparation of this study, only a few single-center studies and one multi-center trial had retrospectively investigated toxicity profiles of Lu-177 PSMA RLT in mCRPC patients. Until today, only one single-center study with prospective data of PRLT is available and salivary gland toxicity of Lu-177 PSMA has only been investigated by detecting subjective xerostomia in a larger number of patients. This study therefore aimed:

- To systematically investigate salivary gland toxicity of Lu-177-PSMA RLT in mCRPC patients by using a standardized protocol for subjective (symptoms-related) and objective (diagnostic) measurements
- To quantify salivary gland toxicity and compare it with published data of other treatments known to potentially cause salivary gland dysfunction, e.g. external radiotherapy and radioiodine therapy
- To evaluate short-term and long-term effects of Lu-177 PSMA on the salivary gland function
- To correlate the symptom “xerostomia” to objectively detectable salivary gland impairment
- To detect potential risk factors for salivary gland toxicity after Lu-177 PSMA RLT

In a separate investigation, early effects on the salivary gland function of Tandem-PRLT in highly advanced prostate cancer patients have been studied. This novel concept of co-administering Ac-225- and Lu-177 PSMA in patients, that have become resistant to all available treatment options – including Lu-177 PSMA monotherapy - aims to minimize adverse effects of PRLT while enhancing treatment efficacy. Objectives of this sub-study were:

- To create systematic, objective data of salivary gland toxicity after Tandem-PRLT
- To compare Tandem-PRLT with data of Lu-177 and Ac-225 PSMA monotherapy
- To investigate, how the occurrence of xerostomia after Tandem-PRLT correlates to salivary gland hypofunction by means of salivary gland scintigraphy and PSMA-PET/CT

3 Materials/ Subjects and Methods

3.1 Patients

Data acquisition and analysis of this study was conducted retrospectively. This investigation was approved by the Medical Faculty of the Friedrich Schiller University of Jena. All participating patients were informed in detail and had consented to an anonymized use of their data for non-commercial research purposes at the ZBB in advance before commencing radioligand therapy.

Written informed consent of all patients was available before inclusion. A sample of the information sheets being used in the context of this investigation is attached in the supplemental section 8.2.

The following ethical and regulatory laws and requirements were complied with:

- German Medicinal Products Act (section 13, subsection 2b)
- the 1964 Declaration of Helsinki (World Medical Association 2013) and the responsible regulatory body (Government of Thuringia)
- "compassionate use" clause of the German Medicinal Products Act (BfArM 2010)
- German Federal Agency for Radiation Protection.

3.1.1 Inclusion/ exclusion criteria

After successful treatment of patients with metastatic prostate cancer using the radiopharmaceutical Lu-177-PSMA-I&T by the ZBB group (Baum et al. 2016) and thereafter by applying Lu-177 PSMA-617 (published by the Heidelberg group (Kratochwil et al. 2015b) a consensus paper by the German Society of Nuclear Medicine (DGN) was elaborated (Fendler et al. 2016), that contained the following recommendations:

- PRLT with Lu-177 PSMA in mCRPC patients should be considered after failure of all approved treatments and should be determined by a multi-disciplinary team and carried out as a so called "Compassionate Use".
- The indication should be determined patient-individual and not be based on strict defined inclusion criteria

Based on the prerequisites for PRLT of this DGN consensus paper and criteria previously published by the Bad Berka group (Baum et al. 2016, Baum et al. 2017, Kulkarni et al. 2016) the preconditions listed in Table 5 were applied to all three patient groups in this study:

Disease specific	- histologically confirmed prostate carcinoma - castration resistance - non-resectable metastases - disease progression under guideline-based therapy - proven PSMA expression by PSMA-PET/CT imaging
Progression after chemotherapy (a or b or c must apply):	a.) s.p. taxane-based chemotherapy b.) unsuitable for chemotherapy c.) refusal of chemotherapy
Laboratory findings	- sufficient bone marrow reserve (hemoglobin ≥5,5 mmol/l; leukocyte count >3.000/µl; thrombocyte count >75,000/µl) - sufficient organ function (creatinine < 2 times the upper standard limit; AST or ALT below 5 times the upper standard limit)
Other	- ECOG performance status 0 or 1/Karnofsky index >60% - more than a 6 week-interval to the last potentially myelosuppressive therapy - written informed consent of the patient about an individual character of the treatment (a sample of the information sheet is given in the Supplements section)

Table 5 Inclusion criteria for PRLT with Lu-177 PSMA at Klinik für Molekulare Radiotherapie, Zentralklinik Bad Berka, Germany and to this study

In addition to the criteria mentioned above, the following conditions had to be met in addition for the patients in this study (group I-III) (Table 6):

- - written informed consent to salivary gland scintigraphy including a consent to data collection on salivary gland toxicity of PRLT (a sample of the information sheet is given in the Supplements section)

Specific criteria for each group are listed in the following respective sections.

Inclusion to this study	- Radioligand therapy with Lu-177 PSMA (patient group I+II) - Tandem Radioligand therapy with Ac-225 PSMA-617 and Lu-177-PSMA-617 (patient group III) - written informed consent to salivary gland scintigraphy including a consent to data collection on salivary gland toxicity of PRLT (a sample of the information sheet is given in the Supplements section)
Exclusion to this study	- s.p. external radiotherapy to the head and neck region - known history of chronic disease affecting the baseline salivary gland function (e.g. Sjogren's syndrome, mumps) - s.p. radioiodine therapy

Table 6 General Inclusion and Exclusion criteria for this study

3.1.2 patient group I: Lu-177 PSMA pre/post

The purpose in this patient group was a systematic, standardized and objective investigation of salivary gland toxicity after 2 cycles of Lu-177 PSMA (Lu-177 PSMA-617 or Lu-177 PSMA I&T) administered to mCRPC patients at ZBB, selected for the treatment according to the criteria listed in section 3.1.1.

91 patients who received their initial PRLT cycle between November 2015 and June 2018 were included in this analysis. The following parameters were evaluated and procedures accordingly performed before and after PRLT (baseline/follow-up) (Table 7):

Procedure/data	**Baseline**	**Follow-up**
Ga-68 PSMA-11 PET/CT parameters: maximum standardized uptake value (SUVmax) and metabolic volume (MV) of the parotid glands and the submandibular glands (section 3.3.4)	Yes	Yes
Validated questionnaire for xerostomia: "shortened xerostomia inventory" (sXI, section 3.3.2) (Thomson et al. 2011)	Yes	Yes
Detailed oral clinical examination (section 3.3.1)	Yes	Yes
Mouth dryness according to Common Terminology Criteria for Adverse Events (CTCAE v.5.0)	Yes	Yes
Dynamic, quantitative salivary gland scintigraphy using Tc-99m-pertechnetate (Bohuslavizki et al. 1997) (section 3.3.3)	Yes	Yes

Table 7 Procedures performed in patient group I at baseline and follow-up

The following parameters were analyzed (acquired co-factors) (Table 8):

Parameters acquired for analysis	• Cumulative administered radioactivity after 2 cycles of PRLT • Age • Gleason score • manifestation of metastasis (lymph nodes, bones, visceral) • Comorbidities with an increased risk of xerostomia (section 1.2.1) • concomitant medication with an increased risk of xerostomia (section 1.2.1) • Number of treatment lines before PRLT • Status post taxane-based chemotherapy • Status post 2nd generation antiandrogen therapies (section 1.1.1) • Tumor burden visually assessed on baseline Ga-68 PSMA-11 PET/CT (Gaertner et al. 2017) (section 3.3.4; Figure 17)

Table 8 parameters/ co-factors obtained for analysis group I

3.1.3 patient group II: Lu-177 PSMA long-term follow up

For long-term evaluation of salivary gland toxicity of Lu-177 PSMA RLT 40 mCPRC patients were selected for analysis, that had commenced PRLT at ZBB between April 2014 and April 2017 according to the criteria in section 3.1.1. The following data was collected (Table 9):

Procedure/ data	**Baseline**	**Follow-up**
Ga-68 PSMA-11 PET/CT parameters: maximum standardized uptake value (SUVmax) and the metabolic volume (MV) of the parotid glands and the submandibular glands (section 3.3.4)	Yes	Yes
Validated questionnaire for xerostomia: "shortened xerostomia inventory" (sXI, section 3.3.2) (Thomson et al. 2011)	No	Yes
Detailed oral clinical examination (section 3.3.1)	No	Yes
Mouth dryness according to Common Terminology Criteria for Adverse Events (CTCAE v.5.0)	Yes, if available	Yes
Dynamic, quantitative salivary gland scintigraphy using Tc-99m-pertechnetate (Bohuslavizki et al. 1997) (section 3.3.3)	Yes, if available	Yes

Table 9 Procedures performed in patient group II at baseline and follow-up

The following parameters were analyzed (acquired co-factors) (Table 10):

Parameters acquired for analysis	• Cumulative administered radioactivity of PRLT • Time of follow-up after 1st PRLT • Age • Gleason score • manifestation of metastasis (lymph nodes, bones, visceral) • Comorbidities with an increased risk of xerostomia (section 1.2.1) • concomitant medication with an increased risk of xerostomia (section 1.2.1) • Number of treatment lines before PRLT • Status post taxane-based chemotherapy • Status post 2nd generation antiandrogen therapies (section 1.1.1) • Tumor burden visually assessed on baseline Ga-68 PSMA-11 PET/CT (Gaertner et al. 2017) (section 3.3.4; Figure 17)

Table 10 parameters/ co-factors obtained for analysis group II

3.1.4 patient group III: Ac-225+ Lu-177 PSMA (Tandem-PRLT) pre/post

In early 2018, Ac-225 PSMA-617 (Alpha-PRLT) was started in end-stage mCRPC patients at ZBB, that had shown failure to PRLT with Lu-177 PSMA (Kulkarni et al. 2018a). Due to published data of severe xerostomia of Ac-225-PSMA-617 monotherapy (Kratochwil et al. 2017) (section 1.1.2.3), the concept of co-administration of Lu-177 and lower activities of Ac-

225 labeled PSMA-617 was introduced for the first time (thereafter referred to as "Tandem-PRLT") (Kulkarni et al. 2019).

To systemically investigate, objectify and compare the initial experience of this Tandem-PRLT approach in heavily pretreated, late-stage mCRPC patients regarding salivary gland toxicity, 18 patients were retrospectively analyzed, who received a first Tandem-PRLT cycle between February and September 2018. The same criteria as listed in section 3.1.1 had been applied. For all patients, the follow-up data at 2 months after treatment were analyzed. The following parameters were evaluated and the procedures listed were performed before and after 1 cycle of Tandem-PRLT (baseline/follow-up) (Table 11):

Procedure/ data	**Baseline**	**Follow-up**
Ga-68 PSMA-11 PET/CT parameters: maximum standardized uptake value (SUVmax) and the metabolic volume (MV) of the parotid glands and the submandibular glands (section 3.3.4)	Yes	Yes
Validated questionnaire for xerostomia: "shortened xerostomia inventory" (sXI, section 3.3.2) (Thomson et al. 2011)	Yes	Yes
Detailed oral clinical examination (section 3.3.1)	Yes	Yes
Mouth dryness according to Common Terminology Criteria for Adverse Events (CTCAE v.5.0)	Yes	Yes
Dynamic, quantitative salivary gland scintigraphy using Tc-99m-pertechnetate (Bohuslavizki et al. 1997) (section 3.3.3)	Yes	Yes

Table 11 Procedures performed in patient group III at baseline and follow-up

The following parameters were detected for analysis (acquired co-factors) (Table 12):

Parameters acquired for analysis	• administered radioactivity of Ac-225 and Lu-177 during Tandem-PRLT • cumulative administered radioactivity of Lu-177 PSMA prior to Tandem-PRLT • Age • Gleason score • manifestation of metastasis (lymph nodes, bones, visceral) • Comorbidities with an increased risk of xerostomia (section 1.2.1) • concomitant medication with an increased risk of xerostomia (section 1.2.1) • Number of treatment lines before PRLT • Status post taxane-based chemotherapy • Status post 2nd generation antiandrogen therapies (section 1.1.1) • Tumor burden visually assessed on baseline Ga-68 PSMA-11 PET/CT (Gaertner et al. 2017) (section 3.3.4; Figure 17)

Table 12 parameters/ co-factors obtained for analysis group III

3.2 PSMA-Radioligand therapy at Zentralklinik Bad Berka

At the time of analysis (June 2019), radioligand therapy using PSMA-targeting radiopharmaceuticals was not approved in any country of the world. As stated above, PRLT in Germany was applied under the "compassionate use" clause of the German Medicinal Products Act. Recently, procedure guidelines were published by the European Association of Nuclear Medicine (Kratochwil et al. 2019). Treatment of the patients in group I and II was performed based on the methodology by the Bad Berka group (Baum et al. 2016, Kulkarni et al. 2016) (Figure 10), which is similar to the guidelines published by the DGN (Fendler et al. 2016).

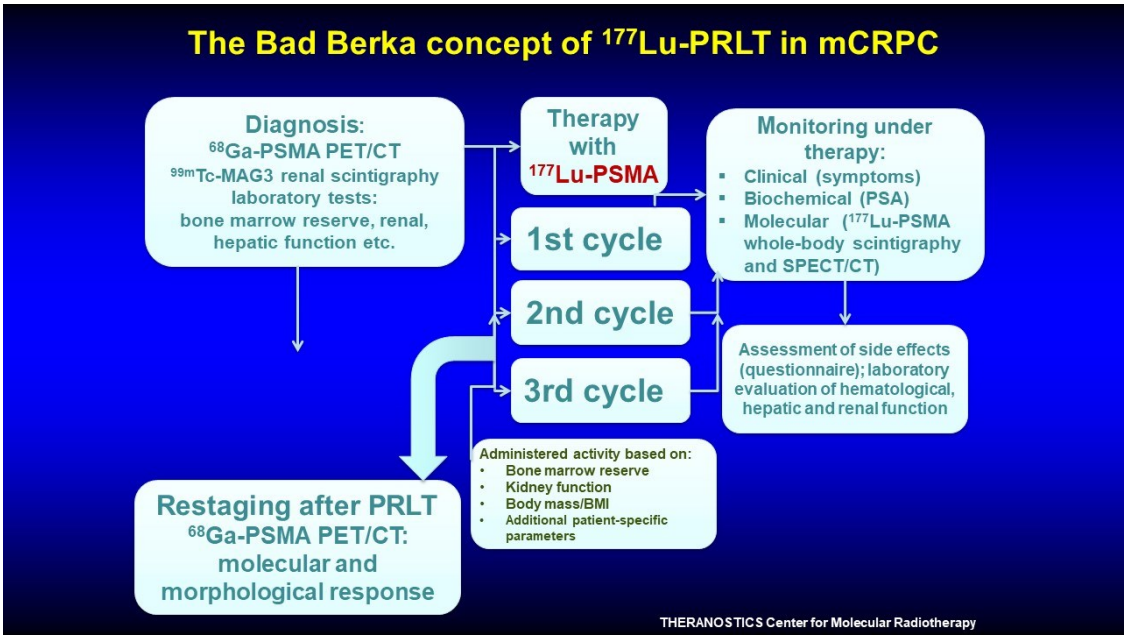


Figure 10 Therapy concept of PRLT with Lu-177 PSMA in patients with mCRPC at the Klinik für Molekulare Radiotherapie, Zentralklinik Bad Berka, Germany. *Courtesy of Prof. Dr. R. Baum, Zentralklinik Bad Berka, 2018*

3.2.1 Pre-therapeutic diagnostics

Ga-68 PSMA-11 PET/CT (Biograph mCT Flow 64; Siemens Healthineers AG, Erlangen, Germany) was performed in all patients 1–5 days before therapy to confirm high PSMA-expression at baseline and to evaluate molecular and morphologic response during follow-up based on European Organization for Research and Treatment of Cancer (EORTC) and RECIST 1.1 criteria. For procedural and technical acquisition details see section 3.3.4. To rule out a post-renal obstruction, Tc-99m-MAG3 renal scintigraphy was performed.

With the aim of 'personalized medicine' (Lee und Scott 2018), treatment activities of Lu-177 PSMA and the number and time intervals of the PRLT cycles were individualized to

the patient on the basis of e.g., uptake of the metastases on Ga-68 PSMA-11 PET/CT scan, renal function, hematologic status, previous treatments, and further patient-specific parameters.

3.2.2 Radiolabeling of Lu-177 PSMA

For Lu-177 PSMA I&T the labeling of the DOTAGA-based PSMA ligand [DOTAGA-(I-y)fk(Sub-KuE)] with Lu-177 has been published by Weineisen et al. and was carried out using the same method (Weineisen et al. 2015). The PSMA ligand was incubated at 90°C for 30 min in sodium acetate buffer (0.4 M, pH 5.5) with the required radioactivity of Lu-177-Cl_3. Radiolysis was avoided by adding 5–10 mg of gentisic acid.

The methodology of labeling the alternative precursor PSMA-617 with Lu-177 has been performed as previously described (Kratochwil et al. 2016b). The precursor was obtained from ABX Advanced Biochemical Compounds (Radeberg, Germany) and dissolved with dimethyl sulfoxide. 20 nmol of this solution were used per 1 GBq of Lu-177-Cl_3, mixed with ascorbic acid and sodium acetate buffer and incubated at 95°C for 10 min. In general, as shown by high-performance liquid chromatography and instant thin-layer chromatography, a radiochemical purity of at least 97 up to >99 % could be achieved with both precursors.

3.2.3 Hospitalization / Treatment application

According to German radiation protection laws, the patients received PRLT as inpatients on the nuclear medicine ward at ZBB for at least 48 hours after treatment. Lu-177 PSMA was administered over 5 min via a special pump system dedicated for radionuclide therapy (Figure 11). Vital parameters (temperature, pulse, and blood pressure) were monitored during administration. To ensure good hydration the patients were encouraged to drink at least 1.5 – 2 L of water. Additionally, 1,000 mL of saline with 20–40 mg of furosemide were applied intravenously after therapy (Kulkarni et al. 2016).

Figure 11 Dedicated pump system for the administration of Lu-177 PSMA (Homepage Zentralklinik Bad Berka, Copyright obtained by Rhön-Klinikum AG, Bad Neustadt an der Saale, Germany; Link: *https://www.zentralklinik.de/unsere-medizin/unsere-fachbereiche/nuk/nuklearmedizinische-therapien.html)*

Post-therapeutic imaging/dosimetry:

To confirm tumor uptake and detect off-target uptake of the administered Lu-177 PSMA qualitatively all patients received at least one whole-body scintigraphy 24-48 hours after treatment injection. Planar anterior and posterior whole body scintigraphy was performed with a dual-headed gamma camera (SPIRIT DH-V dual-head g-camera, Mediso Medical Imaging Systems, Budapest, Hungary; Figure 12). The following scintigraphy parameters were used: medium-energy general-purpose collimator; a 15% energy window; a peak at 208 keV; scan speed of 15 cm/min.

In some patients, dosimetry studies were conducted based on the MIRD scheme (Siegel et al. 1999). An adapted protocol of 5 serial planar whole-body scintigraphy at 0.5 h, 2.5 h, 24 h, 48 h, and 72 h post-injection (p.i.) with an additional Single Photon Emission Computed Tomography/Computed Tomography (SPECT/CT) was applied (Hybrid dosimetry protocol) (Schuchardt et al. 2013). Time–activity curves were calculated to estimate mean absorbed doses for tumor lesions and organs using the OLINDA/EXM software (Stabin et al. 2005).

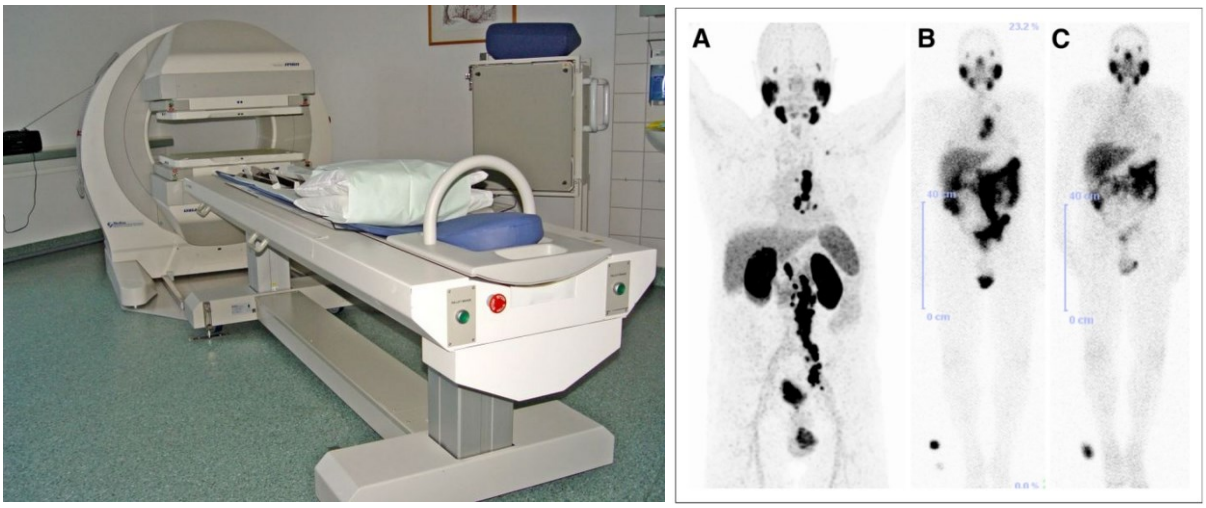


Figure 12 **Left:** SPIRIT DH-V dual-head g-camera (Mediso Medical Imaging Systems) was used for post-therapeutic imaging and dosimetry after application of Lu-177 PSMA on the nuclear medicine therapy ward at Zentralklinik Bad Berka.

Right: Maximum intensity projection (MIP) of a Ga-68-PSMA-11 PET/CT in a 70 year-old mCRPC patient before PRLT (A) showing widespread PSMA-avid lymph node metastases. Whole body scintigraphy after first PSMA RLT (B) and second PSMA RLT (C) showed a distinct therapy response. *From (Baum et al. 2016)*

3.2.4 Follow-up after PRLT

Between the PRLT cycles and after the treatment phase was completed, examinations were carried out routinely in accordance with the above-mentioned guidelines (Fendler et al. 2016). These involved clinical examinations, laboratory tests (including hematological parameters, kidney values, liver transaminases, serum-PSA) and renal scintigraphy using Tc-99m-MAG3 (determination of the tubular extraction rate/ clearance). To evaluate the treatment response, Ga-68 PSMA-11 PET/CT was performed.

3.2.5 Specifics of PRLT with Ac-225 PSMA/ Tandem-PRLT

Patients were selected for Tandem-PRLT after failing or becoming refractory to PRLT with Lu-177 PSMA and went basically through the same pre-therapeutic diagnostic process. Rationale and background of concomitantly administering Ac-225 and Lu-177 PSMA has been described (Kulkarni et al. 2018b) and already discussed above in section 1.1.2.3.

Ac-225 was purchased from ITG Isotope Technologies Garching GmbH, Garching, Germany. Quality control by instant thin-layer chromatography and determination of radiochemical purity by high-resolution gamma spectrometry was carried out before administration, obtaining a radiochemical purity of ≥ 98 %. A treatment activity of 3-5 MBq of Ac-225 PSMA-617 was used. On the day of treatment, first, PRLT with Lu-177 PSMA was administered as described in section 3.2.3. Subsequently, the intravenous application of Ac-225 PSMA-617 was carried out with a slow freehand injection over 1 minute through a sterile filter with low protein binding, similar to the procedure described by the Heidelberg group (Kratochwil et al. 2017).

3.3 Investigation of the salivary gland function

3.3.1 Clinical examination

Every patient received a comprehensive oral examination at the time points as stated previously. To clinically evaluate hyposalivation, the following pathognomonic signs, that had been proposed before (Osailan et al. 2011, Villa et al. 2015), where examined and documented:

- sticking of an intraoral mirror to the buccal mucosa or tongue
- frothy saliva
- no saliva pooling in floor of mouth
- loss of papillae of the tongue dorsum
- altered/smooth gingival architecture
- glassy appearance to the oral mucosa especially the palate

- lobulated/deeply fissured tongue
- cervical caries (more than two teeth)
- mucosal debris on palate (except under dentures)

According to a validated clinical scoring system, "The Challacombe Scale of clinical oral dryness" (Das und Challacombe 2016) clinical signs were categorized into 3 groups as suggested (Table 13):

Clinical degree of xerostomia	**mild**	**moderate**	**severe**
Clinical signs in oral examination	• Mirror sticks to buccal mucosa • Mirror sticks to tongue • Saliva frothy	• No saliva pooling in floor of mouth • Tongue shows generalized shortened papillae (mild depapillation) • Altered gingival architecture (i.e. smooth)	• Glassy appearance of oral mucosa, especially palate • Tongue lobulated / fissured • Cervical caries (more than two teeth) • Debris on palate or sticking to teeth

Table 13 Clinical grading of signs of xerostomia. *Adapted from (Das und Challacombe 2016)*

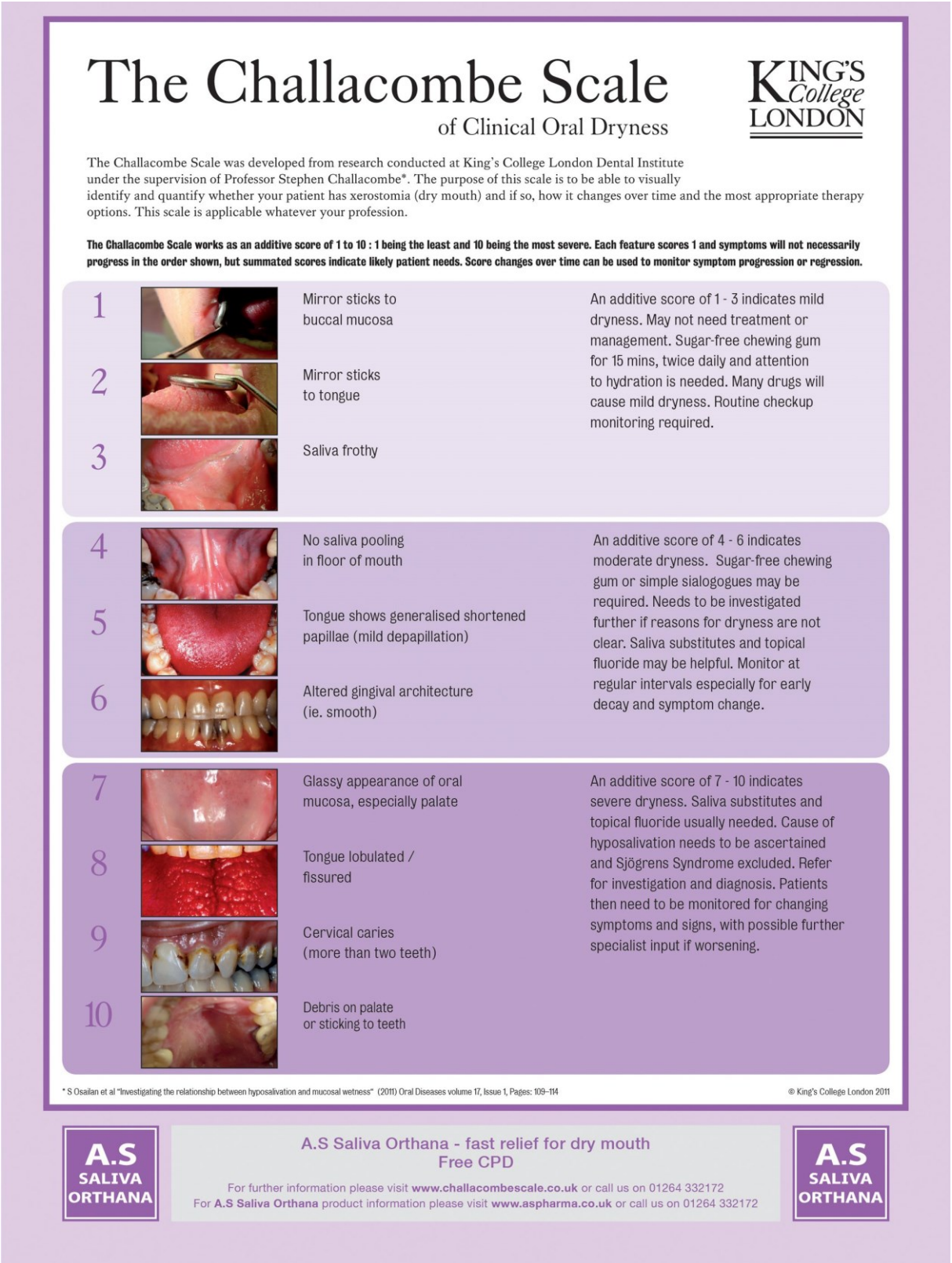


Figure 13 The Challacombe Scale of Clinical Oral Dryness. A validated clinical scoring system for mouth dryness (source: *https://www.nature.com/articles/bdjteam201826/figures/1*)

3.3.2 Interrogation/ Questionnaires

To assess and quantify the subject feeling of xerostomia, mouth dryness was documented in 2 ways.

A. Symptoms of dry mouth according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (Table 14).

Dry mouth	**Grade 1**	**Grade 2**	**Grade 3**
Definition	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods)	Inability to adequately aliment orally; tube feeding or TPN indicated

Table 14 Definition and grading of Dry mouth symptoms according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

B. A validated questionnaire for xerostomia, that has been elaborated by Thomson et al. was used as patient-reported outcome measures (PROM) (Thomson et al. 1999). Initially, this questionnaire had been created as a multi-item instrument consisting of 11 specific questions for mouth dryness, whose responses were summated to a single Xerostomia Inventory score (XI). Answers for each item were ranging from “never” (1) to “always” (5). Therefore, the summated score can range between 11 and 55. This questionnaire tool has been already used for assessment of mouth dryness in the context of Ac-225 PSMA-617 RLT (Rathke et al. 2019).

To increase applicability in a patient group with end-stage disease - partly in very poor clinical condition - a shortened version of the Xerostomia inventory score was utilized in this study. In this version (originally named summated Xerostomia Inventory-Dutch Version, sXI) only 5 items were used, that had been validated in different large clinical and epidemiologic patient populations by the same research group (Thomson et al. 2011). Each item ranged similarly from 1 (“never”) to 5 (“always”), the summated score consequently ranges between 5 and 25 points (Table 15).

In addition, the single item “*How often does your mouth feel dry?*” was used for correlation and validation of the sXI score. Patients were asked to answer the statements according to their experience during the last 4 weeks before completing the questionnaire. Patients in this study answered to the sXI before and/or after PRLT as stated above. A sample of the applied questionnaire is attached in the supplements (section 8.1).

question/statement	answer possibilities
My mouth feels dry	*"never"* = 1 *"hardly ever"* = 2 *"occasionally"* = 3 *"frequently"* = 4 *"always"* = 5
I have difficulty in eating dry foods	
My mouth feels dry when eating a meal	
I have difficulties swallowing certain foods	
My lips feel dry	
How often does your mouth feel dry?	*"never"* *"occasionally"* *"frequently"* *"always"*

Table 15 The adapted version of the validated shortened xerostomia inventory (sXI), that was applied to obtain patient-reported outcome measures (PROM) for quantification of mouth dryness. *Adapted from (Thomson et al. 2011).*

3.3.3 Salivary gland scintigraphy

Dynamic, quantitative salivary gland scintigraphy (SGS) is considered a routine clinical procedure and was conducted in the same way as described before (Bohuslavizki et al. 1997, Klutmann et al. 1999). To increase the diagnostic quality of the procedure patients were asked to fast for at least 6 hours prior to the study, also brushing of the teeth and e.g., chewing gum were not allowed to avoid unwanted premature stimulation of the salivary glands.

After written informed consent, approximately 70 ± 10 MBq Tc-99m-pertechnetate were intravenously administered. Anterior planar images of the head and neck region in supine position on a dual-headed gamma camera (SPIRIT DH-V dual-head g-camera, Mediso Medical Imaging Systems, Budapest, Hungary; Figure 14) were started to be acquired directly after injection. Dynamic acquisition was carried out with a low-energy high resolution collimator at 60 seconds/frame, acquired over 30 minutes and stored in a 128×128 matrix. After 20 min p.i. a standardized excretion stimulus of 5 ml of lemon juice was administered orally and the patient was asked to swish it around the mouth and swallow it.

Figure 14 Patient positioning for salivary gland scintigraphy and application of oral stimulus. *Courtesy of Dr. Mark Tulchinsky, Nuclear Medicine at Penn State Hershey Medical Center, Hershey, PA, USA*

The raw data was analyzed with the software module 'Salivary' of the 'Hybrid NM Processing' by Hermes Medical Solutions, Stockholm Sweden. A total of 4 symmetric oval regions of interest (ROIs) were drawn manually on summed dynamic images over both parotid and submandibular glands, one ROI over the thyroid gland and a rectangle ROI over the brain for background correction (Figure 15). First, the derived time-activity curves were assessed visually/qualitatively by sorting them to predefined categories varying in the degree of impairment of the salivary gland function. This grading has been used before to investigate salivary gland toxicity of radioiodine therapy (Solans et al. 2001) (Figure 16).

Stage of dysfunction	**Uptake**	**Excretion**
Stage 0 – normal	Normal	Normal
Stage 1 – mild	Mildly reduced	Normal – mildly reduced
Stage 2 – moderate	Reduced	Reduced
Stage 3 – severe	Severly reduced	No significant excretion

Table 16 Visual grading of the salivary gland scintigraphy adopted from *(Solans et al. 2001)*

In a normal SGS study with a healthy salivary gland function a uniform, symmetric uptake curve can be observed, commonly reaching a saturation-like plateau phase after 15 - 20 minutes. After stimulation with lemon juice a rapid washout phase is detectable (excretion phase) followed by a new tracer accumulation phase (Figure 15).

In a second step, a quantitative analysis was performed by calculating 2 parameters for all 4 salivary glands: the uptake rate at the maximum tracer uptake (Umax) and the excretion fraction (EF) after an external stimulation of salivation with lemon juice. Similar to the ejection fraction of the heart this fraction was defined as the ratio of washed out tracer compared to the highest uptake rate (see both equations below). To quantify the uptake rate at maximum, the exact administered radioactivity was determined by subtracting the remaining radioactivity of Tc-99m-pertechnetate in the syringe after injection. The calibration factor, measured in count rate/MBq was specific for the gamma camera and calculated as 68.3 counts/s*MBq^{-1} by using a defined amount of Tc-99m pertechnetate as a standard prior to the studies.

$$\text{Uptake (Umax) [\%]} = \frac{\text{count of gland} * \text{calibration factor}}{\text{activity injected}} * 100 \qquad \text{(Klutmann et al. 1999)}^1$$

$$\text{Excretion fraction (EF) [\%]} = \frac{U(12\text{–}14) - U(18\text{–}20)}{U(12\text{–}14)} * 100 \qquad \text{(Bohuslavizki et al. 1997)}^2$$

[1] Equation for calculation of the uptake rate at maximum (Umax)
[2] Equation for calculation of the excretion fraction (EF). $U_{12\text{-}14}/U_{18\text{-}20}$ = Tracer uptake averaged from 12–14/18-20 minutes p.i.

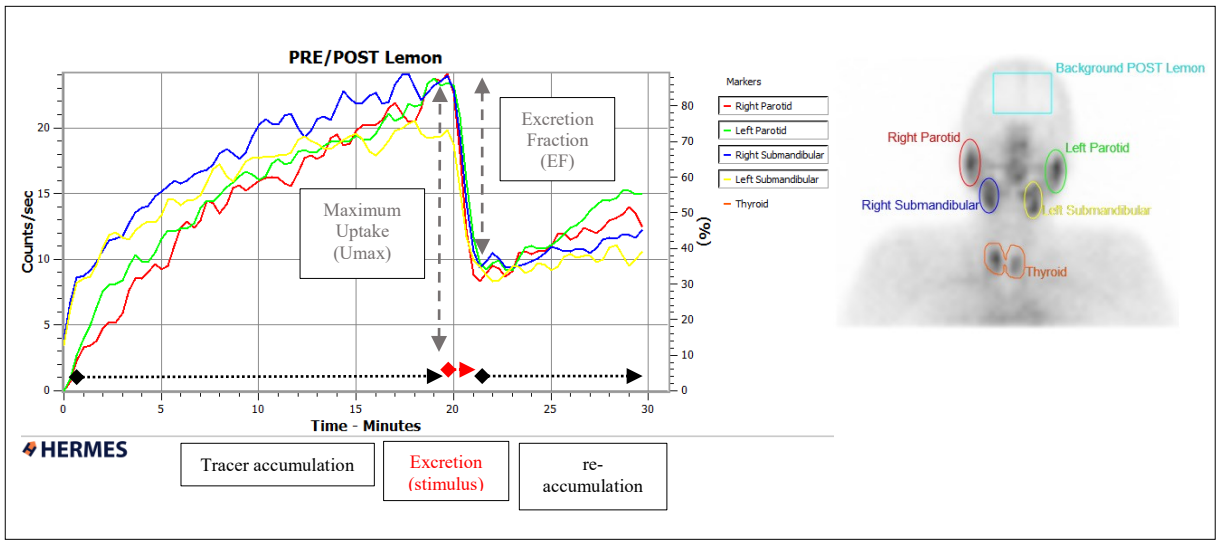


Figure 15 Physiologic time-activity curves as shown by salivary gland scintigraphy: increase of activity in all 4 major salivary glands and adequate drop of the curves after stimulation with lemon juice.

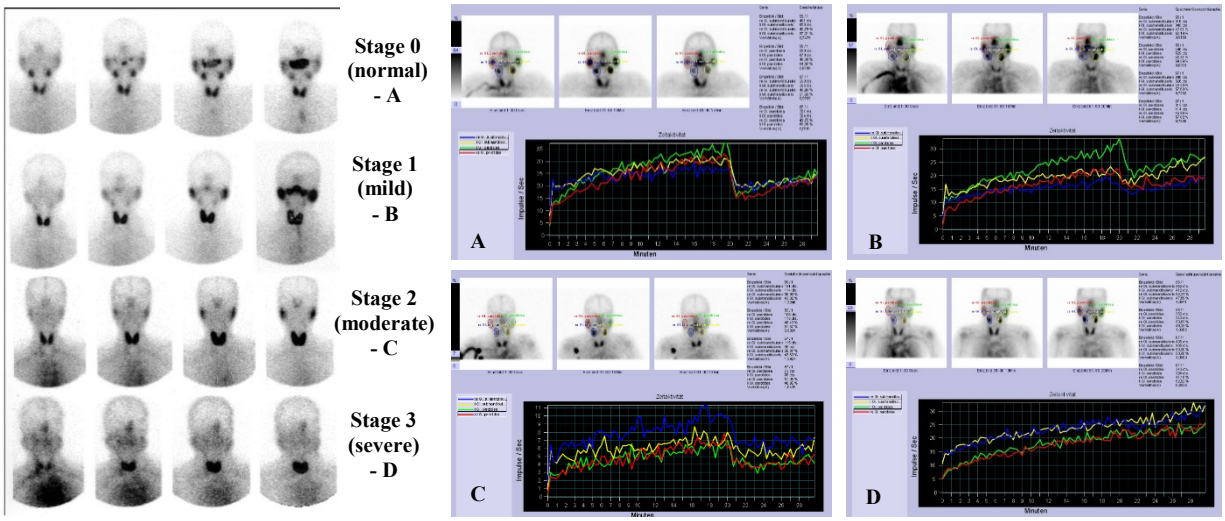


Figure 16 **Left:** Visual grading of the salivary gland scintigraphy studies adapted from *(Solans et al. 2001*). **Right:** Representative examples of different stages of impairment seen on the SGS.

3.3.4 PET/CT parameters

As previously published, PSMA radioligand uptake can be used for functional assessment of the salivary glands by detecting the maximum standardized uptake values (SUVmax) and the metabolic volume on Ga-68 PSMA PET/CT (Scarpa et al. 2017, Zhao et al. 2020). Despite lacking a structured validation of this method, Scarpa et al. could show a correlation between xerostomia after Lu-177 PSMA RLT and a significant decrease of SUVmax and MV of the SG on Ga-68 PSMA PET/CT.

In this study, Ga-68 PSMA PET/CT scans of all 3 patient groups were retrospectively analyzed by acquiring the SUVmax and MV of both parotid and submandibular glands. PSMA

PET/CT scans were performed in clinical routine at the ZBB and as previously described (Baum et al. 2016) in accordance with EANM guidelines(Fendler et al. 2017).

In-house radiolabeling of Ga-68 PSMA-11 in good manufacturing practice (GMP) quality was performed similarly as published (Afshar-Oromieh et al. 2013). Ga-68 was obtained from a Ge-68/Ga-68 radionuclide generator, the precursor PSMA-11 was purchased from ABX Advanced Biochemical Compounds (Radeberg, Germany). High radiochemical purity was confirmed by reversed-phase high performance liquid chromatography and thin layer chromatography.

Ga-68 PSMA PET/CT imaging (Biograph mCT Flow 64; Siemens Healthineers AG, Erlangen, Germany) was acquired from the skull through the midthigh, 60–80 min after intravenous injection of 1.8-2.2 MBq Ga-68-PSMA-11 per kg bodyweight (~ 130 – 160 MBq). For fast renal tracer washout, 20 mg of furosemide were intravenously administered. Contrast-enhanced CT imaging was performed using iodinated contrast media. The following imaging and reconstruction parameters were applied: 120 kV; 160 mA; gantry rotation time, 0.3 s; slice thickness, 0.4 mm, with increments of 0.1–10 mm; 40 images/s; and 512 x 512 matrix.

To obtain SUVmax and MV 3-dimensional, circular volumes of interest (VOIs) with an isocontour threshold of 20 % of the SUVmax were manually drawn over the salivary glands using the software “syngo.via” (Siemens Healthineers AG, Erlangen, Germany). This method was adopted from clinical routine in oncologic imaging with fluorine-18 fluorodeoxyglucose (F-18-FDG) PET/CT based on EANM-guidelines (Boellaard et al. 2015). Based on the uptake (visual assessment) in the baseline Ga-68 PSMA PET/CT, patients were stratified into 3 subgroups (low, moderate or high) as previously described (Gaertner et al. 2017) (Figure 17).

3.4 Statistical analysis

The statistical analysis was performed using the software SPSS Statistics, version 24 (IBM Corp., USA). Descriptive statistical results have been reported as frequency (%), mean ± standard deviation, ranges and/or 95% confidence intervals, and median with ranges and/or 95% confidence intervals and were named in the respective sections.

To examine normal distribution of the samples, graphical methods by histograms and quantile-quantile plots (QQ plot) were used and the Shapiro-Wilk test was applied. In case of normal distribution parametric test were applied (students t-test for paired or unpaired samples, univariate analysis of variance (one-way ANOVA) with post-hoc analysis using the Tukey-HSD test), in case of non-normal distribution non-parametric tests were applied (Wilcoxon’s

signed ranks test, Mann–Whitney U test, Kruskal-Wallis-H test). For each test a result was declared statistically significant if the 2-sided *p* value was less than 0.05.

For univariate analysis averaged values of all 4 salivary glands were created, to analyze multiple dependent variables a multivariate analysis of variance (one-way MANOVA) was conducted with a post-hoc analysis using the Bonferroni procedure and Scheffe test. Also a *p* value less than 0.05 was considered statistically significant.

Correlation analysis with subsequent linear regression was performed using Pearson's or Spearman's correlation.

4 Results

4.1 Patient group I – Lu-177 PSMA pre/post

Ninety-one patients (median age 68 years; range 46-90) were selected for analysis that had met all inclusion criteria mentioned in section 3.1. Table 17 provides an overview of the patient characteristics. The median Gleason score was 4+4=8, most frequent localizations of metastases were observed in bones (77/91; 84.6 %) and lymph nodes (73/91; 80.2%). 23 % of the patients in this group showed visceral metastases before receiving their first PRLT cycle. Based on the visual tumor burden assessed on the baseline Ga-68 PSMA PET/CT (section 3.3.4), subgroups with low (37.4%), moderate (33.0%) or high tumor load (29.7%) were formed (Figure 17).

48.4 % of the patients (44/91) had undergone chemotherapy prior to PRLT, 61.5 % received 2nd generation antihormonal treatment with either enzalutamide or abiraterone or both. Diabetes mellitus - being a known risk factor for xerostomia (section 1.2.1) – was prevalent in 12/91 patients (13.2 %). A median cumulative treatment activity of 14.3 (range 9.5 – 20.2) GBq Lu-177 PSMA was administered during both RLT cycles with a time interval of 62 days in average between both cycles. Follow-data was acquired at a median of 69 (42-283) days after the second cycle had been applied (Table 18).

Characteristic	**Data; *n*= 91**
Age at first cycle of RLT (median; range)	68 years (46 – 90)
Gleason score (median; range)	8 (6 – 10)
Gleason score 6	3 (3.3)
Gleason score 7	22 (24.2)
Gleason score 8	16 (17.6)
Gleason score 9	33 (36.3)
Gleason score 10	5 (5.5)
Metastases (no. of pts/ % of pts)	91 (100)
Bone metastases	77 (84.6)
Lymph node metastases	73 (80.2)
Visceral metastases	23 (25.3)
Diabetes mellitus (no. of pts/ % of pts)	12 (13.2)
Tumor burden based on base PSMA PET/CT	
Low	34 (37.4)
Moderate	30 (33.0)
High	27 (29.7)
Treatment before PRLT	
Chemotherapy	44 (48.4)
docetaxel	40 (44.0)
cabazitaxel	16 (17.6)
ADT	91 (100)
2nd generation ADT	56 (61.5)
enzalutamide	45 (49.5)

abiraterone	37 (40.7)
Other treatments before/during PRLT	
Ra-223-dichlorid	12 (13.2)
bisphosphonates	27 (29.7)
Denosumab	24 (26.4)
Sipuleucel-T	6 (6.6)
Samarium-153-EDTMP	1 (1.1)

Table 17 Baseline characteristics of patient group I included for analysis

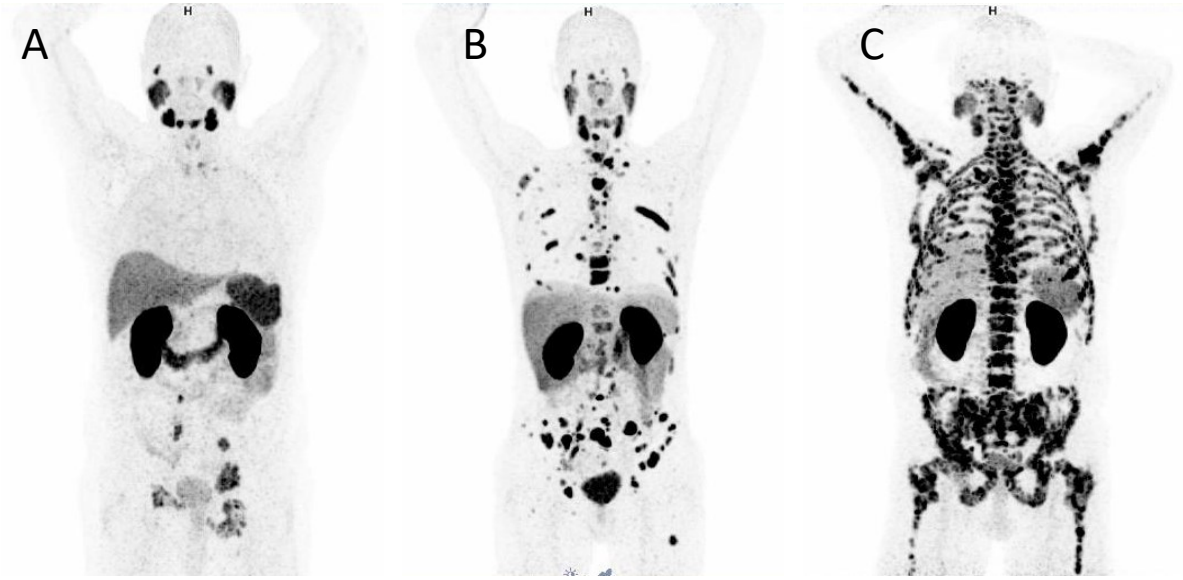


Figure 17 Representative examples of subgroups based on the visual tumor burden on the Ga-68 PSMA PET/CT at baseline. Maximum intensity projections (MIPs) of patients with A – low, B – moderate and C – high tumor load.

Characteristics	Data
Cumulative radioactivity administered (GBq, median; range)	14.3 (9.5 – 20.2)
PSMA ligand	
PSMA-617	87 (95.6)
PMSA-I&T	4 (4.4)
Time between both RLT cycles (days, median; range)	62 (40-247)
Follow-up after 2nd cycle (days, median; range)	69 (42-283)

Table 18 Treatment and follow-up characteristics

4.1.1 Symptoms of mouth dryness and clinical examination

Mouth dryness grade 1 according to Common Terminology Criteria for Adverse Events (CTCAE v.5.0) was reported in 14.3 % of the patients at baseline, while that number increased significantly to 24.2 % of the cases after 2 cycles of RLT with Lu-177 PSMA ($p < 0.01$; Wilcoxon test). On the other hand, the vast majority of patients stated no complaints of

xerostomia both before and after the treatment (85.7 % and 75,8 %, respectively). This was in line with the findings of the shortened xerostomia inventory score before and after PRLT. The median sXI-score rose only slightly, but significantly from 7 (± 3.9) to 8 (± 3.9) ($p < 0.05$; Wilcoxon test). A moderate but highly significant correlation between the xerostomia according to CTCAE and the sXI-score at follow-up was found (Spearman's correlation $r = 0.425$, $p = 0.001$). All patients were carefully examined clinically based on the "Challacombe Scale of Clinical Oral Dryness" (section 3.3.1), however, none of the pathognomic signs of chronic hyposalivation as also discussed in section 1.2.1 were observed.

4.1.2 Salivary gland scintigraphy

For all 91 patients, at least salivary gland scintigraphies at baseline and after 2 cycles of PRLT were available for analysis. The visual assessment (Figure 16; Table 16 section 3.3.3), carried out first showed no significant differences in the qualitative grading of the studies before and after treatment (Wilcoxon test). Noteworthy, in about one third of the patients a mildly impaired function of the salivary glands could be detected visually already at baseline (36 % stage 1 or 2, Figure 18).

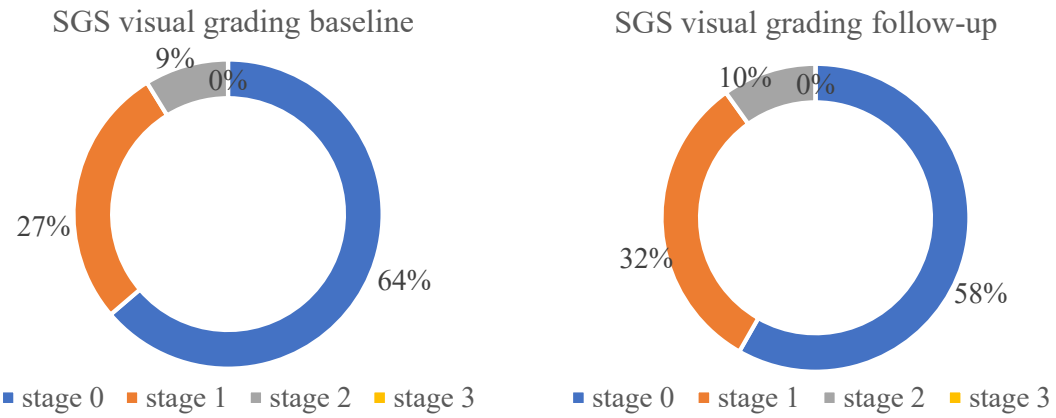


Figure 18 Visual grading of the salivary gland scintigraphy studies at baseline and follow-up (according to (Solans et al. 2001). No significant differences were observed.

Subsequently, a quantitative assessment of the maximum tracer uptake (Umax) and the excretion fraction (EF) of all 4 major salivary glands (right/left parotid and submandibular gland) before and after treatment was conducted. No statistically significant changes were observed for all salivary glands (Wilcoxon test). Detailed results are shown in Table 19.

	Umax						p*	EF						p*
	baseline			follow-up				baseline			follow-up			
	Mean	Min	Max	Mean	Min	Max		Mean	Min	Max	Mean	Min	Max	
right pg	0,32	0,11	0,73	0,31	0,12	0,63	*n.s.*	57,9	2,4	88,8	54,9	13,9	83,5	*n.s.*
left pg	0,35	0,10	0,82	0,34	0,12	0,73	*n.s.*	57,1	23,2	82,7	52,5	5,7	73,9	*n.s.*
right smg	0,31	0,15	0,84	0,32	0,10	0,85	*n.s.*	49,9	24,9	67,9	49,1	19,7	67,7	*n.s.*
left smg	0,33	0,13	0,67	0,33	0,10	0,91	*n.s.*	48,8	20,7	70,1	47,5	6,1	68,4	*n.s.*

Table 19 Detailed results of the dynamic, quantitative salivary scintigraphy performed at baseline and follow-up. No significant differences of the maximum tracer uptake (Umax) and the excretion fraction (EF) were observed in all salivary glands (pg = parotid gland; smg = submandibular gland). Values for Umax are shown as percentage of the injected tracer activity, values for EF are percentage of Umax. *Wilcoxon test was applied for each variable.

A significant correlation of both the Umax and EF of the parotid glands in the follow-up SGS and the occurrence of subjective xerostomia after PRLT was found (*Spearman's correlation r Umax= - 0.287, p = 0.006; EF r= - 0.335, p = 0.001*). In patients without mouth dryness the Umax and the EF of the parotid glands were significantly higher than in patients with xerostomia (*Umax 0.35 ± 0.12 vs. 0.27 ± 0.09 and EF 56.2 ± 11.3 % vs. 46.0 ± 13.8; p < 0.01 Mann–Whitney U test*). However, no similar correlation could be demonstrated for the submandibular glands.

4.1.3 Ga-68 PSMA-11 PET/CT parameters

The SUVmax and the metabolic volume (MV) of the parotid and submandibular glands were acquired at baseline and in follow-up PET/CTs for all 91 patients. No significant changes of the SUVmax were found (Wilcoxon test). In contrast, the metabolic volume of all 4 examined salivary glands showed a distinct decline of 7.3 to 9.7 % ($p < 0.001$; Wilcoxon test) (Table 20; Figure 19). In absolute numbers a mean decrease of the metabolic volume of the right parotid gland of 3.5 cm^3 (± 4.2), of the left parotid gland of 3.4 cm^3 (± 4.7), of the right submandibular gland of 1.1 cm^3 (± 1.9) and of the left submandibular gland of 1.0 cm^3 (± 1.8) was detected.

	SUVmax						p*	MV (cm^3)						p*
	baseline			follow-up				baseline			follow-up			
	Mean	Min	Max	Mean	Min	Max		Mean	Min	Max	Mean	Min	Max	
right pg	21,3	5,4	41,9	20,5	9,3	37,0	*n.s.*	36,7	11,2	61,0	33,2	3,1	57,1	*< 0.001*
left pg	21,1	7,7	38,6	20,2	8,3	37,3	*n.s.*	37,1	22,7	60,6	33,8	17,4	59,5	*< 0.001*
right smg	23,2	10,1	44,6	23,4	9,8	52,1	*n.s.*	13,0	2,7	24,2	11,9	3,6	20,1	*< 0.001*
left smg	23,8	10,1	49,8	23,8	9,3	45,3	*n.s.*	13,0	7,6	26,6	11,9	5,1	19,8	*< 0.001*

Table 20 Salivary gland parameters determined by Ga-68 PSMA PET/CT at baseline and follow-up. After manually drawing an isocontour volume-of-interest (VOI) with a 20 %-threshold, SUVmax and the metabolic volume (MV) of the parotid glands and submandibular glands were captured. A systematic, significant decline of the MV of all 4 salivary glands was observed. *Wilcoxon test was applied for each variable

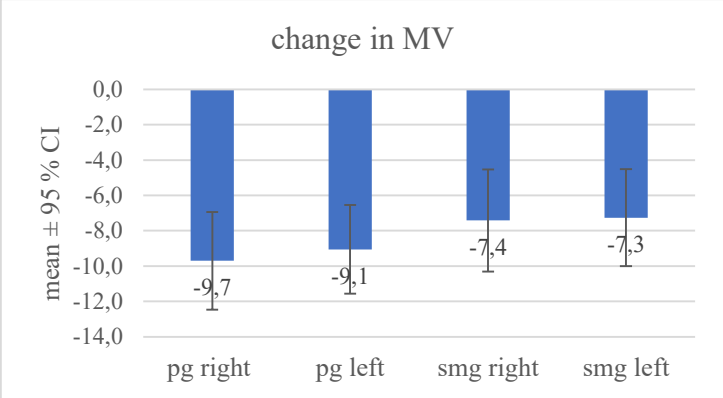


Figure 19 Relative decline of the metabolic volume of all 4 salivary glands on follow-up PET/CT compared to baseline.

4.2 Patient group II – Lu-177 PSMA long-term follow up

Forty patients were selected for retrospective analysis of long-term follow up data. Details of the patient characteristics are displayed in Table 21. In this group a median of 6 cycles of PRLT (range 2-9) had been applied with a cumulative administered activity of 35.3 GBq of Lu-177 PSMA (range 9.9 – 61.8). Follow up interval after the last cycle was median 24 months (range 8 – 52 month) (Table 22).

Characteristic	**Data; *n*= 40**
Age at first cycle of RLT (median; range)	68 years (50 – 90)
Gleason score (median; range)	8 (5 – 10)
Metastases (no. of pts/ % of pts)	40 (100)
Bone metastases	35 (87.5)
Lymp node metastases	33 (82.5)
Visceral metastases	11 (27.5)
Diabetes mellitus (no. of pts/ % of pts)	8 (20.0)
Tumor burden based on base PSMA PET/CT	
Low	15 (37.5)
Moderate	13 (32.5)
High	12 (30.0)
Treatment before PRLT	
Chemotherapy	19 (47.5)
docetaxel	19 (47.5)
cabazitaxel	4 (10.0)

ADT	40 (100)
2nd generation ADT	32 (80.0)
enzalutamide	22 (55.0)
abiraterone	23 (57.5)
Other treatments before/during PRLT	
Lu-177 BPAMD	1 (2.5)
bisphosphonates	14 (35.0)
denosumab	9 (22.5)

Table 21 patient characteristics of group II

Characteristics	Data
Cumulative radioactivity administered (GBq, median; range)	35.3 (9.9 – 61.8)
Total cycles of Lu-177 PSMA (median; range)	6 (2 – 9)
2 cycles	2 (5.0)
3 cycles	5 (12.5)
4 cycles	7 (17.5)
5 cycles	6 (15.0)
6 cycles	8 (20.0)
7 cycles	7 (17.5)
8 cycles	3 (7.5)
9 cycles	2 (5.0)
Follow-up time (month; median; range)	24 (8 – 52)

Table 22 Treatment characteristics of group II

4.2.1 Symptoms of Mouth dryness and clinical examination

Compared to baseline, there was a significant increase of xerostomia according to CTCAE v.5.0 observable. While 38/40 patients reported no xerostomia and only 2/40 patients showed mild mouth dryness at baseline (grade 1), 15 patients (37.5 %) stated xerostomia grade 1 and 1 patient experienced grade 2 xerostomia ($p < 0.001$; Wilcoxon test). At no time point during follow-up grade 3 xerostomia was detected. Data of the shortened xerostomia inventory for this patient group was only available at follow-up. Again, a moderate, significant correlation of xerostomia and the sXI-score at follow-up was found (Spearman's correlation coefficient= 0.405, $p < 0.05$).

Due to missing baseline values, a comparison with previously published, epidemiologic data from different countries based on the same questionnaire was conducted (Table 23) (Thomson et al. 2011). The mean sXI-score was 9.2 (95 % CI 7.9 – 10.5, range 5 – 17). With strong limitations, this score appeared within a comparable range (mean sXI ranging from 7.6 – 9.8).

Epidemiologic sample	Number of pts.	Age (mean, range)	Mean sXI-score (95 % CI)
This study	40	68 (50-90)	9.2 (7.9 – 10.5)
South Australia	637	70 (60-95)	7.6 (7.4 - 7.8)
The Netherlands	50	78 (53-98)	7.8 (7.1 - 8.5)
Melbourne, Australia	245	84 (51-103)	8.1 (7.8 - 8.4)
Osaka, Japan	401	66 (60-84)	8.7 (8.5 - 8.9)
New Zealand, community sample	86	72 (50-90)	9.8 (9.1 - 10.5)
New Zealand, geriatric sample	167	82(65-98)	8.6 (8.2 - 9.0)

Table 23 Comparison of the shortened xerostomia inventory score at follow-up with data from several epidemiologic samples from Thomson et al. 2011. The mean sXI score appeared with the range of all cohorts mentioned.

At follow-up, a detailed clinical examination was performed in all patients. No signs of chronic hyposalivation listed in section 1.2.1 were observed.

4.2.2 Salivary gland scintigraphy

In 20 out of 40 patients, salivary gland scintigraphy had been performed at baseline, and for all 40 patients at least one follow-up SGS study was available. Based on visual grading, no significant changes were seen in the follow-up studies. At baseline, 40 % exhibited grade 0, 40 % grade 1 and 20 % grade 2 while on follow-up in 40 % grade 0, in 50 % grade 1 and in 10 % grade 2 was found. The detailed quantitative assessment of the SGS is shown in Table 24. There were no significant changes observed for the Umax and EF of all 4 salivary glands (Wilcoxon test).

	Umax						***p****	**EF**						***p****
	baseline			**follow-up**				**baseline**			**follow-up**			
	Mean	Min	Max	Mean	Min	Max		Mean	Min	Max	Mean	Min	Max	
right pg	0,29	0,12	0,50	0,35	0,13	0,70	*n.s.*	53,1	27,2	75,1	48,5	1,9	72,2	*n.s.*
left pg	0,35	0,15	0,82	0,36	0,12	0,66	*n.s.*	52,6	36,3	72,1	48,8	8,0	71,1	*n.s.*
right smg	0,32	0,20	0,48	0,34	0,17	0,51	*n.s.*	45,5	15,7	67,0	44,6	19,7	63,7	*n.s.*
left smg	0,34	0,22	0,58	0,35	0,19	0,56	*n.s.*	45,3	34,6	62,6	46,7	16,1	65,1	*n.s.*

Table 24 Quantitative results of the SGS studies of group II. No significant changes of Umax and EF were observed. *Wilcoxon test was applied for each variable

Similar to group I, the reported xerostomia at follow-up showed a highly significant correlation with the EF values of the parotid glands (*Spearman's correlation r = - 0.501, p = 0.001*). In patients without mouth dryness, the EF of the parotid glands were again significantly higher than in patients with xerostomia (*EF 54.0 ± 11.7 % vs. 40.0 ± 16.4; p < 0.01 Mann–Whitney U test*). No correlation of the Umax to the subjective complaints were found and no similar correlation could be demonstrated for the submandibular glands.

4.2.3 Ga-68 PSMA-11 PET/CT parameters

For all 40 patients, PET/CT studies were available at baseline and in follow-up. Although a slight tendency towards lower values was observable after PRLT, no statistically significant changes of the SUVmax of all SGs were found (Wilcoxon test). However, a significant decline of the metabolic volume of the SGs was detectable ($p < 0{,}001$; Wilcoxon test) with an average decrease of 12.1 % (95 % CI ± 5.3 %) to 14.1 % (95 % CI ± 5.0 %) (Table 25, Figure 20).

	SUVmax						***p****	**MV (cm³)**						***p****
	baseline			**follow-up**				**baseline**			**follow-up**			
	Mean	Min	Max	Mean	Min	Max		Mean	Min	Max	Mean	Min	Max	
right pg	20,0	5,4	37,3	18,6	7,1	38,2	*n.s.*	40,5	23,6	60,7	34,5	16,5	56,4	*< 0.001*
left pg	20,1	7,6	38,6	18,0	4,9	35,6	*n.s.*	38,9	5,7	60,7	33,9	5,9	55,9	*< 0.001*
right smg	21,3	9,8	39,4	20,6	10,8	46,9	*n.s.*	14,1	9,3	27,4	11,9	7,2	20,2	*< 0.001*
left smg	21,6	10,5	38,9	21,0	9,2	46,5	*n.s.*	14,1	7,6	28,2	11,9	6,6	22,5	*< 0.001*

Table 25 SUVmax and metabolic volume (MV, 20 %-isocontour VOI) of the salivary glands on Ga-68 PSMA PET/CT at baseline and follow-up. A significant decrease of the MV of all 4 salivary glands was observed. *Wilcoxon test was applied for each variable

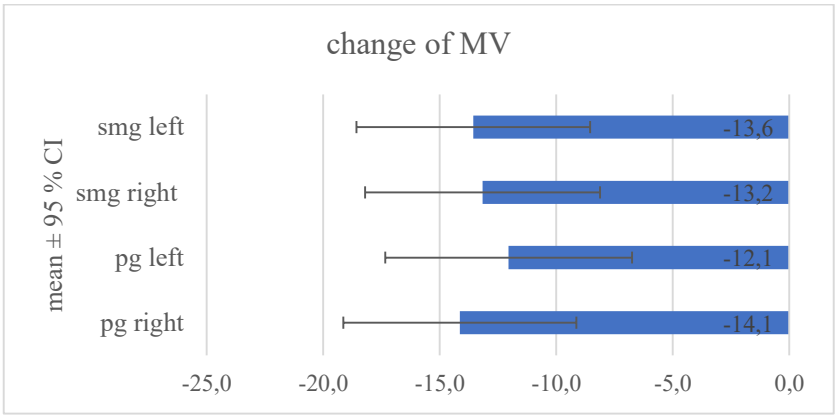


Figure 20 Relative decline of the metabolic volume of all 4 salivary glands on follow-up PET/CT compared to baseline.

4.3 Patient group III – Ac-225 / Lu-177 PSMA (Tandem-PRLT) pre/post

18 mCRPC patients were selected for analysis that had undergone at least one cycle of combined Ac-225 and Lu-177 PSMA co-administered on the same day (Tandem-PRLT). All cases exhibited a far advanced stage of the disease, about 28 % of the patients had visceral metastases. 39 % of the patients had undergone taxane-based chemotherapy prior to the treatment, 14 of 18 patients (78%) had failed or became resistant to Lu-177 PSMA RLT before Tandem-PRLT. Further details can be taken from Table 26. An average of 4.0 MBq (range 2.0 - 7.0 MBq) Ac-225 PSMA and 4.25 GBq Lu-177 PSMA (range 3.6 – 7.2 GBq) were administered intravenously for Tandem PRLT.

Characteristic	Data; *n*= 18
Age (median; range)	65 years (52 – 82)
Age > 75 y (no. of pts/ % of pts)	5 (27.8)
Gleason score (median; range)	8 (6 – 10)
Gleason score 6 (no. of pts/ % of pts)	1 (5.6)
Gleason score 7 (no. of pts/ % of pts)	4 (22.2)
Gleason score 8 (no. of pts/ % of pts)	4 (22.2)
Gleason score 9 (no. of pts/ % of pts)	8 (44.4)
Gleason score 10 (no. of pts/ % of pts)	1 (5.6)
Metastases (no. of pts/ % of pts)	18 (100)
Bone metastases (no. of pts/ % of pts)	17 (94.4)
Lymph node metastases (no. of pts/ % of pts)	15 (83.3)
Visceral metastases (no. of pts/ % of pts)	5 (27.8)
Diabetes mellitus (no. of pts/ % of pts)	3 (16.7)
Tumor burden based on base PSMA PET/CT	
Low (no. of pts/ % of pts)	0 (0)
Moderate (no. of pts/ % of pts)	5 (27.8)
High (no. of pts/ % of pts)	13 (72.2)
Treatment before Tandem-PRLT	
ADT (no. of pts/ % of pts)	18 (100)
2nd generation ADT (no. of pts/ % of pts)	14 (77.8)
Enzalutamide (no. of pts/ % of pts)	11 (61.1)
Abiraterone (no. of pts/ % of pts)	10 (55.6)
Chemotherapy (no. of pts/ % of pts)	7 (38.9)
Docetaxel (no. of pts/ % of pts)	6 (33.3)
Cabazitaxel (no. of pts/ % of pts)	3 (16.7)
Lu-177 PSMA RLT (no. of pts/ % of pts)	14 (77.8)
Bisphosphonates (no. of pts/ % of pts)	7 (38.9)
Denosumab (no. of pts/ % of pts)	3 (16.7)
Ac-225 PSMA administered (MBq, median; range)	4.0 (2.0 - 7.0)
Lu-177 PSMA administered (GBq, median; range)	4.25 (3.6 – 7.2)

Table 26 Patient and treatment characteristics of group III

4.3.1 Symptoms of mouth dryness and clinical examination

In contrast to the results of the patients treated with Lu-177 PSMA only (group I and II), the patients reported more distinct symptoms of mouth dryness after Tandem-PRLT. 6 of 18 patients (33.3 %) stated a mild xerostomia grade 1 at baseline, while after the treatment 10/18 patients (55.6 %) reported a grade 1 and 2 patients (11.1%) a grade 2 xerostomia ($p < 0.05$; Wilcoxon test). On the other hand, 6 of 18 patients still denied any complaints of dry mouth at follow-up and no grade 3 xerostomia was observed at all. No discontinuation of treatment due to mouth dryness occurred. The sXI score showed a significant increase as well from 9.5 (95% CI: 7.0 – 14.2) to 14.0 (95% CI: 11.5 – 19.6) after the treatment ($p< 0.01$; Wilcoxon test) (Figure 21).

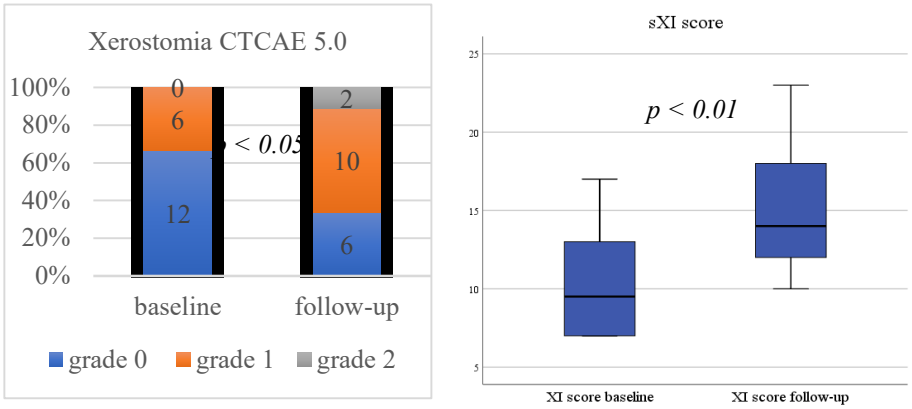


Figure 21 Xerostomia at baseline and follow-up after one cycle of Tandem-PRLT. **Left:** xerostomia according to CTCTAE increased significantly, however, no grade 3 was observed. **Right:** significant increase of the sXI after one cycle (median 9.5 to 14, p< 0.01; Wilcoxon test)

4.3.2 Salivary gland scintigraphy

In all patients, salivary gland scintigraphy was performed before and after Tandem-PRLT. While at baseline 6/18 patients exhibited a visually assessed grade 1 and 2/18 patients a grade 2 SGS study, 8/18 showed a grade 1 and 9/18 a grade 2 SGS function at follow-up, while only one patient visually had a normal SGS study after the Tandem-PRLT ($p < 0.01$; Wilcoxon test). These findings were partly confirmed by the subsequent quantitative analysis. While the Umax values showed no significant changes, the EF of all salivary glands declined significantly ($p < 0.01$; Wilcoxon test) (Figure 22).

	Umax						***p****	**EF**						***p****
	baseline			**follow-up**				**baseline**			**follow-up**			
	Mean	Min	Max	Mean	Min	Max		Mean	Min	Max	Mean	Min	Max	
right pg	0,26	0,14	0,48	0,27	0,12	0,48	*n.s.*	50,4	14,4	71,7	31,9	0,0	55,1	*< 0.01*
left pg	0,28	0,14	0,54	0,27	0,15	0,42	*n.s.*	50,4	15,0	76,5	30,9	0,0	59,1	*< 0.01*
right smg	0,27	0,15	0,51	0,27	0,19	0,45	*n.s.*	43,9	3,9	66,3	30,8	4,7	48,4	*< 0.01*
left smg	0,31	0,21	0,56	0,29	0,20	0,45	*n.s.*	45,2	6,1	59,3	36,1	11,4	56,3	*< 0.01*

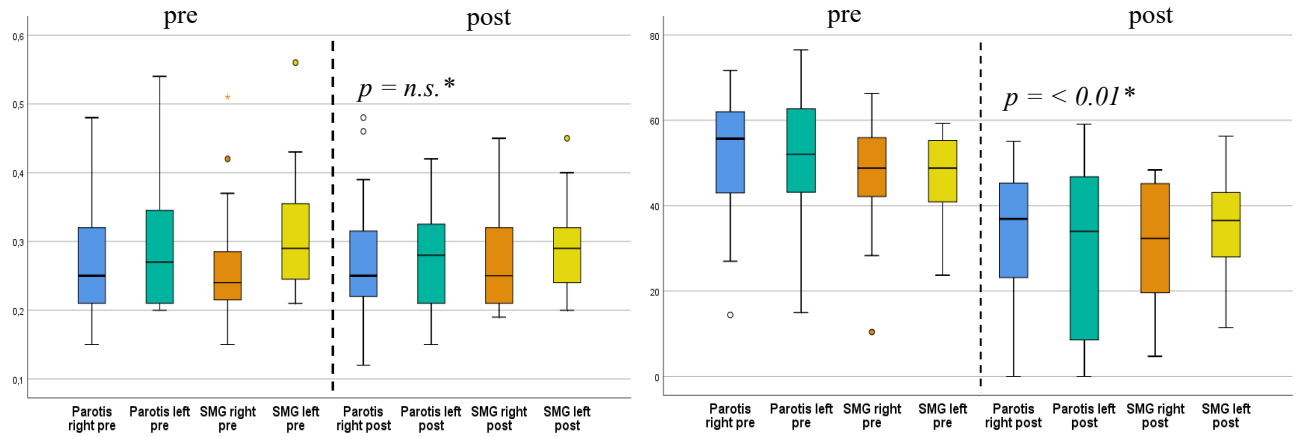


Figure 22 Quantitative analysis of salivary gland scintigraphy before and after Tandem-PRLT. While the Umax showed no significant changes, the EF declined significantly in all salivary glands. *Wilcoxon test was applied for each variable.

4.3.3 Ga-68 PSMA-11 PET/CT parameters

For all 18 patients, PSMA-PET/CT studies at baseline and follow-up were available. The mean SUVmax of all salivary glands had a tendency to decline after treatment, however, only for the left submandibular glands this difference became statistically significant ($p < 0.05$; Wilcoxon test) (Table 27). The metabolic volume of all 4 salivary glands showed a significant decrease ($p < 0.01$ for parotid glands; $p < 0.05$ for submandibular glands; Wilcoxon test). Both parotid glands exhibited a higher relative decline of the metabolic volume, right parotid gland – 14.4 % (95% CI: -22.0 to -6.7 %), left parotid gland – 11.2 (95% CI: - 17.6 to -4.8 %) vs. -6.8 % (95% CI: -13.1 to -0,6 %) for the right submandibular gland and -6.3 % (95% CI: -12.3 to -0,2 %) for left submandibular gland Figure 23.

	SUVmax						***p****	**MV (cm³)**						***p****
	baseline			**follow-up**				**baseline**			**follow-up**			
	Mean	Min	Max	Mean	Min	Max		Mean	Min	Max	Mean	Min	Max	
right pg	13,9	4,8	25,3	11,5	5,3	20,9	*n.s.*	31,0	16,5	55,8	27,2	14,8	58,1	*< 0.01*
left pg	14,6	4,9	29,7	12,2	5,0	22,4	*n.s.*	31,2	17,9	56,0	27,8	16,2	56,1	*< 0.01*
right smg	16,9	11,3	25,7	14,0	5,6	28,8	*n.s.*	11,4	5,7	16,8	10,9	4,6	18,1	*< 0.05*
left smg	18,1	9,2	30,6	14,2	6,0	28,7	*< 0.05.*	11,7	7,1	17,8	11,2	8,0	18,0	*< 0.05*

Table 27 SUVmax and metabolic volume (MV, 20 %-isocontour VOI) of the salivary glands on Ga-68 PSMA PET/CT at baseline and follow-up. SUVmax showed a tendency to lower values, MV of all 4 salivary glands declined significantly. *Wilcoxon test was applied for each variable.

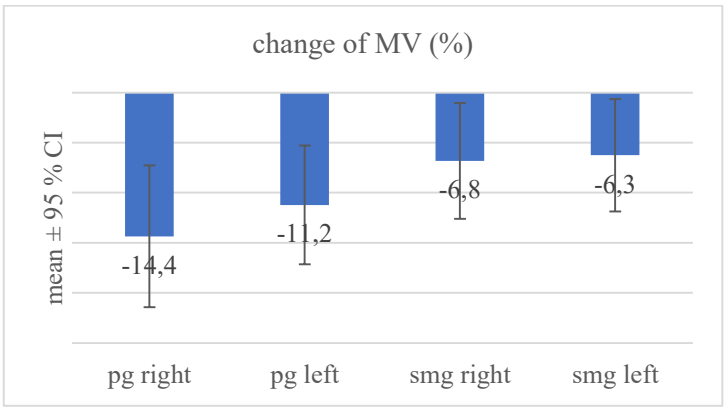


Figure 23 Relative decline of the metabolic volume of all 4 salivary glands on follow-up PET/CT compared to baseline.

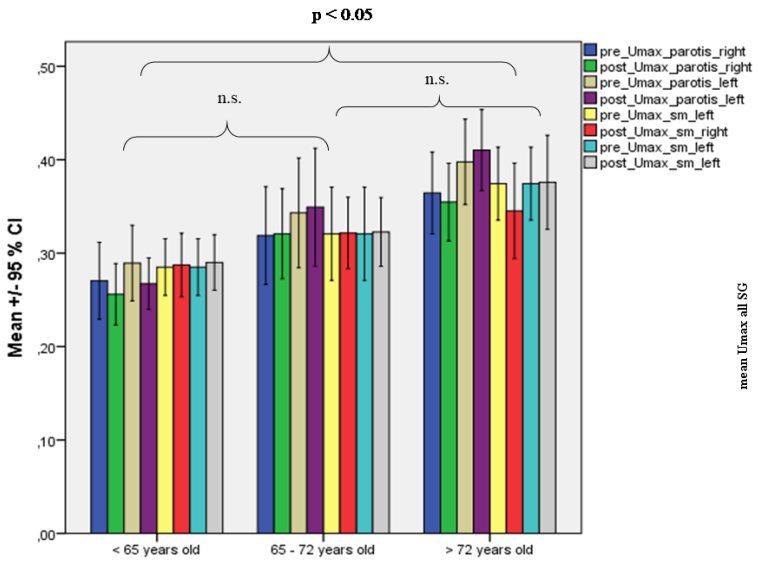
4.4 Possible cofactors influencing salivary gland function

To investigate possible influences on the salivary gland function by creating averaged values of all 4 salivary glands for SGS and PET/CT parameters or by multivariate analysis of variance (one-way MANOVA), the following potential co-factors were examined: Age, s.p. taxane-based chemotherapy, visually assessed tumor burden on baseline Ga-68 PSMA PET/CT and the cumulative administered radioactivity of Lu-177 PSMA.

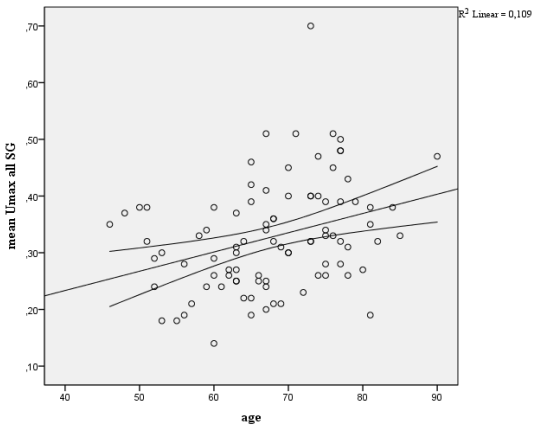
4.4.1 Age

For patient group I, as a first step, three age-based subgroups - evenly distributed by numbers - were created (< 65 years, 65 to 72 years and > 72 years) to investigate the influence of age on the detected parameters. Noteworthy, there was an unexpected highly significant difference of the Umax between the age groups (*F (2, 88) = 8.95, p < 0.001; one-way ANOVA*). A one-way MANOVA showed a significant difference between the age groups on the combined Umax as well (*F(16, 160) = 1.68, p < 0.05, partial η² = .144, Wilk's Λ = .733*) (Figure 24 left).

For older patients, higher maximum uptake values were observed both at baseline and follow-up SGS. These findings were confirmed by linear regression analysis, that showed a small but significant positive correlation (*Pearson's r = 0.109, p = 0.001*; Figure 24 right). However, age had no significant effect on the EF as well as the detected PSMA-PET/CT based parameters. While there were no differences of the SUVmax of baseline and follow-up studies, the metabolic volume declined as discussed in section 4.1.3 unrelated to age. Also, no correlation of age and the subjective patient-reported parameters of xerostomia assessed both by CTCAE and the shortened xerostomia inventory score were observed.



Umax of salivary glands on salivary gland scintigraphy



Correlation of age and Umax averaged over all SGs

Figure 24 **Left:** Umax of the salivary gland scintigraphy in the subgroup analysis stratified by age. A per se significant tendency towards higher Umax values with higher age was observable. **Right:** This was confirmed by linear regression analysis, which revealed a minor correlation ($R^2 = 0.109$, $p = 0.001$)

4.4.2 Taxane-based chemotherapy

Patients of group I, which had undergone chemotherapy prior to Lu-177 PSMA RLT, were compared to chemotherapy-naïve patients. Highly significant differences of the SUVmax of all salivary glands were detectable between those two subgroups with distinctly lower SUVmax of the SG in chemotherapy-resistant patients (*$p < 0.001$; Mann–Whitney U test; one-way MANOVA: $F (8, 78) = 3.48$, $p = 0.002$, partial $\eta^2 = .263$, Wilk's $\Lambda = .737$; Figure 25 left*).

The tumor burden of patients in the subgroups with and without previous chemotherapy, however, differed highly significantly as well (*$p < 0.001$; Mann–Whitney U test*; Figure 25 right).

A chi-square test was used to analyze the correlation of the variables "s.p. chemotherapy" and "tumor burden" on PET/CT. No expected cell frequencies were below 5. A significant correlation between both variables with a moderate grade was found (*$\chi^2 (2) = 14.46$, $p = 0.001$, $\varphi = 0.39$*). No influence of chemotherapy on the SGS parameter or the patient-reported xerostomia parameter were found in the subgroup analysis. The decline of the metabolic volume of the salivary glands after PRLT was statistically not different in chemotherapy-naïve and in chemotherapy–resistant patients.

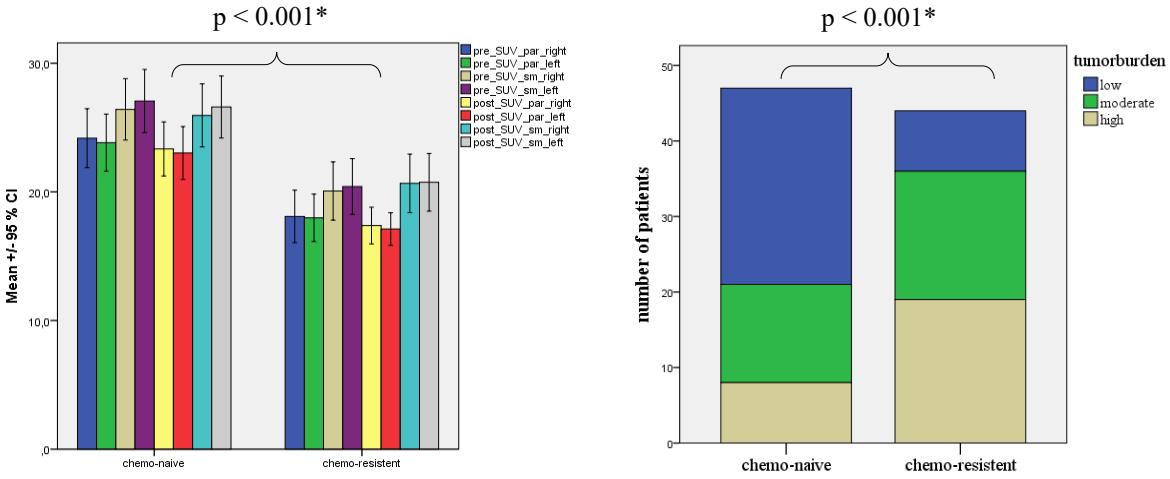


Figure 25 **Left:** SUVmax values in chemotherapy-naïve and chemotherapy-resistant patients. Patients that had undergone chemotherapy showed significantly lower uptake values on PSMA-PET/CT. **Right:** To be noted, there was also a significant difference of proportion of tumor burden between both groups, most probably overlaying this effect. * Mann–Whitney U test

4.4.3 Tumor burden

The SUVmax values of the salivary glands showed a significant difference between the subgroups based on tumor burden on the PSMA PET/CT (*F(2, 88) = 14.45, p < 0.001; one-way ANOVA; one-way MANOVA: F (16, 154) = 2.68, p = 0.001, partial η² = .218, Wilk's Λ = .612*) with moderate negative correlation showing lower SUVmax values in patients with higher tumor load (*Spearman's correlation r= - 0.492, p < 0.001*; Figure 26). No other influence on the analyzed parameters were found, the metabolic volume of the salivary glands showed a decrease independently of the tumor burden. Also, no effects on the SGS and patient-reported variables were detected.

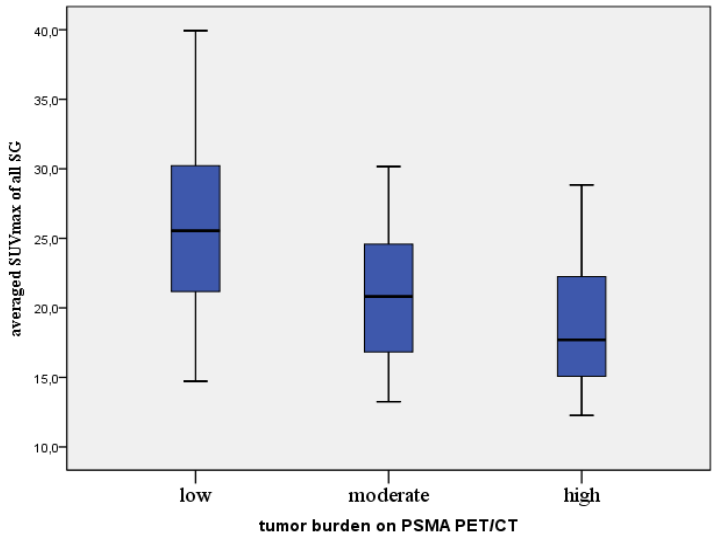


Figure 26 Effect of visually assessed tumor burden on Ga-68 PSMA PET/CT and the SUVmax of the salivary glands. A moderate but highly significant inverse correlation was observed most probably explained by the tumor sink effect (Spearman's correlation r= -0.492, p < 0.001).

4.4.4 Cumulative administered radioactivity

The influence of the cumulatively administered Lu-177 PSMA on the measured parameters of SG function were investigated both for group I and II by creating subgroups. No differences were found in terms of Umax and EF on the SGS, patient-reported parameters or SUVmax values between the subgroups. There was a tendency of a stronger decrease of the MV of all salivary glands after PRLT after higher cumulative activities (Figure 27). However, no statistical significance was reached, probably due to the small number of patients in group II.

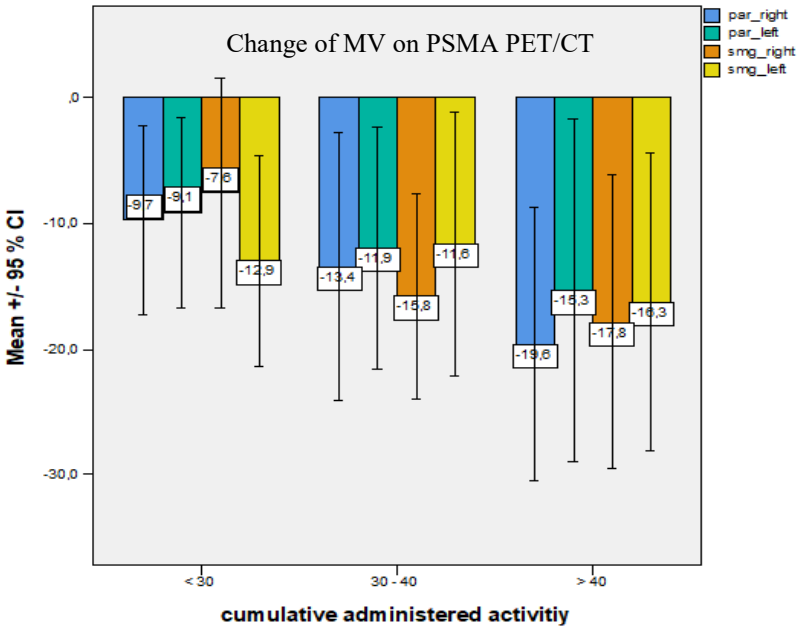


Figure 27 Decline of metabolic volume of salivary glands stratified by different groups of cumulatively administered radioactivity *(p= n.s.)*.

5 Discussion

This study systematically investigated effects of Lu-177 PSMA RLT on the salivary gland function in a group of 91 patients after short-term follow-up and in a group of 40 patients after long-term follow-up by using patient-reported outcome measures in form of a validated questionnaire, standardized clinical examinations, functional imaging with dynamic, quantitative salivary gland scintigraphy and Ga-68 PSMA PET/CT-derived parameters of salivary gland function. Subsequently, possible influencing co-factors were analyzed. In a third group of 18 patients early clinical results of a novel therapeutic strategy (Tandem-PRLT) regarding salivary gland impairment were investigated.

5.1 Lu-177 PSMA: short-term and long-term impact on the salivary glands function

5.1.1 Symptoms and patient-reported outcome measures (PROMs)

In this study, the symptom xerostomia in patients examined after a median early follow-up of about 2 months after 2 cycles of Lu-177 PSMA was reported as mild mouth dryness in only 24.2 % (22/91) of the cases. In long-term follow-up lasting as long as 52 months after a cumulative administered radioactivity of up to 61.8 GBq, 40 % (16/40) of the patients experienced grade 1-2 xerostomia. Compared to prospective data with a prevalence of 87 % of transient grade 1-2 xerostomia at 3-month follow-up (Hofman et al. 2018), those numbers appear considerably lower and are more consistent to retrospective results from other German centers with an occurrence of 8-9 % (Rahbar et al. 2017, Ahmadzadehfar et al. 2016, Kratochwil et al. 2016b), 15.4 % (Seifert et al. 2020), and up to 24 % (Heck et al. 2019) of grade 1-2 xerostomia.

As the authors of the phase II-clinical trial publication discussed themselves, their more frequent observation of mouth dryness could be possibly explained by the specific questioning within a prospective trial setting and might be considered a nocebo effect in this context (Hofman et al. 2018, Colloca und Miller 2011). Also, the time point of asking about dry mouth complaints appears relevant since a transient character of the xerostomia - usually resolving 3 months after therapy - has been described by several authors (Baum et al. 2016).

Initially, external cooling of the salivary glands during Lu-177 PSMA application was recommended (Fendler et al. 2016) and has been controversially stated as a possible explanation for the different rates of mouth dryness in the studies mentioned above (Rahbar et al. 2018). However, in recent years, evidence grew that the uptake of PSMA-targeting radioligands is not effectively reduced by external cooling and no significant protection results from this method (van Kalmthout et al. 2018, Yilmaz et al. 2019). Therefore, no external cooling of the SGs has

been applied to patients treated with PRLT at the ZBB. Eventually, the EANM procedure guidelines for Lu-177 PSMA-RLT do not recommend external cooling for routine application (Kratochwil et al. 2019).

Noteworthy, a minor number of patients in our study (14.3 % and 5.0 % and, respectively) reported a mild mouth dryness already at baseline before PRLT had been commenced. On the other hand, three quarters of the patients in early follow-up did not report any complaints of xerostomia, which is in line with e.g., early findings by Kratochwil et. al reporting only temporary xerostomia in a few cases without relevant loss in quality of life (Kratochwil et al. 2016b).

Subjective complaints of mouth dryness reflected by the results of the shortened Xerostomia Inventory were also in line with the only very mild, but significant increase of the sXI score from a mean value of 7 (± 3.9) to 8 (± 3.9) after the treatment. In long-term follow up, this tendency was confirmed with a mean sXI value of 9.2 (95 % CI 7.9 – 10.5, range 5 – 17). As described in section 4.2.1 several epidemiologic samples were available for comparison showing a mean sXI ranging between 7.6 to 9.8 (Slade und Spencer 1994, Thomson et al. 2002, Thomson et al. 2000, van der Putten et al. 2011). In this context the long-term follow-up sXI scores support the findings of a mild to moderate xerostomia of group II. Furthermore, a moderate, significant correlation of post-therapeutic xerostomia and the follow-up sXI score could be demonstrated, both in short-term and long-term follow up ($r = 0.405$ and 0.425, $p < 0.05$).

Comparing the patient-reported mouth dryness after Lu-177 PSMA with data from patients after external irradiation of the head and neck region, overall xerostomia appears to be a minor problem after PRLT. In a meta-analysis of 79 studies of HNC patients, a 93% overall prevalence of xerostomia during irradiation was found with 43.6–46.0 % of the patients reporting grade 2 xerostomia until 6 months after treatment. At 2-year follow-up, grade 2 xerostomia was present in 23.9% and grade 3 in 15.6 % of the cases, respectively. The occurrence of xerostomia after 2 years was lowered using IMRT technique instead of conventional RT (68.1 vs. 90.9 %) (Jensen et al. 2010). Another prospective study mentioned xerostomia of grade 2 or higher in 83 % of HNC patients after conventional radiotherapy and in 29 % of the patients after IMRT at 24-month follow-up (Nutting et al. 2011). The prevalence of chronic mucositis after IMRT was reported between 22%–79% (Kouloulias et al. 2013).

Data of salivary gland toxicity after radioiodine therapy stated partly comparable, partly higher rates of side effects than the ones we found for Lu-177 PSMA in our study.

Unfortunately, in many publications the grading of mouth dryness was not sufficiently described. With a wide variance, acute sialadenitis after RIT was reported in 2% to 67% of the cases, while after high-dose I-131 treatment in DTC patients the prevalence was 26 % (Hyer et al. 2007) to 42.9 % (Alexander et al. 1998). Therefore, the majority of the authors postulate a correlation of severity of mouth dryness to the cumulative administered activity of I-131.

A low occurrence of xerostomia has been observed in about 5% of patients within a few days after low-dose radioiodine treatment (Lin et al. 1996), which appears similar to the common prevalence of xerostomia in the normal population (Nederfors et al. 1997) and corresponds to the data at baseline in group II in our study. However, the prevalence of xerostomia 1–2 years after high-dose iodine treatment was reported as high as 37.8% (Solans et al. 2001, Walter et al. 2007). Regardless of the exact severity of xerostomia, this is comparable to the long-term follow up data in our study (40 % of the patients in group II with grade 1-2).

Interestingly, early clinical data of the iodine labeled PSMA-targeting ligand I-131 MIP-1095 showed a tendency towards more severe salivary gland toxicity (Zechmann et al. 2014). 7 of 16 patients reported mild to moderate xerostomia and in one patient mucositis was detected. In our study, no patient treated with Lu-177 PSMA revealed signs of mucositis or other enoral manifestations of severe hyposalivation during early and or late follow-up.

5.1.2 Salivary gland scintigraphy

Dynamic salivary gland scintigraphy, both assessed qualitatively and quantitatively has been used in a variety of studies on the subject of salivary gland dysfunction e.g., after external radiotherapy (Roesink et al. 2004, Münter et al. 2004, Bussels et al. 2004), radioiodine therapy (Solans et al. 2001, Upadhyaya et al. 2017, Badam et al. 2016) or for the diagnosis of Sjögren's syndrome (Bohuslavizki et al. 1995). The high reliability and validity of this safe and minimally invasive procedure as well as the good correlation to symptoms of hyposalivation is known for decades (Gates und Work 1967, Klutmann et al. 1999, Kaldeway et al. 2019, Schmidt-Kreppel et al. 2020). Functional impairments of the salivary glands can be already detected in early stages (Roesink et al. 2004). Furthermore, a high correlation to saliva flow rates of the major salivary glands in both healthy patients and patients suffering from hyposalivation has been proven (Kohn et al. 1992).

In order to obtain more objective results of the SGS, a quantitative analysis was carried out in addition to visual assessment as previously proposed (Bohuslavizki et al. 1997). Results of Umax and EF at baseline of group I were within the range of a previously published reference

database from 312 healthy patients (Bohuslavizki et al. 1997, Klutmann et al. 1999) (parotid glands: mean Umax = 0.33 ± 0.12 (ref. values = 0.45 ± 0.14), mean EF = 57.5 ± 11.6 (ref. values = 49.5 ± 10.6); submandibular glands: mean Umax = 0.32 ± 0.11 (ref. values = 0.39 ± 0.12); mean EF = 48.6 ± 11.8 (ref. values = 39.1 ± 9.2)).

In contrast to the slight increase of mild xerostomia in group I at early follow-up after 2 cycles of Lu-177 PMSA – also reflected by the sXI score- no significant changes of the salivary gland function were found both visually and quantitatively. While there was no intra-patient difference for both Umax and EF observable pre- and post-therapeutically, a correlation of the parotid gland values in the follow-up SGS and subjectively perceived xerostomia was found ($r = -0.287$ to -0.335; $p < 0.01$) showing significantly higher values in asymptomatic patients. These early findings were confirmed in the long-term follow-up group II, in which a similar correlation of the EF values of the parotid glands and reported xerostomia could be demonstrated ($r = -0.501$, $p = 0.001$). Interestingly, this effect could not be observed for the submandibular glands in both groups.

These findings are in line with previously published data about the SG function after radioiodine therapy in DTC patients in which a bilateral parotid gland dysfunction was the most commonly observed condition (Jeong et al. 2013). However, the authors described - in contrast to our data – that clinical symptoms were more frequent in patients with dysfunctional submandibular glands than in those with parotid gland dysfunction.

In comparison, SGS studies in patients after external radiotherapy revealed much more distinct findings. 7 months after RT with a mean dose of 22.5 Gy to the parotid glands a 50% loss of the salivary excretion fraction was observed (Bussels et al. 2004). Furthermore, another prospective investigation in HNC patients demonstrated a significant decrease of the tracer uptake of the parotid glands 6 weeks and 1 year after RT (Roesink et al. 2004), while the EF decreased from 44.7 % to 18.7 % at 6 weeks post-therapeutically. However, a re-improvement to 32.4 % at 12 months after RT could be detected.

SGS data in patients after radioiodine therapy showed similarly significant changes of the salivary gland parameters with a correlation to the cumulatively applied radioactivity. Despite salivary gland stimulating procedures using sialologs during the treatment, even after 0.4 – 0.6 GBq I-131 a parenchymal damage (detected by a decline of the maximum uptake) of 14 % has been observed, while after cumulative 24 GBq I-131 a 90 % decrease of the Umax was found (Bohuslavizki et al. 1997). The authors, however, pointed out that the 14 – 35 % loss of function for the SG observed in treatment activities less than 9 GBq usually do not translate

into clinical Sicca symptoms and a much higher threshold of relative parenchymal damage has to occur before becoming clinically apparent.

5.1.3 Ga-68 PSMA PET/CT parameters

Salivary gland uptake of Ga-68 PSMA on baseline and follow-up PET/CTs was assessed by semiquantitative SUVmax values and the metabolic volume using isocontour-VOIs, a method which has been described before showing valid and reliable results (Scarpa et al. 2017, Klein Nulent et al. 2018, van Kalmthout et al. 2018). In the early follow-up in group I no significant changes of the SUVmax were found, however, a significant decline of the MV was observed in all SGs already after 2 cycles of Lu-177 PSMA with a decline of about 7.3 % (95% CI: ± 2.8) in the submandibular glands and 9.4 % (95% CI: ± 2.8) for the parotid glands. Those findings were confirmed in the long-term follow up group II in which a significant decline of the MV of all SGs of up to 14.1 % (95 % CI ± 5.0 %) was detectable. Also, the SUVmax values showed a tendency towards lower values for all SGs at follow-up, however, possibly due to a low patient number these findings did not reach significance.

Overall, our findings confirmed previously published data of a case series of 10 mCRPC patients after PRLT (Scarpa et al. 2017). The authors observed a decline of the parotid gland volume of about 20 % and of 9.8 % of the submandibular glands after 2-3 cycles of 6 GBq Lu-177-PSMA. In addition, SUVmax values showed a significant drop of 6 % in the parotid glands and 10.5 % in the submandibular glands. Nevertheless, only in one patient xerostomia occurred without significant impact to the quality of life. This appears in line with results from our study in which a mild to moderate xerostomia occurred only a minor number of patients both in short and long-term follow-up after a mean cumulative radioactivity of 14.3 and 35.3 GBq, respectively.

Therefore, changes in the MV could be considered as a possible early indicator for SG toxicity. However, it also might just exhibit a treatment-related effect to the SGs after PSMA-targeting radioligand therapies without relevance for the salivary gland function. This is supported by the fact, that no significant difference of the MV decline in patients with and without perceived xerostomia has been found both in group I and II of this study. Further investigations with higher patient numbers are needed to evaluate this phenomenon, also in the context of distinct SG hypofunction derived from other diseases or pretreatments.

Note should be taken of the different numbers by Scarpa et al., especially in the MV compared to our study that might occur from different thresholds of the isocontour-VOIs used to analyze the SG (20 % of the SUVmax in our study vs. probably 50 % in the study by Scarpa

et al.). The 20 % cut-off resulted in a subjectively better segmentation of the SGs, however, a 50 % threshold would be the more commonly used value in metabolic imaging studies using PET (Boellaard et al. 2015). In a recent retrospective study of Ga-68 PSMA PET/CT in patients with different degrees of symptomatic salivary gland dysfunction due to Sjogren's syndrome, RT for head and neck cancer or a s.p. surgery of the SGs consistent findings to an additionally performed SGS have been described (Zhao et al. 2020). Therefore, the authors considered this method to be a helpful supplement to SGS.

However, clear limitations have been raised evaluating the SG function using PSMA PET/CT. As previously published, the range of the SUVmax of the SGs appear very wide leading to a high intra- and inter-individual variability (Klein Nulent et al. 2018). SUVmax for the parotid glands of 12.3 (range 5.2-22.9) and 11.7 (range 6.0–22.2) for the submandibular glands have been published and show comparable variations to results of our study, e.g., SUVmax of 20.4 (range 8.8 – 37.2) for the parotid glands and 23.6 (range 9.6 – 48.7) for the submandibular glands in the follow-up PET/CT of group I. Furthermore, PSMA PET/CT cannot be used to assess the excretion function of the SGs and is potentially altered by effects like the tumor sink effect in patients with high tumor burden of PSMA-expressing metastatic prostate cancer (Filss et al. 2018) (section 5.1.4.2).

On the other hand, there are some clear advantages of PSMA PET/CT for evaluation of the SG function in prostate cancer patients. With imaging studies generated automatically during oncologic follow-up, no additional procedure is needed and no special preparation of the patient is required, like e.g. fasting, no tooth brushing etc. Also, when compared to SGS, PET/CT provides functional, 3-dimensional metabolic and morphologic images with high resolution and there is no known interference of thyroid uptake or potential effects of hyper- and hypothyroidism to the tracer uptake as described for Tc-99m-pertechnetate (Hustinx und Muylle 2018).

5.1.4 Possible influencing co-factors

5.1.4.1 Age

Both in patient group I and II no influence of age to the subjectively and objectively assessed salivary gland function could be found. This goes in line with the above mentioned studies on efficacy and toxicity of Lu-177 PSMA in mCRPC patients that did not show any correlation of the occurrence of early and late mouth dryness after PRLT to the age of the patients (Hofman et al. 2018, Rahbar et al. 2017, Baum et al. 2016, Ahmadzadehfar et al. 2016, Heck et al. 2019).

In general, epidemiologic studies have shown an increases in the prevalence and incidence of xerostomia with age (Han et al. 2015, Villa et al. 2015), however, several publications did not consider age as the cause or a major risk factor for mouth dryness (Liu et al. 2012). This could be partially explained by the reserve capacity of the SG that might compensate for the loss of 30 % or more acinar tissue due to involution and fibrosis occurring during the aging process (Scott et al. 1987). In contrast, stimulated saliva flow rates were found to be significantly decreased in patients > 70 years - unrelated to any potential xerogenic medication (Smith et al. 2013).

The important overlay of polypharmacy to aging has to be taken into account since the prevalence of mouth dryness among patients aged 20–80 years was stated with 17% in patients without medication, 33.5% in patients taking 3 medications and 67% with the use of more than or equal to 7 medications (Nederfors et al. 1997).

In our study, patients have been investigated both for short and long-term xerostomia with a median age of 68 years up to 90 years. Therefore, a relevant proportion of patients has to be considered as a risk group for reduced salivation. However, this did not translate to any of the findings, as mentioned above. The only influence of the patients age was exhibited by an unexpected significant correlation of age to the Umax on SGS showing a higher maximum tracer uptake both at baseline and follow-up in older patients, while there was no effect on the EF or the PSMA-PET/CT based parameters detectable. This could be possibly explained by clinically inapparent reduced saliva flow rates, as mentioned above, causing a higher transient tracer accumulation in the SGs. However, to the best of our knowledge, these findings have not been described before and suggest further investigation in a higher patient number.

5.1.4.2 Tumor burden

A highly significant negative correlation of the SUVmax of all SGs to the tumor burden both pre- and post-therapeutically could be demonstrated ($r = -0.492$, $p < 0.001$). The most likely explanation for this result is a known phenomenon of radiopharmaceuticals, called “tumor sink effect”, and has been already described for other radiotracers (Beauregard et al. 2012). It was first observed in bone scintigraphy in the late 1980s (Podoloff und Kim 1989).

Also for PSMA targeting radioligands a high PSMA-expressing tumor load significantly reduces the off-target tracer uptake to e.g., the kidneys and the salivary glands (Filss et al. 2018, Begum et al. 2018). In our study no other influence of the tumor burden on the analyzed subjective and objective parameters of salivary gland dysfunction were observed.

5.1.4.3 Previous therapies/preconditions

To rule out possible disproportions in the investigated groups and overlays by known preconditions causing salivary gland dysfunction, patients were excluded for analysis having received external radiotherapy to the head and neck region or radioiodine therapy prior to PRLT. Also, patients with a history of chronic diseases affecting the baseline salivary gland function (e.g. Sjogren's syndrome, mumps) had been excluded as stated in section 3.1.1. Therefore, on the other hand, a limited evidence is generated by our data regarding possible influencing preconditions on short and long-term salivary gland toxicity of Lu-177 PSMA.

At first sight, previous taxane-based chemotherapy before PRLT appeared to have a significant effect on the SUVmax of all salivary glands both before and after PRLT. However, a careful investigation regarding the tumor burden of both chemotherapy-naïve and chemotherapy-resistant patients revealed a highly uneven distribution of patients with a higher tumor load in the chemotherapy-resistant subgroup. As mentioned above, this affect might be strongly overlaid by the tumor burden and its resulting tumor sink effect (section 5.1.4.2).

There was no influence of chemotherapy on the SGS parameter or the subjective parameter of hyposalivation detectable. Therefore, the risk of developing SG dysfunction after Lu-177 PSMA might not be altered by a previous taxane-based chemotherapy. In a study comparing efficacy and toxicity of PRLT in mCRPC patients a longer PFS and OS was found in chemotherapy-naïve patients (Barber et al. 2019). However, the authors stated minimal toxicity rates in both chemotherapy-naïve and chemotherapy-resistant subgroups without mentioning a difference regarding the occurrence of xerostomia.

In both patient group I and II no influence on the subjective and objective SG toxicity rates were observed for e.g., pre-existing diabetes mellitus or a s.p. systemic treatment like first or second generation anti-hormonal therapies.

5.1.4.4 Administered cumulative radioactivity /dose

The cumulatively administered radioactivity of Lu-177 PSMA did not show any influence on the investigated subjective and objective parameter of salivary gland toxicity both in short and long-term follow. However, a tendency of a stronger decrease of the MV of all salivary glands after PRLT with a high cumulative activity could be observed without reaching statistical significance. Given the limited patient number that had received high activities of up to 61.8 GBq those effects might become significant in a larger amount of patients.

Only few data have been published of patients receiving a high number of cumulative activity or therapy cycles. The only prospective data of Lu-177 PSMA in mCRPC patients so

far is based on a mean cumulative activity of 24.7 GBq in up to 4 cycles (Violet et al. 2020). In a case series of patients receiving re-introduction of Lu-177 PSMA RLT after initial response ("rechallenge") only a mild xerostomia grade 1 in 2/8 patients has been observed (Gafita et al. 2019). Rathke et al. discussed applying higher activities per treatment cycle of up to 9.3 GBq (Rathke et al. 2018). However, a higher rate of xerostomia was not explicitly mentioned. Also shortening the treatment intervals to a 4-week protocol did not seem to increase the rate of reported mouth dryness (Rasul et al. 2020).

Instead of correlating toxicity observations to applied treatment activities a more profound and causal approach would be to investigate mean absorbed organ doses by conducting dosimetry studies. Due to a relatively high logistical effort this could not be performed within this study and might be subject to future endeavors. In addition, until today there have been limited research on the exact radiobiological effect of beta-emitters like Lu-177 to the salivary glands tissue. Also, dosimetry data and profound correlations to salivary gland toxicity with strong evidence are lacking.

The median absorbed dose averaged to all salivary glands were published with about 0.5 - 1.4 Gy/GBq (Kratochwil et al. 2016b, Baum et al. 2016, Okamoto et al. 2017, Violet et al. 2019). Based on these findings by administering 6.0 GBq an estimated mean absorbed dose of 3.0 – 8.4 Gy per cycle Lu-177 PSMA would be delivered to the salivary glands, with 7.5 GBq applied Lu-177 PSMA the dose could increase to 3.8 – 10.5 Gy/cycle.

Still, there is a controversial discussion regarding the threshold of the maximum tolerable dose without irreversible damage to the salivary glands in patients receiving external radiotherapy to the head and neck region. A mean dose of 26 Gy was proposed until the normal function of the parotid glands can be restored (Eisbruch et al. 1999). Another study of HNC patients receiving RT suggested a maximum tolerable dose of 45 Gy for the parotid glands, and 30 Gy being the threshold for a possible total recovery within 2 years after therapy (Li et al. 2007).

As a consequence, Scarpa et al. estimated a maximum tolerable administered activity of Lu-177 PSMA of 60 GBq assuming a mean dose of 0.5 Gy/GBq for the salivary glands (Scarpa et al. 2017). However, with regards to the very limited radiobiological comparability of external irradiation and endoradiotherapies using beta-emitters, such estimates must be undertaken with caution. Future dosimetry studies of Lu-177 PSMA RLT like a currently enrolling, multi-center, prospective sub-study of the ongoing VISION trial in Germany will help to create stronger evidence to answer some of the mentioned uncertainties (Kurth et al. 2020).

5.2 Ac-225 PSMA: TANDEM concept vs. Ac-225-PSMA only

In 18 mCRPC patients the effects of a same-day co-administration of Ac-225 and Lu-177 PSMA on both subjective and objective SG function parameters were investigated after one cycle of this so called Tandem-PRLT concept (Kulkarni et al. 2019). The use of alpha-emitters like Ac-225 as part of a targeted oncological endoradiotherapy has been already described in 1993 (Geerlings et al. 1993) and since then has been studied for the treatment of leukemia (Jurcic et al. 2002, Rosenblat et al. 2010), lymphoma (Zalutsky und Pozzi 2004), malignant melanoma (Allen et al. 2005), brain tumors (Kneifel et al. 2006), neuroendocrine tumors (Kratochwil et al. 2015a), and bladder cancer (Autenrieth et al. 2018).

20 years later, the radiopharmaceutical Ac-225 PSMA-617 was synthesized for the first time at the Joint Research Centre (JRC) in Karlsruhe, Germany. Until today, only a few centers worldwide are using Ac-225 PSMA - possibly due to the limited supply and certain radiopharmaceutical laboratory requirements (Morgenstern et al. 2020). First clinical breakthrough achievements were presented by the Heidelberg group in series of publication on the use of Ac-225 PSMA in mCRPC patients demonstrating outstanding response rates, even after failing to Lu-177 PSMA (Kratochwil et al. 2016a, Kratochwil et al. 2018).

The drawback of this novel tracer soon became apparent when 4 out of the initial 40 patients discontinued treatment because of intolerable xerostomia or loss of taste, despite promising initial PSA responses. Another 15 patients with a partial remission but PSMA-positive residual lesions on follow-up imaging refused further treatment because of severe xerostomia. Another early single-center experience of Ac-225 PSMA published by the Munich group also showed drastic rates of severe mouth dryness that had led to treatment discontinuation in about one third of the patients (Feuerecker et al. 2019).

Sathekge et al. therefore introduced a de-escalation protocol with declining treatment activities of Ac-225 PSMA. In a group of 17 chemotherapy-naïve patients with advanced, metastatic PC a non-detectable PSA was found in 41% of the cases at 12 month-follow-up. Although xerostomia grade 1-2 was found in all patients, no grade 3 and no treatment discontinuation due to mouth dryness was reported (Sathekge et al. 2019a). A follow-up publication of overall 73 mCRPC patients with a share of 37 % chemotherapy-resistant patients showed a comparable toxicity profile in terms of subjective salivary gland toxicity after this dose de-escalation concept. Xerostomia grade I-II was reported in 85% of the patients while no patient showed grade III (Sathekge et al. 2019b).

12 of 18 patients (66.7 %) in our study showed a grade I-II mouth dryness already after on cycle of Tandem-PRLT which was also reflected in a significant increase in the sXI score.

While after Lu-177 PSMA a sXI score of 7 and 9.2 was observed in short (group I) and long-term follow-up (group II), respectively, Tandem-PRLT led to a mean sXI score of 14.0. On the other hand, one third of the patients have not noticed any mouth dryness and no grade III xerostomia or therapy discontinuation occurred.

However, the clearly limited comparability of the above mentioned studies must be underlined in this context. Data from Heidelberg, Munich and Pretoria refer to more than one therapy cycle and differ substantially in the therapy activity applied. Kratochwil et al. investigated different dose regimes regarding treatment efficacy and toxicity rates and considered 100 kBq/kg body weight of Ac-225-PSMA per cycle the best compromise (Kratochwil et al. 2017). With a median applied radioactivity of 8MBq (range 4.4–12.8) Ac-225 PSMA the numbers by the Munich group appear to be based on the same regime (Tauber et al. 2019). Patients in the South Africa group were treated with a mentioned declining protocol of 8, 7, 6 and 4 MBq. Based on the concept of the Tandem approach, patients in our study also received comparably low treatment activities of 4 MBq (range 2 - 7) Ac-225 PSMA by intention. Also a high variability in terms of pre-treatments prior to Ac-225 PSMA (e.g., chemotherapy, Lu-177 PSMA monotherapy) between the study cohorts has to be taken into account.

Another recently published study investigated the concept of co-administering lower alpha-emitting radioactivities with a mean applied activity of 5.3 MBq Ac-225 PSMA in combination with commonly administered activities of Lu-177-PSMA (mean 6.9 GBq) in 20 mCRPC patients (Khreish et al. 2020). In case of response to one cycle of this Tandem-PRLT a maintenance therapy was continued with Lu-177 PSMA monotherapy. Comparable to results of our study less severe salivary gland toxicity rates were observed, reporting 8/20 patients with grade 1 and 5/20 patients with grade 2 xerostomia. No grade 3 mouth dryness and no treatment discontinuation has been observed.

Rathke et al. applied salivary gland scintigraphy in 11 patients of the Heidelberg cohort after up to 4 cycles of Ac-225-PSMA and reported a distinct decline of both the maximum tracer uptake and the excretory function of the parotid and submandibular glands (Rathke et al. 2019). In contrast to that findings, there was no change of the Umax observable after Tandem PRLT in our study. However, the excretion fraction of all salivary glands dropped significantly as well by 37.7 % for the parotid glands and 25.0 % for the submandibular glands.

This seems in line with findings by the Heidelberg group that observed a higher tolerance to radiation of the submandibular glands showing a residual excretory function even

after several cycles of Ac-225 PSMA - in opposite to the parotid glands (Rathke et al. 2019). One possible reason for the early mouth dryness after Ac-225 PSMA RLT might be the occurrence of severe duct stenosis or obstruction, as it has been described before in patients after radioiodine therapy and external radiotherapy to the head and neck (Cung et al. 2017, Roesink et al. 2004). The authors stated that the initial impairment of the parotid glands might be based on the gland excretion dysfunction and long-term hyposalivation might be a result of damage to the SG parenchyma. This might explain why patients showed response to sialendoscopic duct dilatation and saline irrigation (Rathke et al. 2019).

While the SUVmax of the SGs declined only slightly in our study after Tandem-PRLT, the metabolic volume showed a significant decrease of 12.8 % in the parotid glands and 6.6 % in the submandibular glands. These slight but significant findings support the tendency of a higher radiation sensitivity of the parotid glands compared to the submandibular glands.

Overall, the objective parameters of salivary gland dysfunction investigated in our study suggest a combination of both PET/CT and SGS parameters for an early SG toxicity assessment. While radiopharmaceutical uptake values (SUVmax on PET/CT and Umax on SGS) did not correlate with patient-reported hyposalivation, changes of the MV (PET/CT) and the EF (SGS) on the other hand appeared to be sensitive indicators for early salivary gland toxicity of Tandem-PRLT and therefore could be a useful diagnostic instrument for future investigations.

5.3 Limitations of this study

This study has certain limitations, particularly associated with the retrospective and single-center design of the analysis. The statistical power of the study is limited by the number of patients, especially in the context of subgroup analysis conducted for group I and II and the analysis for group III. However, results might serve as encouragement for further prospective, multi-institutional studies to evaluate the presented findings on a larger scale.

Methodological drawbacks of the patient-reported xerostomia are the uncertainty of the best time point to interview patients for their complaints. Many studies mentioned above stated the dynamic, transient character of dry mouth complaints during and after PRLT. During follow-up patients in our study were asked to retrospectively asses their mouth dryness within the last 4 weeks. As discussed above, the very question of dry mouth itself might already increase the prevalence, becoming a kind of “nocebo” because of its very subjective perception (section 5.1.1).

Limitations of salivary gland scintigraphy are the vulnerability of the results to inadequate patient compliance, such as e.g., the lack of fasting before the SGS or movement of head during image acquisition. Besides, occult conditions of the salivary glands, like e.g., s.p. epidemic parotitis (mumps) during childhood or asymptomatic duct obstruction due to chronic inflammation or sialolithiasis might have significantly influenced the outcome. The interference of the thyroid uptake and potential effects of hyper- and hypothyroidism to the Tc-99m-pertechnetate uptake of the SG must be considered, because no laboratory values for serum thyroid-stimulating hormone (TSH) were routinely available for most of the patients included to this investigation. Also, a different nutritional iodine supply is known to alter the quantitative analysis of the SGS.

Both the investigated PET/CT and SGS parameter might have been adversely affected by an asymptomatic atrophy of the SGs or a s.p. resection of a SG not being specified in the medical history of the patient. The PSMA-ligand uptake of the SGs showed a high intra-patient variability, whose cause, however, has not been understood yet. One known influence is the tumor burden, which can lead to a so-called tumor sink effect. A changing tumor load due therapy response therefore might have an influence on the salivary gland uptake. In summary, quantitative measurements such as SUVmax might rather be used carefully for inter-individual comparison.

5.4 Outlook/ perspectives

Some of the limitations of our study mentioned above might be soon answered by an ongoing international, prospective, phase-3-trial (VISION trial) aiming for approval of Lu-177 PSMA-617 and from which first results are expected to be published later in 2020 (Endocyte 2018).

With regard to possible preventive or curative strategies of salivary gland toxicity after PSMA-targeting radioligand therapies only a few proposals have been published and discussed so far and are addressed by the following publications enclosed below that should complement this work:

- Langbein T, Chausse G, Baum RP. 2018. Salivary Gland Toxicity of PSMA Radioligand Therapy: Relevance and Preventive Strategies. J Nucl Med, 59 (8):1172-1173.

- Baum RP*, Langbein T*, Singh A, et al. 2018. Injection of Botulinum Toxin for Preventing Salivary Gland Toxicity after PSMA Radioligand Therapy: an Empirical Proof of a Promising Concept. Nucl Med Mol Imaging, 52 (1):80-81. *(*contributed equally to this work)*

HOT TOPICS

Salivary Gland Toxicity of PSMA Radioligand Therapy: Relevance and Preventive Strategies

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Since the first clinical use of ^{131}I-labeled prostate-specific membrane antigen (PSMA) (*1*), xerostomia has been identified as a relevant side effect of PSMA radioligand therapies (PRLTs) for metastatic castration-resistant prostate cancer. Given the remarkable progress when using ^{177}Lu-labeled compounds and the impressive results of ^{225}Ac-PSMA PRLT (*2*), we believe that effective preventive strategies for salivary gland (SG) toxicity need to be developed to preserve the extremely attractive side effect profile of PRLT (*3*) as compared with standard treatments. Although the highest off-target uptake is seen in the SG (*3*), multicenter data on ^{177}Lu-PSMA PRLT revealed only mild to moderate reversible xerostomia in 8% of patients (*4*). In a systematic analysis, our group confirmed these findings (*5*).

The largest available data on ^{225}Ac-PSMA were published by Kratochwil et al. (*2*). In the Heidelberg cohort, severe xerostomia occurred frequently and became the dose-limiting toxicity. Among the 40 patients, treatment had to be discontinued in 4 patients despite an initial response. Our group's first clinical results in 6 patients treated with ^{225}Ac-PSMA were in line with those findings. After a first treatment cycle, 1 of 3 patients with sufficient follow-up data had experienced (tolerable) mouth dryness, whereas another patient treated with 5 MBq of ^{225}Ac-PSMA (83 kBq/kg of body weight) had subsequent markedly decreased uptake in all SGs (Fig. 1).

With respect to the potential survival benefit of PSMA-directed radionuclide therapies, we believe that severe reduction in quality of life will gain more significance in the future. Recently, Taïeb et al. focused on SG toxicity from PRLT and discussed several approaches (*6*), including a reference to xerostomia after external-beam radiotherapy of patients with head and neck cancer. Although the exact molecular principles of tracer accumulation, in particular the ratio of nonspecific over specific uptake in SGs, are still insufficiently understood, PRLT, unlike external-beam radiotherapy, offers potential routes to prevent radiation exposure to SG tissue by avoiding or reducing radionuclide uptake. In multicycle therapy, declining tumor volume—and thus target PSMA binding—increases off-target uptake (*7*), greatly burdening the dose-limiting SGs. Reduction of administered activity to limit xerostomia hence comes at the expense of tumor dose, especially in responding patients.

Alternatively, labeling of PSMA-targeting antibodies such as J591 instead of small molecules such as PSMA-617 might be able to lower the sialotoxicity of ^{225}Ac-PSMA PRLT because there is no significant SG uptake on ^{89}Zr-J591 or ^{177}Lu-J591 imaging (*8,9*). This effect unfortunately comes at the cost of increased myelotoxicity due to longer blood circulation. The difference in molecular weight between PSMA-targeting antibodies and small molecules (~150 vs. 1.4 kD) could explain some of the variation in SG uptake. Along these lines, the ionic charge of PSMA radioligands might also play a role in SG distribution, though changing molecular electronegativity risks an impact on tumor affinity.

External cooling of the SGs using icepacks was initially expected to reduce PSMA radioligand uptake due to vasoconstriction but failed to prove helpful in a systemic analysis (*10*). Considering the intense blood supply of organs near the head, insufficiency might be explained by a reflex hyperperfusion.

Preclinical animal data on potential radioprotective substances injected into the SGs, such as botulinum toxin A, short-acting anticholinergic agents, and local anesthetics, appear promising (*11*). Other radioprotectors have also been tested, such as histamine, vitamin E, statins, and amifostine, exploiting mechanisms of radiation resistance. In humans, Teymoortash et al. investigated the effect of botulinum toxin injections to the SGs with head and neck cancer undergoing external-beam radiotherapy (*12*). Earlier this year, our group translated that approach into tracer uptake blockade and achieved a 64% decrease in ^{68}Ga-PSMA uptake in an injected parotid gland, leading to the first proof-of-concept publication on the topic (*13*) and heralding a hypothesis of nonspecific tracer accumulation. Given the possibility of some specific binding of PSMA radioligands in the SGs, local application of cold compounds or inhibitors of PSMA such as 2-(phosphonomethyl) pentanedioic acid (*14*) are also being investigated. However, the potential inhibition of PSMA-targeted tumor caused by systemic absorption from intraparenchymal application of 2-(phosphonomethyl)pentanedioic acid (because of the relevant blood supply, especially of the parotid glands) warrants careful consideration.

Sialendoscopy data on thyroid cancer patients with radioiodine-induced sialadenitis suggest another outlook. Therapy-refractory xerostomia could be explained by duct stenosis and mucous plugs in 86% of occurrences; sialendoscopy intervention resulted in 89% of patients with partial or complete resolution of symptoms (*15*). Of note, time does matter, because better results were obtained for earlier endoscopic treatment than for intervention for chronic symptoms (*16*).

Another salvage approach might be regeneration of the SGs. In a clinical trial of head and neck cancer patients after radiotherapy, ultrasound-guided transplantation of adipose tissue–derived mesenchymal stem cells to the submandibular glands for treatment of radiation-induced xerostomia achieved an increase in salivary flow of 33% after 1 mo and 50% after 4 mo (*17*).

Received May 8, 2018; revision accepted Jun. 7, 2018.
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Published online Jun. 14, 2018.

DOI: 10.2967/jnumed.118.214379

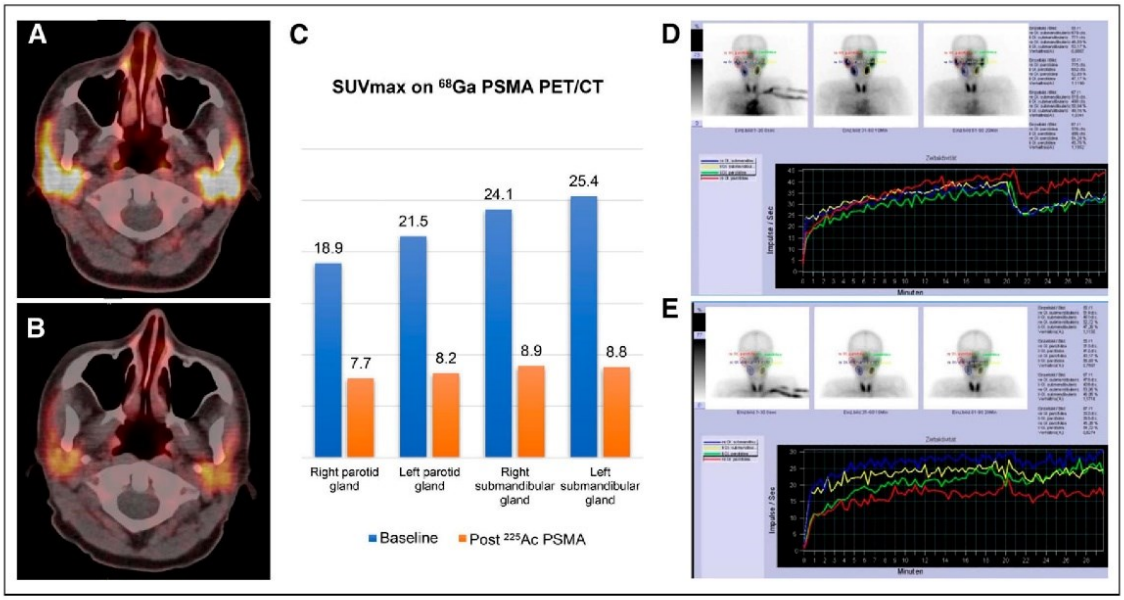

FIGURE 1. Physiologic tracer uptake is detected in SGs of 59-y-old metastatic castration-resistant prostate cancer patient on pretherapeutic ^{68}Ga PET/CT study (A), whereas PSMA uptake in SGs declines by up to 65% on follow-up imaging (B and C) after PRLT using ^{225}Ac. Dynamic SG scintigraphy demonstrates regular baseline function (D); however, posttherapeutic study reveals functional impairment despite absence of clinical symptoms of xerostomia (E).

The reasons why SGs take a bigger hit than most of the other exposed organs could lie in the biology of the glands themselves. A high propensity to trigger apoptosis and the myriad of secretory granules that potentiate formation of radiation-induced free radicals are promising hypotheses (*18*). Perhaps current radiopharmaceuticals hit the SG sweet spot of low-dose hyperradiosensitivity. Whether by optimized doses, compounds with better biodistribution, new radioprotectors, blockers of PSMA binding, better posttherapy management, or cellular transplantation, PRLT requires us to solve the SG enigma.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s13139-017-0508-3

INTERESTING IMAGE

ISSN (print) 1869-3482
ISSN (online) 1869-3474

Injection of Botulinum Toxin for Preventing Salivary Gland Toxicity after PSMA Radioligand Therapy: an Empirical Proof of a Promising Concept

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Received: 30 October 2017 / Revised: 7 December 2017 / Accepted: 11 December 2017

Abstract
The dose-limiting salivary gland toxicity of ^{225}Ac-labelled PSMA for treatment of metastatic, castration-resistant prostate cancer remains unresolved. Suppressing the metabolism of the gland by intraparenchymal injections of botulinum toxin appears to be a promising method to reduce off-target uptake. A ^{68}Ga-PSMA PET/CT scan performed 45 days after injection of 80 units of botulinum toxin A into the right parotid gland in a 63-year-old patient showed a decrease in the SUVmean in the right parotid gland of up to 64% as compared with baseline. This approach could be a significant breakthrough for radioprotection of the salivary glands during PSMA radioligand therapy.

Keywords Prostate cancer · PSMA radioligands · Salivary glands · Positron emission tomography · Botulinum toxin · Xerostomia

A 63-year-old patient with advanced metastatic castration-resistant prostate cancer underwent ^{68}Ga-PSMA PET/CT imaging before and 45 days after receiving multifocal, ultrasound-guided injections of a total of 80 units botulinum toxin A into the right parotid gland (Fig. 1) according to a clinically approved method used in patients who have suffered from sialorrhoea for over two decades [1–3]. The SUVmean of the radioligand in the injected parotid gland showed a highly significant decrease of up to 60% compared with the left side, especially in the pars profunda of the gland, and a decrease of up to 64%, but no significant change in the left parotid gland, compared with the baseline PET/CT study. At the time of this report, after a follow-up of 3 months, the patient had not reported any adverse effects of the injections. The impressive decrease in PSMA radioligand uptake in the salivary glands, which is described here for the first time, could be a significant breakthrough for salivary gland protection, which is highly needed in the context of targeted alpha therapy using ^{213}Bi-PSMA and ^{225}Ac-PSMA [4, 5].

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Published online: 11 January 2018

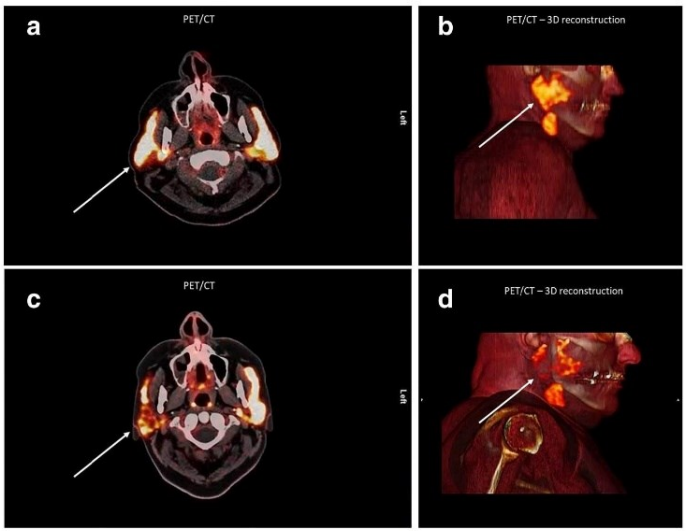

Fig. 1 Axial fused (**a**, **c**) and sagittal reconstructed 3D (**b**, **d**) ^{68}Ga-PSMA PET/CT images in a 63-year-old patient with advanced metastatic castration-resistant prostate cancer before (**a**, **b**) and 45 days after (**c**, **d**) multifocal, ultrasound-guided injections of a total of 80 units botulinum toxin A into the right parotid gland. The SUVmean of the radioligand in the injected parotid gland shows a highly significant decrease of up to 60% compared with the left side (**c**, **d** *white arrows*), especially in the pars profunda of the gland, and a decrease of up to 64%, but no significant change in the left parotid gland, compared with the baseline PET/CT study (**a**, **b**)

Acknowledgements We thank Dr. Anthony Chang, Rethink Imaging, USA, for providing 3D reconstructed PET/CT images. We are also grateful to Dr. Guillaume Chaussé, Nuclear Medicine, McGill University, Montreal, Quebec, Canada, for his remarks on pharmacological and cellular mechanisms in the salivary glands after injection of botulinum toxin.

Compliance with Ethical Standards

Conflict of Interest Richard P. Baum, Thomas Langbein, Aviral Singh, Mostafa Shahinfar, Christiane Schuchardt, Gerd Fabian Volk, Harshad Kulkarni declare that they have no conflict of interest.

Ethical Statement All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from the patient who was the subject of the study.

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6 Conclusion

Despite an overall low toxicity profile of PSMA-targeting radioligand therapies in mCRPC patients, dosimetry studies of this promising novel endoradiotherapy revealed the highest off-target dose to the lacrimal and salivary glands and, as a consequence, varying rates of xerostomia have been clinically observed. A validated questionnaire on mouth dryness and a feasible, easy-to-perform salivary gland scintigraphy and PSMA-PET/CT parameters may help to objectify, standardize and quantify clinical results. This might become crucial in order to compare outcomes of future research on this topic.

Consistent with published data our results indicate, that salivary gland toxicity after Lu-177 PSMA RLT appears to have minor clinical relevance and only a very mild to moderate mouth dryness occurs in a minority of patients both in short and long-term follow up. The prevalence of xerostomia was significantly lower than e.g. after external irradiation, radioiodine therapy and especially after PRLT with Ac-225 PSMA.

Both after Lu-177 PSMA and Tandem PRLT a significant decrease of the metabolic volume of the salivary glands on PSMA PET/CT could be observed, which might be a surrogate of the impairment. Influence of increasing cumulative activities of Lu-177 PSMA on this observation could be shown and should be further investigated in prospective studies. However, even after high cumulative activities above 60 GBq Lu-177-PSMA no severe salivary gland dysfunction could be detected both subjectively and objectively.

By far the most critical factor influencing salivary gland toxicity of PSMA-targeting RLT therefore is the selection of the radionuclide itself. Even after a combination of Ac-225 and Lu-177 PSMA (Tandem concept) with significantly lower applied activity of Ac-225 than in data published for Ac-225 PSMA monotherapies, significantly higher rates of xerostomia can be observed than after Lu-177 PSMA alone. These results also correlate with objective findings investigated by salivary gland scintigraphy and PSMA-PET/CT.

Other factors analyzed, such as patient age or previous therapies, did not show any influence on the degree of the salivary gland dysfunction. Nevertheless, tumor burden does have an impact on the biodistribution of radioligands and should be considered when planning therapy protocols. A de-escalation of the applied radioactivity in consecutive treatment cycles might be currently the most effective concept to minimize xerostomia after Ac-225 PSMA.

Both a profound comprehension of the exact uptake mechanisms of PSMA radioligands to the salivary glands as well as effective preventive strategies based on these findings are still urgently needed. This plays a particular role since ambitions of applying this type of therapy in earlier stages of prostate cancer have been mentioned.

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8 Supplements

8.1 Questionnaire: shortened Xerostomia Inventory (sXI) – English/German version

xerostomia questionaire

date: *patient:*

The following statements refer to your experiences of mouth dryness during the last 4 weeks. For each statement, please circle the response which applies to you.

My mouth feels dry	□ NEVER	□ HARDLY EVER	□ OCCASION-ALLY	□ FREQUENTLY	□ ALWAYS
I have difficulty in eating dry foods	□ NEVER	□ HARDLY EVER	□ OCCASION-ALLY	□ FREQUENTLY	□ ALWAYS
My mouth feels dry when eating a meal	□ NEVER	□ HARDLY EVER	□ OCCASION-ALLY	□ FREQUENTLY	□ ALWAYS
I have difficulties swallowing certain foods	□ NEVER	□ HARDLY EVER	□ OCCASION-ALLY	□ FREQUENTLY	□ ALWAYS
My lips feel dry	□ NEVER	□ HARDLY EVER	□ OCCASION-ALLY	□ FREQUENTLY	□ ALWAYS

How often does your mouth feel dry? (circle the appropriate response)

□ NEVER □ OCCASIONALLY □ FREQUENTLY □ ALWAYS

Fragebogen Mundtrockenheit

Datum: *Patient:*

Die folgenden Aussagen beziehen sich auf Ihre Erfahrungen hinsichtlich Mundtrockenheit in den vergangen 4 Wochen. Bitte markieren Sie für jede Aussage die Antwortmöglichkeit, welche am ehesten auf Sie zutrifft.

Mein Mund fühlt sich trocken an	□ NIE	□ KAUM	□ GELEGENTLICH	□ HÄUFIG	□ JEDERZEIT
Ich habe Schwierigkeiten, trockene Nahrung zu essen	□ NIE	□ KAUM	□ GELEGENTLICH	□ HÄUFIG	□ JEDERZEIT
Mein Mund fühlt sich trocken an, wenn ich esse	□ NIE	□ KAUM	□ GELEGENTLICH	□ HÄUFIG	□ JEDERZEIT
Ich habe Schwierigkeiten, bestimmte Speisen zu schlucken	□ NIE	□ KAUM	□ GELEGENTLICH	□ HÄUFIG	□ JEDERZEIT
Meine Lippen fühlen sich trocken an	□ NIE	□ KAUM	□ GELEGENTLICH	□ HÄUFIG	□ JEDERZEIT

Wie oft fühlt sich Ihr Mund trocken an? (Bitte markieren Sie die passendste Antwortmöglichkeit)

□ NIE □ GELEGENTLICH □ HÄUFIG □ JEDERZEIT

8.2 Patient information /Declaration of consent - PRLT with Lu-177 PSMA (ZBB)

Patientenetikett

Patienteninformation / Einverständniserklärung

Radio-Therapie mit Lutetium-177 markierten PSMA-Liganden

Die Radio-Liganden-Therapie (RLT) dient zur nuklearmedizinischen Behandlung von PSMA-positiven malignen Tumoren. Hierzu wird ein mit dem radioaktiven Betastrahler Lutetium-177 markiertes Molekül verwendet.

Das mit dem **Betastrahler markierte Molekül** wird unter Kreislaufüberwachung als Infusion in eine Vene appliziert und reichert sich schnell in den vorher durch eine Ga-68-PSMA-PET/CT nachgewiesenen Tumoren bzw. Metastasen an. Dadurch werden diese Tumoren / Metastasen lokal bestrahlt und in ihrem Wachstum gebremst oder sie bilden sich zurück. Der Therapie-Effekt hängt von der Intensität der Speicherung ab.

Da die **Therapiesubstanz nicht allgemein zugelassen** ist (d.h. es handelt sich nicht um ein Handelspräparat eines Pharmakonzerns, sondern die Therapiesubstanz wird individuell für jeden einzelnen Patienten in der Radiopharmazie der Zentralklinik Bad Beka unter GMP-Bedingungen hergestellt), liegt ein sogen. Heilversuch vor. Der Heilversuch dient primär der Heilung, Erkennung, Verhütung oder Linderung einer Krankheit oder eines Leidens bei einem Patienten, allerdings mit nicht voll erprobten Mitteln. Der Heilversuch stellt einen Sonderfall der **Heilbehandlung** dar, wenn noch nicht voll erprobte Methoden oder Mittel mangels anderer erfolgversprechender Mittel vom Arzt mit dem konkreten **Ziel einer individuellen Heilmaßnahme** angewendet werden. Durch diesen auf den Patienten gerichteten Zweck unterscheidet sich der Heilversuch vom wissenschaftlichen Experiment. Dieser Anwendungsfall unterliegt daher nicht der Genehmigungspflicht nach § 23 StrlSchV.

Die Therapie kann **nicht angewendet** werden bei

- hochgradiger Niereninsuffizienz oder Knochenmarkdepression/Blutbildveränderungen

Folgende **Nebenwirkungen** können durch die Therapie verursacht werden:

- Die Zahl der Blutkörperchen (Erythrozyten), der Blutplättchen (Thrombozyten) und der weißen Blutkörperchen (Leukozyten) kann abnehmen. Deshalb muss Ihr Blutbild nach der Therapie 2-wöchentlich bis monatlich kontrolliert werden.
- Bei mehrmaliger Therapie kann es zu einer Einschränkung der Nierenfunktion kommen, diese wird sorgfältig überwacht.
- Akut können direkt nach der Therapie Übelkeit und Erbrechen auftreten.
- Aufgrund einer Anreicherung in den Tränen – und Speicheldrüsen kann es zu einer radiogenen Sialadenitis (Mundtrockenheit) kommen.
- Es können allergische Reaktionen unter der Verabreichung auftreten (extrem selten – bisher nicht beobachtet).
- Paravenöse Injektionen können zu lokalen Entzündungen im Arm führen (sehr selten).
- Langzeitwirkungen oder schädliche Langzeiteffekte sind selten (bisher keine bekannt).

Vor der Verabreichung der Therapiesubstanz erfolgt eine Infusion zur Hydrierung und zum Nierenschutz. Diese Infusion wird nach der Therapie noch über einige Stunden fortgeführt.

1. Liegt bei Ihnen eine **Nierenfunktionsstörung** vor? ☐ ja ☐ nein

2. Liegt bei Ihnen eine **Beeinträchtigung des Blutbildes** vor? ☐ ja ☐ nein

3. Kommt es bei Ihnen zu **unwillkürlichem Harnabgang** oder **Harnverhalt**? ☐ja ☐ nein

4. Erfolgte innerhalb der vergangenen 6 Wochen eine **Chemotherapie**? ☐ ja ☐nein

5. Erfolgte innerhalb der vergangenen 6 Wochen eine **Strahlentherapie**? ☐ ja ☐nein

Am Therapietag müssen mehrere Liter Flüssigkeit getrunken werden, um die Belastung der Niere so gering wie möglich zu halten (beschleunigte Ausscheidung).

In einem Aufklärungsgespräch wurde ich über die Radio-Liganden-Therapie ***ausführlich informiert,*** *auch darüber, dass es sich um einen sogenannten Heilversuch handelt und keine Gewähr für den gewünschten Erfolg der Therapie übernommen werden kann.*

Mein Einverständnis bezieht sich auch auf eventuell während der Behandlung notwendig werdende Folgemaßnahmen sowie auf die Erfassung meiner Daten in einer Datenbank und die damit verbundene (anonymisierte) wissenschaftliche Auswertung der Daten.

Die Notwendigkeit von Kontrolluntersuchungen auch zur Dokumentation des Therapieerfolges wurde mir erläutert.

Ich hatte Gelegenheit und ausreichend Zeit, alle mir wichtigen Fragen über die Art und Notwendigkeit der Behandlung und die mit der Therapie verbundenen Risiken und Nebenwirkungen zu stellen. Ich wurde über evtl. notwendige Folgemaßnahmen und Behandlungsalternativen umfassend unterrichtet und habe hierzu keine weiteren Fragen.

Ich wurde darüber informiert, dass ich während des stationären Aufenthaltes keinen Besuch auf der Therapiestation D3 empfangen und für 48 Stunden die Station nicht verlassen darf.

Ich habe das Informationsblatt zum Verhalten auf der Isotopen-Therapie-Station gelesen und verstanden, und möchte, dass die Behandlung bei mir durchgeführt wird.

Bad Berka, den

Unterschrift des Patienten/
der Patientin _____

8.3 List of Tables

8.4 List of Figures

8.5 Acknowledgments

First and foremost, I would like to thank my mentor, Prof. Dr. med. Richard P. Baum, for his scientific and methodical support, the possibility to write this dissertation in his department and for paving the way for my future career.

Furthermore, I would like to express my gratitude to my doctoral supervisor, PD Dr. med. Gerd Fabian Volk for all the help, patience and trust he placed in me during the preparation of this thesis.

I will be always grateful to my friends and colleagues, Dr. Harshad Kulkarni and Dr. Aviral Singh, from whom I learned a lot of essentials both for work and life as a doctor. Many thanks also to all my other former colleagues at the Zentralklinik, Bad Berka for their continuous help.

My special thanks go to my family and friends, in particular my parents and my brother, for their love and limitless support during my medical training and on the way to this thesis.

Especially, I want to thank my wife Cigdem and my grandmother for their tireless support and love. Without them, I would never have been able to walk this path.
I dedicate this work to them.

8.6 Curriculum vitae

Persönliche Daten	Thomas Langbein geboren am 2. September 1986 in Mühlhausen
Schulausbildung	
1993 bis 1997	Grundschule: Puschkinschule Erfurt
1997 bis 2005	Gymnasium: Königin-Luise-Gymnasium Erfurt
Zivildienst	
08/2005 – 04/2006	Klinik für Innere Medizin, Abteilung Hämatologie und internistische Onkologie, Helios Klinikum Erfurt
Studium	
10/2006 – 09/2013	Studium der Humanmedizin an der Universität Leipzig
Famulaturen	
03/2009 Innere Medizin	- Klinik für Kardiologie und internistische Intensivmedizin, Helios Klinikum Erfurt
09/2009 Neurochirurgie	- Klinik und Poliklinik für Neurochirurgie, Universitätsklinikum Leipzig
03/2010 Chirurgie	- Zentrale Notaufnahme, Universitätsklinikum Leipzig
08/2010 Anästhesie	- Klinik für Anästhesie und Intensivmedizin, Hufeland Klinikum Bad Langensalza
10/2010 HNO	- Klinik und Poliklinik für Hals-, Nasen-, Ohrenheilkunde Universitätsklinikum Leipzig
Praktisches Jahr	
02/2012 – 01/2013	
Innere Medizin	- Klinik für Kardiologie und Geriatrie, Evangelisches Diakonissenkrankenhaus Leipzig
Chirurgie	- Klinik für Chirurgie, Evangelisches Diakonissenkrankenhaus Leipzig
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Hals-, Nasen-, Ohrenheilkunde	- Klinik und Poliklinik für Hals-, Nasen-, Ohrenheilkunde, Universitätsklinikum Leipzig
Berufliche Tätigkeit	
03/2014 – 10/2014	- Arzt in Weiterbildung in der Klinik für Hals-, Nasen- und Ohrenheilkunde, Plastische Operationen, Helios Klinikum Erfurt
11/2014 – 06/2016	- Spendearzt im Haema Blutspendezentrum Erfurt Haema AG, Leipzig
07/2016 – 12/2018	- Arzt in Weiterbildung für Nuklearmedizin Klinik für Molekulare Radiotherapie, Zentralklinik Bad Berka
seit 02/2019	- Assistenzarzt Nuklearmedizinische Klinik und Poliklinik; Klinikum rechts der Isar, TU München

Jena, 31.08.2021 Thomas Langbein

8.7 Ehrenwörtliche Erklärung

Hiermit erkläre ich,

- dass mir die Promotionsordnung der Medizinischen Fakultät der Friedrich-Schiller-Universität bekannt ist,
- dass ich die Dissertation selbst angefertigt habe und alle von mir benutzten Hilfsmittel, persönlichen Mitteilungen und Quellen in meiner Arbeit angegeben sind,
- dass mich folgende Personen bei der Auswahl und Auswertung des Materials sowie bei der Herstellung des Manuskripts unterstützt haben:
  PD Dr. med. habil. Gerd Fabian Volk
  Prof. Dr. med. Richard P. Baum
- dass die Hilfe eines Promotionsberaters nicht in Anspruch genommen wurde und dass Dritte weder unmittelbar noch mittelbar geldwerte Leistungen von mir für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen,
- dass ich die Dissertation noch nicht als Prüfungsarbeit für eine staatliche oder andere wissenschaftliche Prüfung eingereicht habe und
- dass ich die gleiche, eine in wesentlichen Teilen ähnliche oder eine andere Abhandlung nicht bei einer anderen Hochschule als Dissertation eingereicht habe.

Jena, 11.09.2021

_____

(Vorname Name)