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Treatment with a ^{177}Lutetium-radiolabeled ligand targeting prostate-specific membrane antigen in metastatic castration-resistant prostate cancer: toxicity, efficacy and survival.

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1 List of abbreviations

ADT	-	Androgen deprivation therapy
AP	-	Alkaline phosphatase
BPI	-	Bone-PET-Index
BPI_{VOL}	-	Bone tumor volume
CI	-	Confidence interval
cPFS	-	Clinical progression free survival
CTCAE	-	Common terminology criteria for adverse events
DCE	-	Dynamic contrast enhancement
DRE	-	Digital rectal examination
DWI	-	Diffusion-weighted imaging
EBRT	-	External-Beam Radiation Therapy
ECOG.	-	Eastern Cooperative Oncology Group
HB	-	Hemoglobin
IMRT	-	Intensity-modulated radiation therapy
LDH	-	Lactate dehydrogenase
LHRH	-	Luteinising-hormone-releasing-hormone
mCRPC	-	Metastasized castration-resistant prostate cancer
mpMRI	-	Multiparametric Magnetic Resonance Imaging
OS	-	Overall survival
PC	-	Prostate cancer
PCWG	-	Prostate Cancer Working Group
PET	-	Positron-Emission-Tomography
PET/CT	-	Positron-Emission-Tomography/ Computed Tomography
PET/MRI	-	Positron-Emission-Tomography/Magnetic Resonance Imaging
PI-RADS-	-	Prostate Imaging and Data System Score
PSA	-	Prostate specific antigen
PSMA	-	Prostate-specific-membrane-antigen
RECIST	-	Response Evaluation Criteria in Solid Tumors
RLT	-	Radioligand therapy
SUV	-	Standardized uptake value
TRUS	-	Transrectal ultrasound

TUM	-	Technical University of Munich
TURP	-	Transurethral resection of prostate
^{177}LU -	-	^{177}-Lutetium
^{68}Ga	-	^{68}-Gallium

2 Introduction and aims

“Theranostic” is a new term describing the combination of diagnostic and therapeutic strategies to improve local effects of interventions. The recent success of targeted therapies is based on therapeutic substances which bind with high affinity to biomolecules involved in a specific disease process. Maximizing the concentration of such therapeutic agents in affected tissues reduces systemic side effects and, thus, minimizes toxicity. Molecular imaging employs the same principle, to visualize biological targets, which are specifically overexpressed in abnormal tissue. Exploiting the ligand principle by applying radioactive agents to detect and to destroy unwanted tissue has been the rationale for treatment of thyroid disease employing radioiodine. This therapy has been used for the last 70 years as an successful first example of radiotheranostics (Seidlin, Marinelli, & Oshry, 1946). This principle has now been widely recognized as an attractive tool for detection and therapy of cancer. It has become a standard adjunct to the therapy of thyroid cancer and has been recently approved by the FDA as therapeutic option in neuroendocrine tumors using somatostatin receptors as targets (Strosberg et al., 2017).

The introduction of the prostate specific membrane antigen (PSMA) as target for the specific identification of prostate cancer has opened the door for targeted destruction of malignant prostate tissue in advanced metastatic castration-resistant prostate cancer. The rapid acceptance of PSMA-ligands as diagnostic imaging agents for PET/CT and PET/MR was followed by the therapeutic application using ^{177}Lutetium labelled PSMA-617 ligand by the University of Heidelberg (Afshar-Oromieh et al., 2016). Following the same strategy, a similar tracer approach has been introduced by the nuclear medicine department at Technical University of Munich (TUM). The group of Prof. Wester developed the agent ^{177} Lutetium PSMA I&T which has also shown in animal experiments promising tracer kinetics for therapy of prostate cancer (Weineisen et al., 2015).

The aim of this doctoral thesis was to retrospectively analyze the first experience regarding toxicity, efficacy and safety of this new therapeutic approach at the Klinikum rechts der Isar of TUM. The tracer is not yet approved as therapeutic agent but has been applied under rules of compassionate use after exhaustion of approved treatment regimens. The results presented in this doctoral thesis summarize clinical observations obtained in the first 100 patients treated at Klinikum rechts der Isar.

The reported results have been recently published in the European Journal of Urology (Heck et al., 2019).

The rapid translation of this new radiotheranostic approach has revolutionized the treatment of patients with advanced prostate cancer. This treatment option is already part of the German S3 guideline for the treatment of advanced prostate cancer (Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizi- nischen Fachgesellschaften e.V. (AWMF)). The eagerly awaited results of prospective clinical evaluation in phase III protocols will hopefully confirm first promising results und provide the necessary medical evidence or future widespread clinical applications (NCT03511664).

3 Prostate Cancer

3.1 Epidemiology

In 2013, prostate cancer (PC) accounted globally for 1.4 million new cases and 293,000 deaths. The highest incidence can be observed in high-income areas such as North America, while the lowest incidence is seen in Asian countries. In 104 out of 188 countries world-wide PC is the most common male malignancy and in 24 countries the leading cause of cancer deaths for men (Global Burden of Disease Cancer et al., 2015).

In Europe, PC has an incidence of 417 new cases per 100,000 males, it represents the most common malignancy in males and has the third highest mortality rate after lung and colon cancer with 92 deaths per 100,00 males. Globally, a 3-fold increase of PC incidence can be observed since 1990 (454.000 in 1990, 1.4 million in 2013) (Global Burden of Disease Cancer et al., 2015). The dramatic changes of incidence may be represented by the increasing age of our growing population as well as more accurate diagnostic methods. A revolution in the diagnostics of PC was the introduction of prostate specific antigen measurements (PSA) in blood (1994), which provides the possibility of early, cost-efficient diagnosis and follow up of prostate cancer. The high incidence in the age-group of 75 to 79 year old men (Latvia) is partially explained by the much higher prevalence in developed countries compared to developing countries with lower life expectancies. Overall, during the last decade, the 5-year relative survival percentages steadily increased from 73.4% in 1999-2001 to 83.4% in 2005-2007 in Europe (Etzioni R, April 2013).

3.2 Etiology

Risk factors of PC are ill defined. Established risk factors are increased age, ethnic origin and heredity. The risk at least doubles, if a first-line relative has PC. If more than one relative is affected, the risk increases by 5-11 fold (Jansson et al., 2012).
Only around 9% of men have a true autosomal dominant hereditary form of PC, which is defined by three or more affected relatives or at least two relatives who have developed early onset disease (<55 Years). Hereditary PC usually has its onset six to seven years earlier than idiopathic cases. The pathology does not differ in any other way (Hemminki, 2012). PC incidence varies widely between geographical areas, being very high in the US and northern Europe and low in South-East Asia. Environmental factors are thought to have an influence on the pathogenesis of PC, as studies show that the risk for a Japanese man to suffer from PC increases if he moves from Japan to Hawaii. It can even exceed the average risk of an American, if the Japanese man moves to California (Zaridze, Boyle, & Smans, 1984). Factors which have been discussed as etiological important risk factors are foods consumed, patterns of sexual behavior, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation and occupational exposure (Leitzmann & Rohrmann, 2012; Nelson, De Marzo, & Isaacs, 2003).
Additionally, hypertension and waist circumference were shown to be significantly linked to an increasing risk of PC by 15% and 56%, respectively (Esposito et al., 2013).

In summary, determining risk factors for PC are hereditary as well as exogenous factors. By now, there is insufficient evidence to give specific recommendations for lifestyle modification, such as a special diet, in order to lower the risk of PC (Richman, Kenfield, Stampfer, Giovannucci, & Chan, 2011).

3.3 Pathophysiology

PC growth results in the imbalance of epithelial proliferation rate and rate of apoptosis. After the initial transformation event, further mutations of multiple genes lead to tumor progression and metastasis. PC presents in 95% of cases as adenocarcinoma. Only around 4% of all cases have transitional cell morphology and arise from the urothelial lining of the prostatic urethra.

Squamous cell carcinoma constitutes for less than 1% of all PC. The growth behavior of PC shows that approximately 70% arise in the peripheral zone, 15-20% in the central zone and 10-15% in the transitional zone.

Usually PC presents with involvement of multiple zones due to multifocal clonal and non-clonal tumor growth (Gerald W Chodak). In carcinogenesis of prostate cells, prostate specific antigen (PSA) has an influence on various growth factor molecules, which potentially enhance the proliferation, cell detachment, invasion and metastases (Bok & Small, 2002). The metastatic spread of prostate cancer occurs relatively late and frequent sites of distant metastases are bones and lymph nodes. Locally invasive cancers with the origin in the transitional zone tend to extend into the bladder neck, whereas peripheral-zone cancers tend to extent in the ejaculatory ducts and seminal vesicles. The mechanism of distant metastasis is poorly understood, as sometimes bone metastases are discovered without significant local lymphadenopathy.
The “mechanical theory” and the “seed-and-soil” theory are currently the two predominant theories for the spread of PC. The mechanical theory supposes the direct spread to the lumbar spine through the lymphatic and venous spaces. The seed-and-soil theory suggests the obligatory presence of tissue factors, that allow preferential growth in certain tissue (Gerald W Chodak, 2017a).
Androgen receptors, which maintain normal function of prostate cells, stimulate the growth and proliferation in case of androgen-dependent prostate cancer. Therefore, androgen receptors are an important target for hormonal treatment of PC.
Hormone-dependent prostate cancer cells develop resistance to hormones over time and transform into castration- resistant prostate cancer (Bok & Small, 2002).

3.4 Clinical presentation

Early-stage PC usually does not present with any symptoms. Late symptoms of advanced disease can be urinary complaints or retention, back and bone pain and hematuria. However, urinary complaints occur mostly due to other prostate diseases such as benign prostate hyperplasia, since PC is mostly diagnosed in early and asymptomatic stages. Most symptoms occur at advanced stages of disease and, thus, limit early detection.

Manifestations of advanced and metastatic PC include weight loss, anemia, bone pain, neurologic symptoms due to local compression of spinal cord as well as lower extremity pain and edema due to venous and lymphatic obstruction by nodal metastasis. Bone pain is mostly present in the spine and pelvic area due to bone metastases which carry the risk of pathologic fractures. Uremic symptoms can occur from ureteral obstruction caused by local prostate growth or retroperitoneal adenopathy secondary to nodal metastasis (Gerald W Chodak, 2016a). Due to the strong predilection to metastasize into bones, bone metastases account for the majority of clinical symptoms and are also the main reason for morbidity and mortality (Apolo, Pandit-Taskar, & Morris, 2008).

3.5 Classification

3.5.1 TNM- Classification

The “European association of Urology” guidelines recommend to follow the TNM classification of PC published by UICC (International Union Against Cancer) in 2009 (*Table 1*). In this classification, the “T” category describes the primary tumor site, the “N” category the regional lymph node involvement and the “M” category the presence of distant metastatic spread. Further separation is made either if the classification is based on clinical examination (“c” is added before the category) or if it was defined by the pathologist (“p” is added before) (Sobin, 1999).

Table 1: TNM classification of prostate cancer UICC 7th edn., 2009

T - Primary Tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor not palpable or visible by imaging
	T1a Tumor incidental histological finding in < 5% of resected tissue
	T1b Tumor incidental histological finding in > 5% of resected tissue
	T1c Tumor identified by needle biopsy
T2	Tumor confined within the prostate T2a Tumor <50% of one lobe T2b Tumor >50% of one lobe T2c Tumor involves both lobes
T3	Tumor extends through the prostatic capsule T3a Extracapsular extension including bladder neck involvement T3b Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles
N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M – Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis M1a Non-regional lymph node(s) M1b Bone(s) M1c Other sides

3.5.2 Gleason Score

Tissue samples (obtained from biopsies or prostatectomy) are histologically classified by the Gleason score. Gleason score predicts the aggressiveness of the adenocarcinoma based on the extent to which the glandular epithelium remains in its normal structure. The predominant as well as the second most common pattern of the tissue samples are graded from 1 to 5, which, added together, defines the Gleason score. The lowest score 2 represents the mildest, whereas the highest score 10 the most aggressive form of prostate cancer.

This histological grading system is very dependent on skills and experience of the pathologist, which results in some degree of individual variation (Gerald W Chodak, 2016b).

In 2014 the WHO and the International Society of Urologic Pathology (ISUP) revised the grading system and introduced Grade Groups using five grades as displayed in Table 2. Grade 1 is the least aggressive and Grade 5 is the most aggressive type of PC.

D'Amico's EAU risk group classification of localized PC combines primary tumor stage, Gleason score and PSA values in order to predict the biochemical recurrence risk for patients after surgery or external beam radiation therapy (Table 3) (Cooperberg et al., 2005).

Table 2: ISUP PC Grade Groups

Grade Group	Gleason score	Gleason pattern
1	≤ 6	≤ 3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

Table 3: EAU risk groups for biochemical recurrence of localized and locally advanced PC

Low-risk	Intermediate-risk	High-risk	
PSA< 10ng/ ml	PSA 10-20 ng/ ml	PSA > 20 ng/ ml	Any PSA
And GS < 7	Or GS 7	Or GS > 7	Any GS
And cT1-2a	Or cT2b	Or cT2c	cT3-4 or cN+
Localized			Locally advanced

3.6 Diagnosis

Digital rectal examination (DRE) and PSA values are usually the basis for detection of PC. The definite diagnosis is then made by histologic examination of biopsy cores or specimens from transurethral resection of prostate (TURP) (N. Mottet, 2015).
Digital rectal examination may detect prostate cancers which are located in the peripheral zone and exceed the size of 0,2 ml. About 18% PC's are detected by DRE alone, irrespective of PSA values. PSA levels alone detect approximately 45% of PC. Therefore combination of DRE and PSA values promises a efficient diagnostic method in all age-groups (Richie et al., 1993).
The use of PSA as a serum marker has revolutionized the diagnosis of PC. The PSA values usually increase with the presence of PC, but as PSA is organ-specific and not cancer specific, non-malignant conditions such as benign prostatic hyperplasia, prostatitis and diagnostic manipulations which stress the prostate shortly before taking the blood sample can elevate PSA levels in blood (Stamey et al., 1987).
A suspicious DRE and/or PSA values are an indication for prostate biopsy, which is made under guidance by ultrasound using a trans-rectal (TRUS) or trans-perineal approach.
Mildly elevated PSA values (4-10ng/ml) should be verified after 4-6 weeks using the same standardized conditions (no ejaculation, manipulation and urinary tract infection) in the same laboratory before considering the biopsy. In young men with a PSA level of 2-3 ng/ml a biopsy is recommended. However, there are no defined values, which justify a prostate biopsy (Eastham et al., 2003). The biopsy should consist of 10 samples cores taken bilaterally from apex to base as far lateral and posterior as possible. Additional cores should be taken from suspect areas detected in DRE/TRUS (Heidenreich et al., 2012). The incidence of false negative biopsies decreases with the number of samples. Overall, TRUS biopsies have a sensitivity of 58% and a specificity of 100% (Djavan, Milani, & Remzi, 2005).

3.7 Imaging

In case of any suspicious finding during the screening process a TRUS is indicated as first imaging evaluation. It gives precise information about the size of the prostate and lesions can be seen as hypoechoic areas with a hyper-perfusion.

The use of multiparametric TRUS with the classic B-Mode sonography allows better differentiation of malignant and benign lesions, however, TRUS is not a tool for primary diagnosis of PC as the differentiation of benign and malignant lesions is difficult. The main use of the sonography is to detect suspicious lesions and assist the biopsy as described above.

Multiparametric magnetic resonance imaging (mpMRI) combines the anatomic information in the T2-weighted sequences but also reveals functional information from diffusion-weighted imaging (DWI) and dynamic contrast enhancement (DCE) (Stabile et al., 2020).

The analysis of MRI images has been standardized and results are evaluated using the prostate imaging and data system score (PI-RADS v2) (Park, Choi, Lee, Kim, & Kim, 2020). A standardized reporting using the PI-RADS score reduces interobserver variability.

Therefore, the mpMRI is a tool for primary diagnosis and also local staging of disease. Especially early detection of extracapsular growth is important and leads to therapeutic consequences.

Re-biopsies using mpMRI as a targeting tool give higher precision biopsies and therefore a higher diagnostic performance for the biopsy-results and is likely to replace the systemic biopsy approach (Elwenspoek et al., 2019).

Prostate specific membrane antigen (PSMA) as target for diagnostic imaging has recently been introduced. Using ^{68}Ga- or ^{18}F- labelled PSMA ligands in combinations with PET/CT or PET/MR has shown to provide high sensitivity and specify in the diagnostic work up of PC.

Especially for the detection of recurrent disease this imaging approach has proven to be superior to conventional imaging methods (Anttinen et al., 2020).

PET-MRI represent the most precise imaging approach combining the strength of high soft tissue contrast offered by MRI and the high sensitivity of radiolabeled tracer methods (Eiber et al., 2015). The reduced availability and the high costs limit the widespread clinical application of PET/MRI as a primary screening method.

However, current S3 guidelines recommend the use of PET/CT for recurrent disease

In addition PET/CT has been added to the German S3 guideline also for patients with primary high risk disease (Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizi- nischen Fachgesellschaften e.V. (AWMF)).

The most commonly used imaging modality for staging of newly diagnosed prostate cancer is bone scintigraphy with 99m-TC labeled bone seeking agents and computed tomography.
This technique is also used for re-evaluation after therapy in advanced metastasized prostate cancer patients.
In addition, quantitative analysis of imaging data can be used to define a bone scan index (BSI), which has been shown to be of prognostic value in advanced prostate cancer (Song, Jin, Xiang, Hu, & Jin, 2020).
Table 4 summarizes the indication for diagnostic use of imaging techniques.

Table 4: Use of diagnostic imaging in prostate cancer

Tumor-detection	Local staging	Systemic staging	Recurrence
TRUS	TRUS	MRI	PET-CT/MRI
mpMRI	mpMRI	CT/ PET-CT	mpMRI
Multiparametric sonography	(CT)	Bone-scintigraphy	

3.8 Conventional therapy

3.8.1 Deferred treatment (active surveillance/watchful waiting)

Around 45% of men with localized PC are candidates for deferred management, as many men are not likely to benefit from definitive treatment (Godtman, Holmberg, Khatami, Stranne, & Hugosson, 2013). “Active surveillance and “watchful waiting” are two conservative treatment strategies with the aim to avoid loss of quality of life and reduce overtreatment in men with comorbidities and limited overall life expectancy.

Active surveillance defines the active decision not to treat prostate cancer right away, in case of a tumor which is localized (cT1c-cT2a), has a Gleason score ≤ 6, PSA ≤ 10 ng/ml, positive cancer cells in ≤ 2 biopsy cores and ≤ 50% cancer involvement in every positive biopsy core (Klotz, 2005). During the first two years of active surveillance the patient should be monitored via DRE and measurement of PSA levels every 3 months, afterwards every 6 months. A biopsy should be repeated every 12-18 months.

A stop of active surveillance strategy is considered if any of the following criteria are present:

- PSA value doubles in less than 3 years
- PSA level increase above 10 ng/mL
- Worsening of Gleason score ≥ 6
- Patients request

“Active surveillance” has compared to “watchful waiting” a curative treatment aim and is only suitable for low-risk patient groups, which fit the inclusion criteria described above (Heidenreich et al., 2012). The treatment strategy of watchful waiting includes patients with localized PC, limited life expectancy of less than 10 years or older patients (>70 years) with less aggressive cancer. It is commonly used, as prostate cancer is predominantly diagnosed in older men with a high incidence of comorbidity and a therefore decreased life expectancy (Adolfsson, 2008). Watchful waiting starts with conservative treatment. At the time of clinical complaints palliative treatment such as transurethral resection of prostate (TUR-P) in case of urinary obstruction or hormone/radiation therapy due to symptomatic metastases is started (Heidenreich et al., 2012).

3.8.2 Radical prostatectomy

Radical prostatectomy is the surgical treatment option for prostate cancer, which involves the removal of the entire prostate gland between the urethra and bladder. In addition a resection of both seminal vesicles along with sufficient surrounding tissue to obtain negative margins is performed. In intermediate and high risk PC, it is usually accompanied by a bilateral lymph node dissection. The aim of surgical therapy is complete eradication of disease (life expectancy of at least 10 years and clinically localized disease) with preservation of continence and, if feasible, potency (Bianco, Scardino, & Eastham, 2005). Traditionally radical prostatectomy has been performed via an open incision with a retropubic or perineal access. Recently laparoscopic and robot assisted prostatectomies have been developed as a minimal invasive approach. Robot assisted radical prostatectomy is already replacing the retropubic radical prostatectomy as standard approach in western-world countries, despite the absence of high quality evidence to support the superiority of robotic surgery (N. Mottet, 2015).

In case of lymphadenectomy, an extended lymphadenectomy should be performed including the removal of nodes overlying the iliac artery and vein, the obturator fossa and the internal iliac artery. Some studies recommend in addition the removal of lymph nodes along the common iliac artery up to the ureteric crossing (Mattei et al., 2008). There is no defined age limit to perform radical prostatectomy (Droz et al., 2010), but patient's comorbidities must be taken into consideration, since they tend to increase risk of death due to complications and prostate cancer independent reasons (Albertsen et al., 2011).
In clinically advanced PC, transurethral prostate resection is only performed to reduce symptoms in men who develop obstruction secondary to local tumor growth.

3.8.3 Radiation therapy

Radiation therapy offers potential curative treatment of localized PC and is performed in the form of external-beam radiation therapy (EBRT) or brachytherapy.
External-beam radiation includes the 3-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) (N. Mottet, 2015). Despite lack of data on long-term complications and survival rates, stereotactic guided higher-dose-rate therapy has also been accepted as standard therapy by radiation oncologists (Geinitz et al., 2011). Proton-beam therapy is with a more conformal dose distribution theoretically an excellent form of EBRT, however, it has shown grade two or greater rectal and bladder toxicity in 2% and 4% of patients, respectively (Michalski et al., 2010).
The quality of life after 2 years comparing IMRT and surgery are similar, although it carries a slightly higher risk of persistent fecal urgency and incontinence of gas (Nihei et al., 2011).
Possible dose and technique dependent complications of EBRT include cystitis, proctitis, enteritis, urinary retention and impotence (Gerald W Chodak, 2017b).
Suitable for low-risk patients, brachytherapy provides high doses of radiation to a localized area by implanting radioactive seeds in the target tissue via a closed ultrasound-guided technique (Lue, 2013).
High-risk patients should receive a combination of EBRT together with androgen-deprivation therapy (Frank et al., 2007).

3.8.4 Androgen deprivation therapy (ADT)

The aim of ADT is to decrease the interaction of androgens with the prostate gland either by inhibiting the production of androgens or by blocking the prostatic androgen-receptors with competing compounds known as anti-androgens. With a combination of those two methods, complete androgen blockage can be achieved (Cornel, 2012).
The goal of testosterone lowering therapy (castration) is to reach a hypogonadal status, known as “castration level”, which is defined by a testosterone level lower than 50 ng/dl (1,7 mmol/L). This value is used by the regulatory authorities and is set as threshold in all clinical trials, even though the castration level has recently been re-defined as 20 ng/dl (1mmol/L). Repeatedly better results having been observed with the lower threshold compared to the previous level, which has been defined more than 40 years ago (Alfred et al., 2015; Klotz et al., 2015; Morote et al., 2009; Pickles, Hamm, Morris, Schreiber, & Tyldesley, 2012).
Testosterone lowering therapy is achieved by surgical castration, a bilateral orchiectomy, or by pharmacological castration. In pharmacological castration luteinising-hormone-releasing-hormone (LHRH) agonists or antagonists are used to decrease testosterone production (N. Mottet, 2015).
The castration level can also be achieved by using oral anti-androgens, which are subdivided by their chemical structure in steroidal or non-steroidal compounds and act by competing with binding to the prostatic androgen receptors.

3.8.5 Metastatic prostate cancer

Metastatic prostate cancer is treated by systemic therapy. To choose the right treatment option, hormonal sensitivity of the tumor tissue must be taken into consideration.
The treatment options for hormone sensitive metastasized PC include a chemohormonal therapy with Docetaxel (Sharma et al., 2018), androgen-deprivation therapy with abiraterone in addition with LHRH- analogue (Kumar, 2020) or androgen deprivation therapy with Apalutamide (Merseburger & Suttmann, 2020).
In the majority of patients with metastatic disease resistance to castration-therapy can be observed.

Castration resistance stage of disease is defined by 3 consecutive elevations of PSA (two times more than 50% over a nadir of >2ng/ml) and/or radiographic progress (≥2 bone metastasis in scintigraphy or enlargement of visceral metastases according to RECIST-criteria) in patients with testosterone levels below 50ng/ml (M. Heck, 2015). The challenge of treating metastatic castration resistant prostate cancer (mCRPC) is to choose the best fitting substrates for the specific therapy sequence.

Therefore, early detection of therapy resistance is one of the most active research areas in urology (Cucchiara et al., 2018). Patients with asymptomatic chemotherapy-naive mCRPC can be treated with abiraterone or enzalutamide.

Abiraterone acts hereby as an androgen-biosynthesis-inhibitor by blocking the for the Androgensynthesis essential CYP-17 enzyme.

Therefore, androgensynthesis is depressed in scrotal-, suprarenal- as well as tumor tissue. Enzalutamid blocks the interaction of androgen and DNA by antagonizing the androgen receptors (M. Heck, 2015).

In mCRPC, which presents with symptomatic bone metastasis and is not spread in the visceral organs, α-radin-dichloride-223 is a very effective available internal radiation therapy aiming specifically at bone lesions. Due to the similarity to calcium, the high energetic α-emitting Alpharadin accumulates in bone-tissue with a high cell turnover as seen in bone metastases and can therefore reduce the symptoms of bone-metastases (Parker et al., 2013).

In case of a previous treatment with primary Docetaxel chemotherapy, additionally Cabazitaxel, taxan-based second line chemotherapeutic medication, can be used to achieve an increased overall survival (de Bono et al., 2010). Table 5 shows current Phase III studies of various drug combinations in patients with and without Docetaxel pre-treatment (Markus Kroenke, 2019).

Table 5: Overview of randomized Phase III studies of new treatment combinations for patients with mCRPC (Markus Kroenke, 2019).

Treatment	Study name	Number of Patients	Survival advantage	Reduction of mortality risk
Before chemotherapy with Docetaxel				
Abirateron plus Prednison vs. Plazebo plus Prednison	COU-AA-302	546 vs. 542	4,2 months (35,3, vs. 30,1 months)	21 % (p = 0,0151)
Enzalutamid vs. Plazebo	PREVAIL	872 vs. 845	2,2 months (32,4 vs. 30,2 months)	29 % (p < 0,0001)
After Chemotherapy with Docetaxel				
Cabazitaxel plus Prednison vs. Mitoxantron plus Prednison	TROPIC	378 vs. 377	2,4 months (15,1 vs. 12,4 months)	30 % (p < 0,0001)
Abirateron plus Prednison vs. Plazebo plus Prednison	COU-AA-301	797 vs. 398	4,6 months (15,8 vs. 11,2 months)	26 % (p < 0,0001)
Enzalutamid vs. Plazebo	AFFIRM	800 vs. 399	4,8 months(18,4 vs. 13,6 months	37%(p<0,001)
Alpharadin (Radium-223-Dichlorid) vs. Plazebo	ALSYMPCA	615 vs. 307	2,8 months (14,0 vs. 11,2 months)	30 % (p = 0,00185)

4 Radiotheranostic

Adding therapeutic interventions after imaging to exploit the availability of targeting radioligands is an emerging medical field labeled as theranostics. The concept of combining imaging and therapy goes far back, however it has progressed rapidly over the past decade (Seidlin et al., 1946). Alone in 2018 more than 1000 publications on this topic were published according to PubMed.

The radiotheranostic approach uses the structure of ligand-linker-radioisotope design. Ligands serve as anchors and therefore allow targeted accumulation of therapeutic radioisotopes in or near cancer cells. Those ligands commonly are peptides, which can be loaded by specific linkers with diagnostic and therapeutic radioisotopes.

We report our theranostic experience using PSMA, which is an increasingly used radioligand for imaging of PC labelled with ^{68}Ga or ^{18}F in combination with PET/CT. PSMA-617 and PSMA-I&T have been labelled with therapeutic ß-emitter ^{177}Lutetium and applied in patients with mCRPC and avid PSMA uptake on PET/CT.

4.1 PSMA as target

PSMA is an excellent target for a theranostic approach. It is a transmembrane protein, which is expressed in all stages of prostatic cancer, it is highly upregulated in androgen insensitive as well as metastatic disease. PSMA is expressed as an integral membrane protein to the cell surface, which allows receptor mediated endocytosis with internalization after ligand-binding and finally it is not released into circulation (Bouchelouche, Choyke, & Capala, 2010).

4.1.1 Biology of PSMA

Prostate-specific-membrane-antigen is a type 2 membrane protein, which is characterized by the murine monoclonal antibody 7E11-C5.3 (Ross et al., 2003). With a 19-aminoacid-internal portion, a 24-amino-acid transmembrane portion and a 707-amino-acid external portion PSMA has a unique 3-part structure (Leek et al., 1995) (Figure 1).

It is located on the short am of chromosome 11, which is a rarely deleted region in PC (O'Keefe et al., 1998). PSMA acts with its enzymatic activity as a glutamate-preferring carboxypeptidase (Pinto et al., 1996).

The internalization signal of PSMA, which allows internalization of the surface protein into the endosomal compartment, is used for diagnostic and therapeutic approaches using PSMA as a target antigen (Rajasekaran et al., 2003).

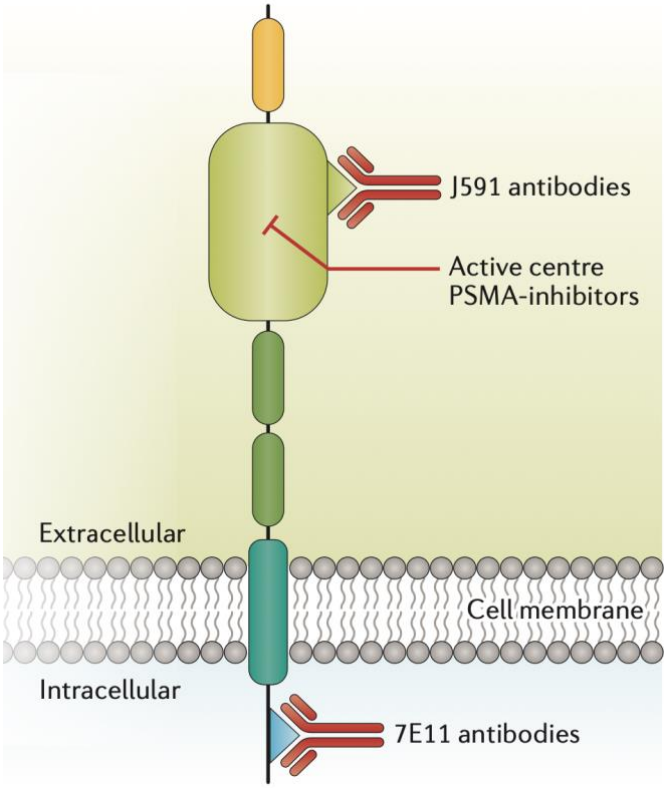

Figure 1 The structure of PSMA, its binding sites for PSMA ligands and the most frequently used antibodies.(Maurer, Eiber, Schwaiger, & Gschwend, 2016)

4.1.2 Ligands

Since urea-based PSMA inhibitors were discovered in 2001, a variety of PSMA-targeted radioligands for imaging of PC were developed (Scher et al., 2012).

PSMA 617 and PSMA I&T are theranostic ligands, which are used as diagnostic ligands, labelled with ^{68}Ga, and as therapeutic ligands, labelled with ß-emitter ^{177}Lu. PSMA 617 has been developed at the German Cancer Centre in Heidelberg, Germany, PSMA I&T was developed at Technical University of Munich (Weineisen et al., 2015). PSMA I&T, DOTAGA-(I-y)fk (Sub-KuE), is used as a diagnostic ligand in

^{68}Ga-PSMA PET scans and showed high potential in the detection of metastatic prostate cancer (Weineisen et al., 2015).

The DOTAGA (1,4,7,10-tetraazacyclododecane-1-(glutamic acid)-4,7,10-triacetic acid) conjugate PSMA I&T allowed fast and high-yield labeling with ^{68}Ga and ^{177}Lu. Uptake of ^{68}Ga-/^{177}Lu-PSMA I&T in LNCaP tumor cells is PSMA-specific and highly efficient, as demonstrated by competition studies both in vitro and in vivo.
In a proof-of-concept study ^{177}Lu-PSMA I&T endoradiotherapy was feasible, safe, and effective in metastatic PC (Heck et al., 2017; Weineisen et al., 2015).

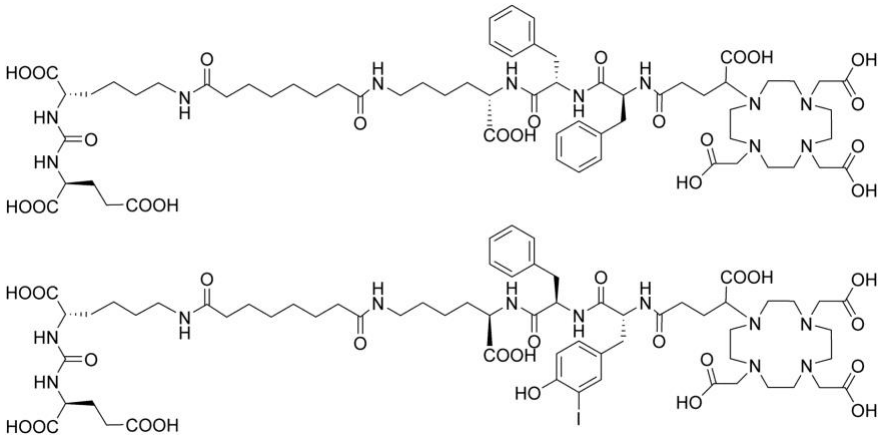

Figure 2: Chemical structures of DOTAGA-FFK (Sub-KuE), a first-generation tracer (upper), and PSMA I&T, a third-generation tracer (Weineisen et al., 2015).

5 Methods

5.1 Patient selection

In the present retrospective analysis, we included 100 consecutive patients, who were treated with ^{177}Lutetium-PSMA I&T-RLT between December 2014 and August 2017 at Klinikum rechts der Isar, TUM.

All patients were identified by physicians of the urology department of Klinikum rechts der Isar Munich. Based on individual clinical indications patients were referred to the department of nuclear medicine for the ^{177}Lutetium-PSMA I&T RLT in compliance with The German Medicinal Products Act, AMG §13 2b (compassionate use/ Heilversuch). The present retrospective data analysis was also approved by the local ethics committee under the reference number 115/18S.

5.1.1 Eligibility criteria

All patients had to be diagnosed with a positive histopathology for adenocarcinoma of the prostate. The patient had to be in a castration resistant state with a previous androgen deprivation therapy (gonadotropin releasing hormone agonist/antagonist, orchiectomy) and testosterone levels less than 50ng/dl. Several previous treatment lines were demanded, including a novel androgen receptor directed therapy with Abiraterone and/or Enzalutamide as well as a taxane-based chemotherapy with Docetaxel and/or Cabazitaxel or ineligibility for chemotherapy. All patients underwent ^{68}Ga-PSMA PET/CT within 4 weeks before treatment initiation, which had to show considerable PSMA expression of all PC lesions to demonstrate high PSMA ligand binding capacity. Considering the use of radioligands, the patients needed to present with an adequate liver and renal and bone-marrow function. Adequate liver function was defined by levels of aspartate aminotransferase or alanine aminotransferase less than 2.5 times upper limit of normal, bilirubin less than 2 times upper limit of normal.

Adequate renal function was defined by a Cockroft-Gault calculated creatinine clearance higher than 60ml per minute.

Adequate bone-marrow function included a hemoglobin of 9mg/dl or greater, a neutrophil cell count of 1,5 x 10^9/l or greater and a thrombocyte cell count of 120 x 10^9/l or greater. Despite all those criteria, the patients general ECOG performance status needed to be 0 or 1.

5.1.2 Exclusion criteria

Patients with inadequate organ function were excluded. This was defined by presence of active infection or symptomatic viral hepatitis, myocardial infarction or thromboembolism within the last 6 months, heart insufficiency grade II-IV according to NYHA (New York Heart Association), acute or chronic glomerulonephritis or untreated hydronephrosis. Also, the use of nephrotoxic co-medication excluded patients from therapy. Other than organic exclusion criteria patients with an active secondary malignancy or previous radiation of the spinal column or pelvis, including greater than 25% of the bone marrow were not admitted for therapy.

5.2 Clinical Characterization

5.2.1 Laboratory tests

Laboratory tests were performed before and after every treatment cycle to control the course of laboratory values and to control the activity and possible adverse events of the therapy. High attention was paid to general organ function in order to detect possible kidney, liver or hematological damage.

The main laboratory indicator for the course of the therapy was defined by PSA dynamics. An important marker defining efficacy of therapy was the best PSA-response as well as the time to PSA progression.

The best PSA-response was analyzed by the best proportional response from baseline PSA value to the nadir during the course of observation. The described PSA response is presented in defined steps of PSA decline by ≥30%, ≥50% and ≥90%.

The Prostate Cancer Clinical Trials Working Group 3 (PCWG3) has defined PSA progression as an increase in PSA greater than 25% and >2 ng/ml above nadir (Scher et al., 2016).

5.2.2 Imaging methods

Before treatment initiation and at least after every 2 cycles of the therapy ^{68}Ga-PSMA-11 PET/CT-imaging was performed to evaluate the course of the disease and analyze PSMA activity.

Adapted from prostate cancer working group (PCWG) 3-criteria progressive disease was defined at least ≥ 2 new bone metastases in ^{68}Ga-PSMA-PET, any new soft tissue

lesion in morphological imaging or ^{68}Ga-PSMA-PET and/or soft-tissue progression according to CT and RECIST1.1.
For 80 of the 100 patients a calculation of the Bone-PET-Index (BPI) was performed by the department of nuclear medicine. The BPI volume displays the percentage of skeleton affected by PSMA-avid tumor. The BPI standardized uptake value (SUV) shows the bone lesions PSMA-metabolic activity.

5.2.3 Adverse events

For standardized and systemic analysis of therapy the adverse events were divided in non-hematological and Hematological adverse events following the “Common Terminology Criteria for Adverse Event” (CTCAE Criteria 4.0) published by the U.S department of health and Human services (Health & National Cancer Institute, 2009).

5.3 Therapy regimen

The radiopharmaceutical ^{177}Lu-PSMA-I&T was prepared by the Department of Nuclear Medicine in accordance with the responsible regulatory body (Government of Oberbayern). Intravenous treatment with 7.4GBq ^{177}Lu-PSMA-I&T (160µg; 107nmoles; 431 MBq/µmoles) was applied every 6-8 weeks and was continued up to a maximum of 6 cycles in patients with absence of radiographic or clinical progression and lack of severe toxicity according to the investigator. Androgen-deprivation therapy (ADT) was continued during ^{177}Lu-PSMA-I&T RLT.
Clinical progression was defined by worsening of the patient’s disease related symptoms or the appearance of new cancer related symptoms.

5.4 Data analysis

Since all patients were treated following the rules of “compassionate use of 177 Lutetium-PSMA”, data analysis was retrospective using individual clinical patient records. Primary data was collected in a Microsoft Access Database, which was programmed for this purpose. Later on, data was exported to IBM® SPSS® version 24.0, where analysis and statistical work was performed. After analyzing baseline patient information, the treatment outcome could be evaluated. A patient follow-up was made up to December 2017 collecting information about the patients from the department of urology and the family doctors.

For evaluation of the treatment, we calculated best PSA response, time to PSA progression, overall survival (OS) and clinical progression free survival (cPFS) which describes the time during or after the therapy without progress of the disease and time of treatment. For further statistical analysis subgroups based on laboratory values at baseline, pre-treatments and metastases groups were created and compared statistically. Adverse events were categorized by CTCAE version 4.0 (Health & National Cancer Institute, 2009). Time to event-analysis for cPFS and OS with corresponding 95% confidence intervals (95% CI) were performed using the Kaplan Meier method (Rich et al., 2010). The Fisher´s exact test was performed for subgroup analysis, to determine the association of baseline factors with maximum PSA decline ≥50%. To determine the association of baseline factors before treatment initiation with cPFS and OS univariable and multivariable Cox regression analyses were used and the corresponding hazard ratios (HR) and 95% CIs were calculated. Only factors showing a significant association on univariable analysis were included in a multivariable model. If more than one risk factor was identified at univariable analysis, a multivariable analysis was performed. Moreover, log-rank statistics using the Kaplan Meier method were implemented. Baseline factors included primary metastatic prostate cancer, visceral metastasis, ECOG status, previous treatment with chemotherapy or ^{223}Radium, number of previous treatment regimens, Gleason score, age, PSA level, hemoglobin level, alkaline phosphatase level, lactate-dehydrogenase level and bone PET-index with regard to bone tumor volume (BPI_{VOL}) and bone standard uptake value (BPI_{SUV}) on PSMA-PET/CT as recently described. For continuous variables we used the median to dichotomize the patient cohort. A P value of <0.05 was considered statistically significant and all statistical tests were performed two-sided.

6 Results

6.1 Patient Cohort

Between December 2014 and August 2017 100 patients with mCRPC were treated with ^{177}Lutetium-PSMA I&T-RLT at the Klinikum rechts der Isar.

6.2 Clinical findings

6.2.1 Baseline characteristics

Of 100 men 39 were diagnosed with primary metastatic PC and median Gleason score at diagnosis was 8 (range 6-10). Median age at treatment initiation with PSMA-RLT was 72 years (46-85 years). The laboratory tests at baseline showed a median PSA level of 165 ng/ml (range 0.23 ng/ml – 6178 ng/ml), median LDH level of 294 U/l (range 66-1950 U/l), median alkaline phosphatase level of 117 U/l (range 33-1988 U/l) and a median hemoglobin of 11.2 g/dl (range 8,4 – 14,6 g/dl).

Of all 100 patients bone, lymph node and visceral metastasis were present in 96, 87 and 35 patients, respectively. Detailed baseline characteristics are depicted in Table 6.

Table 6 - Baseline characteristics of patient cohort

No. patients		100
Age, years, median (range), n=100		72 (46-85)
Primary metastatic prostate cancer, No., n=100		39
PSA, ng/ml, median (range), n=100		165 (0-6178)
LDH, U/l, median (range), n=100		294 (66-1950)
AP, U/l, median (range), n=100		117 (33-1988)
Hb, g/dl, median (range), n=100		11.2 (8.4-14.6)
ECOG, median (range), n=78		1 (0-2)
Gleason score, median (range), n=87		8 (3-10)
Prior systemic treatments, No., n=100		
	Docetaxel	82
	Docetaxel rechallenge	8
	Cabazitaxel	20
	Abiraterone	89
	Enzalutamide	60
	Radium-223	20
	Other systemic treatment for CRPC	6
	Previous chemotherapy	84
Prior lines of systemic treatment, No., n=100		
	1	5
	2	38
	3	33
	4	17
	5	6
	10	1
Site of metastasis, No., n=100		
	lymph node, overall	87
	lymph node only	3
	bone, overall	96
	bone only +/- lymph node	62
	visceral, overall	35
	liver	18
	lung	11
	other	8
	visceral only	0
Bone PET Index, n=80		
	BPI_{vol}, median (range), %	12.7 (0-78.7)
	BPI_{SUV}, median (range)	1.1 (0-8.8)

6.2.2 Previous therapies

Fifty-seven patients had received 3 or more systemic treatment regimens for mCRPC before the start of ^{177}Lutetium PSMA I&T RLT.

Eighty-four patients were pretreated with taxane-based chemotherapies including docetaxel and twenty patients with cabazitaxel. Eight patients had undergone docetaxel rechallenge.

Androgen deprivation therapy with abiraterone and enzalutamide was performed in 89 and 60 patients, respectively. Twenty patients with symptomatic bone metastases were pre-treated with ^{223}radium-dichloride. Apart from those drug groups 6 patients were treated with other systemic therapies for CRPC.

6.3 Number of ^{177}Lutetium-PSMA I&T therapy cycles

Overall, 319 cycles were applied with a median of 2 cycles per patient (range 1-6 cycles). The first cycle was performed in 100 patients, the second in 85, the third in 45, the fourth in 44, the fifth in 25 and the 6th cycle in 20 patients. Only patients who did not show signs of progressive disease continued the therapy. As seen in the flow-chart below (Figure 3) two patients were discontinued after two cycles and five patients after the 4th cycle without clinical progression.

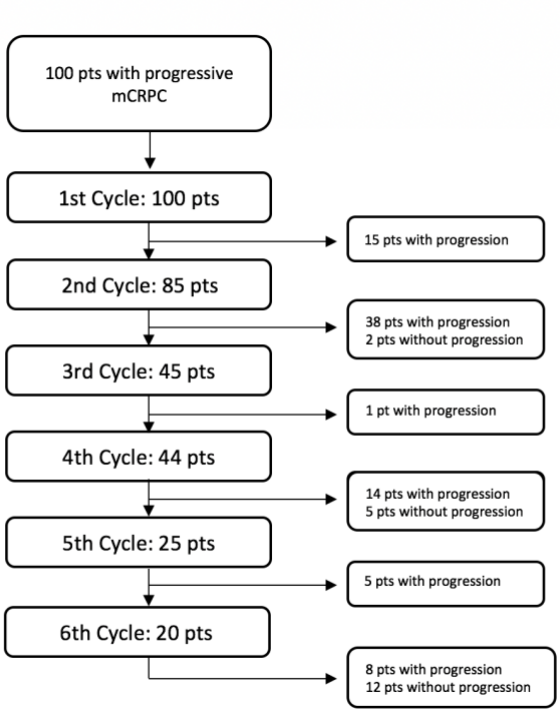

Figure 3 - Flow chart displaying the number of applied cycles with 177Lu-PSMA-I&T radioligand therapy.

6.4 Adverse events

Information about non-hematological adverse events were specifically asked for and documented during the regular consultations before and after every treatment cycle.
Hematological adverse events were analyzed using the baseline laboratory examination in comparison with the following laboratory tests at the beginning of every new cycle and at the end of the therapy.

6.4.1 Non-hematological adverse events

The most common grade 1-2 non-hematological adverse events seen during therapy was transient xerostomia in 24 patients within the first two weeks after therapy start, which is explained by PSMA expression in the salivary glands.
Fatigue was recorded in 20 patients, loss of appetite in 10 patients and diarrhea in 7 patients. Grade 2 paresthesia and obstipation were observed in 1 patient each.
During the entire time of therapy, no grade 3 or 4 non-hematological adverse events were observed.

6.4.2 Hematological adverse events

Hematological adverse events were subdivided in anemia, thrombocytopenia and neutropenia. Grade 1 and 2 hematological adverse events in perspective of anemia were observed in 3 and 24 patients, thrombocytopenia in 22 and 4 patients and neutropenia in 10 and 9 patients. Treatment-emergent grade 3 and 4 adverse events were anemia in 9 patients (all grade 3), thrombocytopenia in 4 patients and neutropenia in 6 patients.

6.5 Antitumor activity and outcome

6.5.1 PSA - response

The best PSA-response is analyzed by the best proportional response from baseline PSA value to the nadir during the course of observation. The number of patients achieving a maximum PSA decline of ≥30%, ≥50% and ≥90% were 47, 38 and 11, respectively. In 7 patients a PSA decline of more than 95% with the highest of 99,9% was noted. Among 38 patients with a PSA-response higher than 50%, 9 occurred after the first cycle, 21 after the second cycle, 4 after the third cycle and 4 more after the

fourth cycle of therapy. Overall, 65 patients achieved any PSA decline during the therapy as shown in Figure 4. The median time to PSA progression was calculated using the Kaplan-Meier method. Of all 100 patients 75 developed PSA progression within a median of 3.6 months (95% CI 2.8 – 4.4 months).

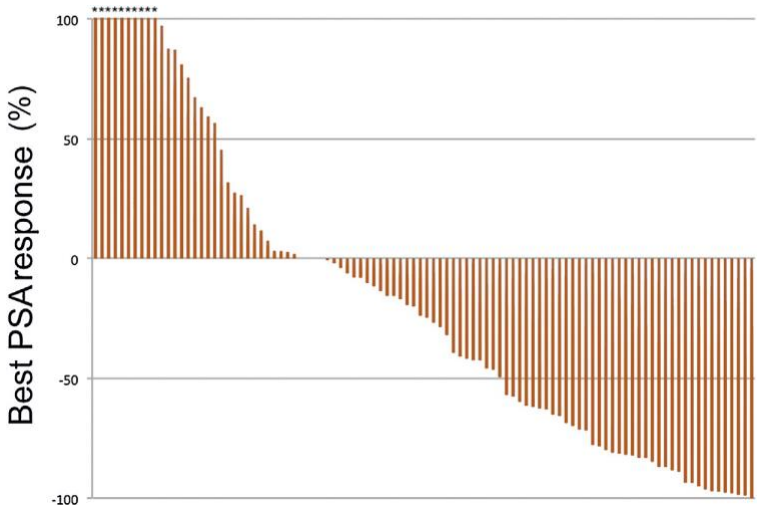

Figure 4: Waterfall plot depicting the best PSA response under ^{177}Lu-PSMA-RLT. Asterisks indicate an increase of >100% in the best PSA response.

6.5.2 Course of therapy and outcome

In all 100 patients the ^{177}Lutetium-PSMA I&T RLT was completed at the time of analysis.

The median duration of the therapy was 3.9 months (95% CI 2.4 – 5.5 months).

Patients which finished all cycles of therapy without clinical or radiographic progression continued therapy after a delay of 6-months in order to decrease the risk of nephrotoxic damage. In the follow-up 90 patients had developed clinical progression and 60 patients had passed away. Median follow-up of patients being alive was 9.5 months (interquartile range 7.0–16.3). Median clinical progression free survival (cPFS) was 4.1 months (95% confidence interval (CI) 2.4–5.7) and median overall survival (OS)was12.9 months (95% CI 9.9–15.9).

Figure 5 displays a swimmer plot displaying the individual treatment outcome. In 19 patients who completed ^{177}Lu- PSMA-I&T RLT without progression, sustained tumor control was achieved.

The median time to clinical progression after completion of RLT in these patients was 6.0 months (95% CI 3.9–8.1 months).

PSA response under RLT was strongly associated with survival. In a landmark analysis after 12 weeks of treatment, we analyzed treatment outcome from that time point depending on PSA response within 12 weeks of RLT (Figure 6). Herein, a maximum PSA decline of ≥ 50% was associated with longer cPFS (median 8.1 (n = 32) vs 0.4 (n = 53) months, p = 0.001; difference 7.4 months (95% CI 5.8–9.0)) and longer OS (median 16.7 (n = 32) vs 6.2 (n = 60) months, p = 0.007; difference 10.5 months (95% CI 1.4–19.6)

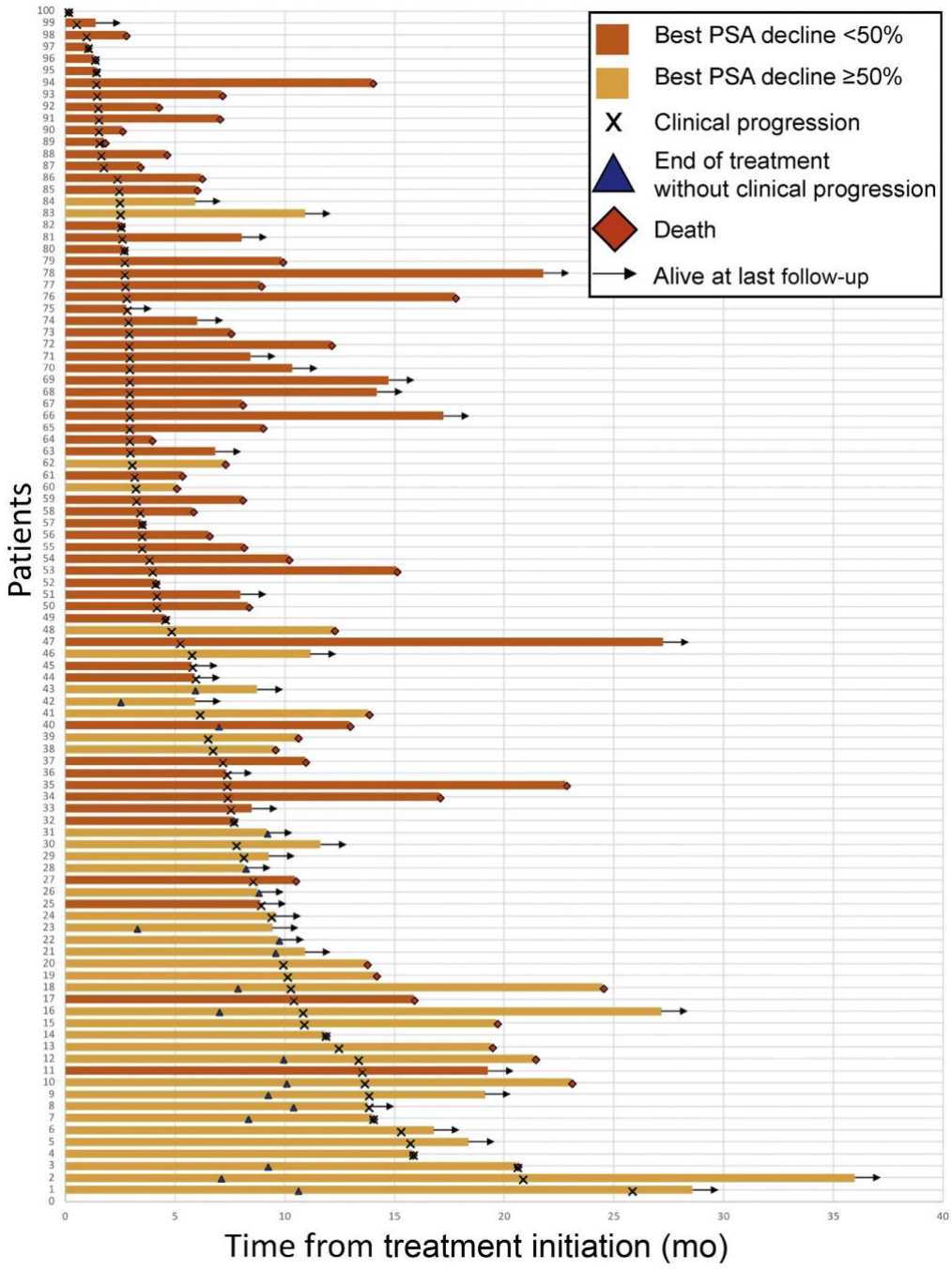

Figure 5: Swimmer plot showing clinical experience with 100 consecutive patients treated with 177Lu-PSMA-I&T radioligand therapy for metastatic castration-resistant prostate cancer

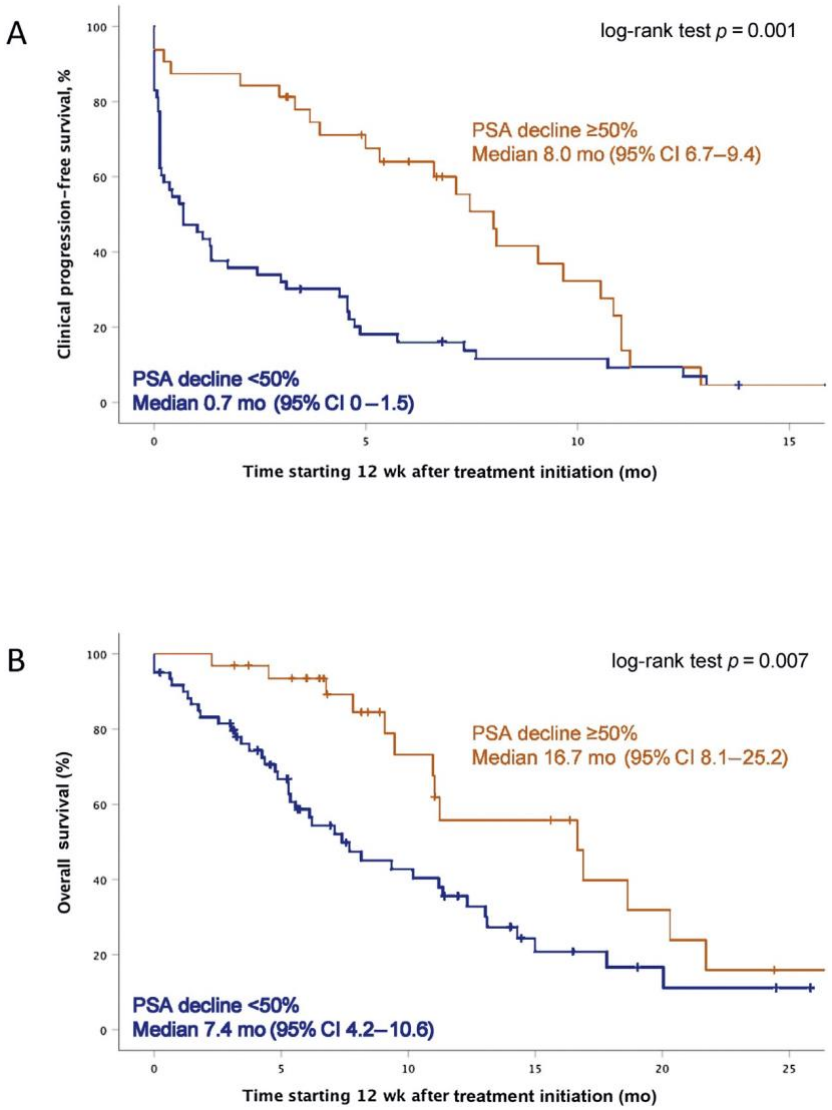

Figure 6: Maximum PSA decline of ≥ 50% was associated with (A) longer clinical progression-free survival and (B) longer overall survival.

6.6 Subgroup analysis

For further analysis of antitumor activity different subgroups of patient characteristics were analyzed with regard to PSA decline of more than 30% and more than 50% as well as OS clinical progression free survival.

The patients were dichotomized by median laboratory values. Values analyzed were hemoglobin, lactate dehydrogenase, alkaline phosphatase and PSA levels. Furthermore, patients were subdivided according to pretreatments, presence of primary metastatic disease and the location of metastasis. For 80 of the 100 patients the department of nuclear medicine defined the Bone-PET-Index (BPI).

The BPI volume displays the percentage of skeleton affected by PSMA-avid tumor. The BPI SUV shows the bone lesions PSMA-metabolic activity.
For maximum PSA decline ≥ 50%, the only factor associated with poor PSA response showed to be the presence of visceral metastases (p=0.049) as displayed in Table 10. A Maximum PSA decline was achieved in only 9 of 35 (26%) patients with visceral metastasis compared to 29 of 65 (45%) patients without visceral metastasis.

Also the presence of visceral metastasis showed to be the only risk factor significantly associated with worse outcome for cPFS (HR 1.8 (95%CI 1.2-2.8); p=0.009) on univariable analysis (Table 7).

Figure 7 A displays the corresponding Kaplan Meier curve which shows a Median cPFS was 3.1 months (95%CI 2.8-3.5) in patients with visceral metastasis in comparison to 5.9 months (95%CI 2.3-9.4) in patients without visceral metastasis (p=0.007).
For OS primary metastatic disease (HR 2.0 (95%CI 1.2-3.7); p=0.008), presence of visceral metastasis (HR 1.9 (95%CI 1.1-3.1); p=0.02), PSA above median of 164 ng/ml (HR 1.9 (95%CI 1.2-3.1); p=0.02), hemoglobin below median of 11.2 mg/dl (HR 1.9 (95%CI 1.1-3.1); p=0.02), LDH above median of 294 U/l (HR 1.7 (95%CI 1.0-2.9); p=0.04) and a BPI_{vol} above a median of 12.7% (HR 1.8 (95%CI 1.0-3.2); p=0.04) were associated with worse outcome on univariable analysis (Table 8*).*
In a multivariable Cox regression model, however, only the independent predictor of poor OS remained the presence of visceral metastasis (p= 0.006) and rising LDH levels (p < 0.001) (Table 9).
The corresponding Kaplan Meier curve is displayed in Figure 7 B. Median OS was 8.0 months (95%CI 5.5-10.6) in patients with visceral metastasis vs. 14.0 months (95%CI 11.4-16.6) in patients without visceral metastasis (p=0.03).

Table 7: Univariable analysis for the association of baseline factors with maximum prostate-specific antigen decline ≥ 50%. Significant associations are marked bold.

	No. of evaluable pts	p=
Primary metastatic prostate cancer No Yes	100	0.45
Visceral metastasis No Yes	100	**0.049**
Lymph node only No Yes	100	0.32
ECOG 2 versus 0,1	78	0.45
3 or more pretreatments No Yes	100	0.05
Previous Radium-223 No Yes	100	0.16
Previous chemotherapy no yes	100	0.40
Gleason 6-7 8-10	88	0.47
Age below median of 72y above median of 72y	100	0.08
PSA below median of 164ng/ml above median of 164ng/ml	100	0.27
Hemoglobin below median of 11.2mg/dl above median of 11.2mg/dl	100	0.46
Alkaline Phosphatase below median of 117U/l Above median of 117U/l	100	0.27
Lactate Dehydrogenase Below median of 294U/l Above median of 294U/l	100	0.07
Bone PET Index	80	
BPI_{vol}_Below median of 12.7 BPI_{vol}_Above median of 12.7		0.25
BPI_{suv}_Below median of 1.13 BPI_{suv}_Above median of 1.13		0.31

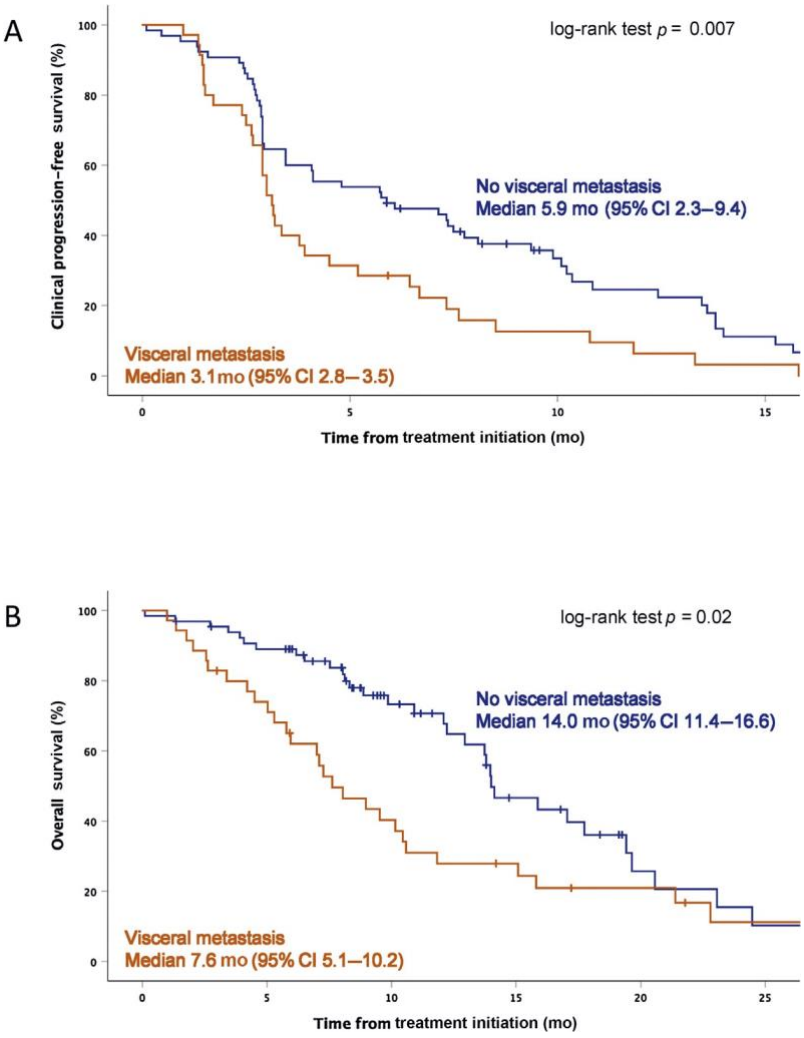

Figure 7: Presence of visceral metastasis was associated with (A) shorter clinical progression-free survival and (B) shorter overall survival. CI = confidence interval.

Table 8 Univariable analysis for the association of baseline factors with overall survival. Significant associations are marked bold.

	No. of evaluable pts	Hazard ratio	95% CI	p=
Primary metastatic prostate cancer	100	2.0	1.2-3.7	**0.008**
No				
Yes				
Visceral metastasis	100	1.9	1.1-3.1	**0.02**
No				
Yes				
Lymph node only		0.4	0.1-2.9	0.36
No	100			
Yes				
ECOG	78	1.2	0.7-2.2	0.55
0				
1				
2				
3 or more pretreatments	100	0.7	0.4-1.2	0.23
No				
Yes				
Previous Radium-223	100	0.6	0.3-1.2	0.14
No				
Yes				
Previous chemotherapy	100	2.5	0.9-6.8	0.08
no				
yes				
Gleason	88	1.0	0.5-2.0	0.93
6-7				
8-10				
Age	100	1.7	1.0-2.8	0.05
below median of 72y				
above median of 72y				
PSA	100	1.9	1.2-3.1	**0.02**
below median of 164ng/ml				
above median of 164ng/ml				
Hemoglobin	100	1.9	1.1-3.1	**0.02**
below median of 11.2mg/dl				
above median of 11.2mg/dl				
Alkaline Phosphatase	100			
below median of 117U/l		1.6	1.0-2.7	0.06
Above median of 117U/l				
Lactate Dehydrogenase	100			
Below median of 294U/l		1.7	1.0-2.9	**0.04**
Above median of 294U/l				
Bone PET Index	80			
BPI_{vol}_Below median of 12.7		1.8	1.0-3.2	**0.04**
BPI_{vol}_Above median of 12.7				
BPI_{suv}_Below median of 1.13		1.7	1.0-3.0	0.06
BPI_{suv}_Above median of 1.13				
BPI_{vol} (%), continuous	80	1.0	1.0-1.0	0.15
BPI_{suv}, continuous	80	1.0	0.9-1.2	0.62

Table 9: Multivariable Cox regression model for the association of baseline risk factors with clinical progression-free survival and overall survival

	Hazard ratio	95% CI	P value
Clinical progression-free survival			
Visceral metastasis	1.7	1.1-2.6	**0.02**
Age, risk change with 10 yr increase	0.7	0.5-0.9	**0.01**
LDH, risk change with 50 U/l increase	1.1	1.0-1.1	**< 0.001**
Overall Survival			
Primary metastatic prostate cancer	1.5	0.8-2.7	0.16
Visceral metastases	2.1	1.2-3.5	**0.006**
Age, risk change with 10 yr increase	0.7	0.5-1.0	0.07
PSA, risk change with 50 ng/ml increase	1.0	1.0-1.0	0.11
AP, risk change with 50 U/l increase	1.0	1.0-1.1	0.5
LDH, risk change with 50 U/l increase	1.1	1.0-1.1	**< 0.001**

Table 10 Univariable analysis for the association of baseline factors with maximum prostate-specific antigen decline ≥ 50%. Significant associations are marked bold.

	No. of evaluable pts	p=
Primary metastatic prostate cancer	100	0.45
Visceral metastasis	100	**0.049**
Lymph node only	100	0.32
ECOG 2 versus 0,1	78	0.45
3 or more pretreatments	100	0.05
Previous Radium-223	100	0.16
Previous chemotherapy	100	0.40
Gleason 6-7 8-10	88	0.47
Age Below median of 72y Above median of 72y	100	0.08
PSA Below median of 164ng/ml Above median of 164ng/ml	100	0.27
Hemoglobin Below median of 11.2mg/dl Above median of 11.2mg/dl	100	0.46
Alkaline Phosphatase Below median of 117U/l Above median of 117U/l	100	0.27
Lactate Dehydrogenase Below median of 294U/l Above median of 294U/l	100	0.07
Bone PET Index BPI_{vol}_Below median of 12.7 BPI_{vol}_Above median of 12.7	80	0.25
BPI_{suv}_Below median of 1.13 BPI_{suv}_Above median of 1.13		0.31

Table 11 Univariable analysis for the association of baseline factors with clinical progression-free survival. Significant associations are marked bold.

	No. of evaluable pts	Hazard ratio	95% CI	p=
Primary metastatic prostate cancer	100	1.5	1.0-2.3	0.07
No				
Yes				
Visceral metastasis	100	1.8	1.2-2.8	**0.009**
No				
Yes				
Lymph node only		0.6	0.2-1.8	0.32
No	100			
Yes				
ECOG	78	0.9	0.5-1.4	0.60
0				
1				
2				
3 or more pretreatments	100	0.8	0.5-1.2	0.28
No				
Yes				
Previous Radium-223	100	0.8	0.5-1.4	0.53
No				
Yes				
Previous chemotherapy	100	1.6	0.8-3.0	0.15
no				
yes				
Gleason	88	1.3	0.7-2.4	0.43
6-7				
8-10				
Age	100	1.3	0.9-2.0	0.20
below median of 72y				
above median of 72y				
PSA	100	1.3	0.9-2.0	0.20
below median of 164ng/ml				
above median of 164ng/ml				
Hemoglobin	100	1.2	0.8-1.8	0.43
below median of 11.2mg/dl				
above median of 11.2mg/dl				
Alkaline Phosphatase	100	1.1	0.7-1.7	0.56
below median of 117U/l				
Above median of 117U/l				
Lactate Dehydrogenase	100	1.3	0.9-2.0	0.19
Below median of 294U/l				
Above median of 294U/l				
Bone PET Index	80			
BPI_{vol}_Below median of 12.7		1.3	0.8-2.0	0.32
BPI_{vol}_Above median of 12.7				
BPI_{suv}_Below median of 1.13		1.3	0.8-2.0	0.34
BPI_{suv}_Above median of 1.13				
BPI_{vol} (%), continuous	80	1.0	1.0-1.0	0.75
BPI_{suv}, continuous	80	1.0	0.9-1.1	0.85

7 Discussion

The results presented in this doctoral thesis suggest that targeted therapy with ^{177}Lutetium PSMA will become a promising addition to systemic therapy of PC.

The combination of targeting ligands and radioactivity has emerged as innovative method not only for specific diagnosis, but also for therapy of cancer. The term “radiotheranostics” has been introduced to describe this combination of imaging for target identification and therapeutic delivery of high radiation dose. PSMA has become an attractive target for the development of such strategy for PC. PSMA, due to its specific delineation of PC cells and its increasing expression of advanced disease has shown to provide an excellent target for imaging and therapy. Numerous ligands for PET imaging have been developed and are currently evaluated in prospective clinical trials. Since the introduction ^{68}Ga-PSMA-11 as PET imaging tracer in 2012 by Eder et al., the application and associated experimental and clinical research has increased rapidly (Afshar-Oromieh et al., 2013).

In 11/2020, Pubmed lists more than 5000 publications triggered by the entry (PSMA).

Especially for the early detection of recurrence of PC PET/CT imaging with radiolabeled PSMA ligands emerged as the most sensitive and specific method which is now widely used and regarded as modality of choice (Maurer, Gschwend, et al., 2016). However, the employed imaging agents are not yet officially approved limiting the reimbursement of this diagnostic procedures in many countries. It is expected that this imaging technique will be widely used in the future as standard technique to detect and stage PC.

First applications of ^{177}Lu-PSMA I&T as therapeutic agent were performed in 2014 (Weineisen et al., 2015). Since this therapeutic agent is also not yet approved by FDA or EMA, the therapies were performed as compassionate use in patients with mCRPC who exhausted approved treatment regimens.

This retrospective analysis addressed the first 100 consecutively treated patients at TUM with PC patients after failure of conventional therapy who were referred to radioligand therapy following the documentation of high PSMA expression by PET/CT or PET/MR imaging. The therapy protocol included up to 6 cycles of ^{177}Lu-PSMA-RLT applications. However only 19 Patients have completed the entire protocol. Radiologic or clinical disease progression caused stop of the therapy regimen in 81 patients. Eighty-five percent of the patients completed 2 cycles and 44% completed 4 cycles.

This high progression rate reflects the fact, that only patients with end stage disease after failure of conventional therapy were included in the study.

This is further documented by the high number of pre-treatments, high baseline PSA values (median 165 ng/l) and widespread evidence of advanced metastatic disease with 96% bone metastases, 87% lymphnode-metastases and 35% visceral metastases).

Despite the advanced stage of disease and failure of previous treatments, a clinically relevant response (> 50%) has been observed in 32 patients after the first cycle and in 38 patients during the entire observation period. The observed range of individual PSA responses from no response in 35 patients to more than 90% decrease in 11 patients indicates a heterogeneous response pattern in our patient population.

Despite a considerable PSA response in the majority of cases, the progression free survival and the overall survival remained at a median of 4.1 months and 12.9 months, respectively. Unfortunately, no historic data defining overall survival in untreated patients at this stage of disease are published. Therefore, the need for more prospective, randomized study-protocol as the TheraP- Study (Michael S Hofman, 2020) is well appreciated to document the beneficial effect of ^{177}Lu PSMA RLT in very advanced stages of PC.

In a multivariable subgroup data analysis, presence of visceral metastases and high LDH levels reached as only predictive factors significance for shorter cPFS and OS which has been recently confirmed by a meta-analysis of published observations after ^{177}Lu-Therapies in prostate cancer (Satapathy, Mittal, & Sood, 2020).

An important result in our patients has been the low level of treatment-induced toxicity. There were no grade 3-4 non-hematologic adverse events observed. The most common non-hematologic grade 1-2 adverse events were transient xerostomia in 24 patients within the first 2 weeks after treatment, fatigue in 20 patients, loss of appetite in 10 patients and diarrhea in 7 patients.

In summary, our retrospective analysis of the first 100 patients revealed very promising results in advanced prostate cancer without significant toxicity but does not allow conclusions regarding outcome benefits due to missing control data.

7.1 Comparison of literature

As of November 2020, there are 143 publications listed in Pubmed searching for ^{177}Lu-PSMA I&T-RLT. There are 4 meta-analyses published focusing on the therapeutic efficacy of the ^{177}Lu PSMA therapy. The latest meta-analysis by Yavad et al. published in August 2019 included all recent studies with employing “high quality inclusion criteria” (Yadav, Ballal, Sahoo, Dwivedi, & Bal, 2019). After this selection process, 17 publications of original articles qualified as “high quality”, excluding duplicates and studies with less than 10 patients. Those 17 papers reported together the results obtained in 744 patients.

Comparing our experience with these published reports indicates, that our cohort included the third largest number of patients. The median age group of patients included in the studies was comparable, while the reported median baseline PSA were higher with 285 ng/ml as compared to our PSA baseline value of 165ng/ml. All publications included patients who had undergone multiple lines of prior treatment before ^{177}Lutetium-PSMA with a median of 3 lines of pre-treatments as in our study ranging from 1-7 lines in all reported cohorts. The metastatic spread to bone and lymph nodes were present in an average of 92% and 75% of the patients. With 96% bone metastases and 87% lymph node metastases, our patient population shows a metastatic progress above the median.

The administered radiation activity per cycle at TUM was with 7,4 GBq the third highest dose regimen as compared to a range from 3,7GBq to 9,3 GBq.

As marker of antitumor activity, PSA decline is reported in all publications. In the three largest patient groups (with more than 70 patients) any PSA decline has been observed with a median of 69 % (73% including all studies) of the patients and a PSA decline of more than 50% with a median of 40 % (47% including all studies).

Our study showed a lower PSA response with any PSA decline in only 57% of the patients and a PSA decline of more than 50% in 38% of the patients. The reason for this lower PSA response rate at TUM is difficult to interpret since mean or median PSA values do not adequately describe the heterogeneity of all patient populations. Our results are very similar to the results of Rahbar et al in 2 large cohorts with around 30% PSA response rate (Rahbar et al., 2018; Rahbar et al., 2016). In contrast, the publication by Kulkarni et al with 80 patients reports a PSA decline >50% in 57% of all patients, but no baseline PSA levels are reported (Kulkarni et al., 2016).

There was a wide range of ^{177}Lutetium PSMA activity levels applied in the reported studies ranging from 3,0 to 8,7 GBq/cycle.

No relationship of applied ^{177}Lutetium PSMA activity level and PSA response can be identified in this meta-analysis. However, applied dose of radiopharmaceuticals allows only very limited conclusion regarding regional dosimetry in tumor tissue. It is well appreciated, that accurate determination of radiation dose will be very useful to define the relationship between administered activity and regional tissue response. Current research focuses on the use of PET/CT and PSMA ligands to determine regional tracer uptake as quantitative predictors of RLT dosimetry. Future studies are needed to show, whether individual dosimetry improves outcome of ^{177}Lu-PSMA therapy and, thus, will be useful for individual dose escalation strategies.

Data about PSA initial progression after the start of therapy was noted in 12 reports including 234 patients. Of those 87 patients (37%) showed an initial PSA progression following the start of therapy. Most of the studies analyzed small numbers of patients with a short follow-up. Only five publications addressed the cPFS and averaged at 11 months. This value exceeds our cPFS of 4,1 Months. We used PSA as well as radiographic progress as markers for clinical progression. In others studies only radiologic progress was recorded, which may explain the prolonged cPFS. Bräuer et al reported a cPFS of 4,5 months with was also based on biochemical progression. (Brauer et al., 2017)

Due to the short observation period death rate was only published in 10 papers. The OS was evaluated in 6 studies. The median of median OS was 7 months (IQR 8-14 months) therefore lying below our results of 12,9 Months.

The low survival rate in most studies is related to the advanced tumorstage of the included patients. The longer cPFS and OS in patients without visceral metastases supports this hypothesis. In a landmark analysis after 12 weeks of RLT, treatment outcome was even more favorable in patients who had achieved a maximum PSA decline of >50%. Starting from this time point, these patients reached median cPFS of 8.1 months and median OS of 16.7 moths.

Additionally, the fact, that we used ^{68}Ga-PSMA-11 positron- emission tomography (PET) imaging at baseline and restaging to identify tumor progression can partly explain the shorter cPFS. The ^{68}Ga-PSMA-11 PET has a higher sensitivity in detecting metastases in soft tissue and bones compared with computed tomography and bone scan, respectively (Maurer, Gschwend, et al., 2016).

This may have led to earlier detection of tumor progression and therefore shortening of cPFS. Overall, the direct comparison of outcome data of these reports is limited and provides only an estimate of outcome related to the therapeutic intervention.

The first prospective single-arm Phase II study including 30 mCRPC pretreated with at least one taxane-based chemotherapy and/or androgen receptor target therapies (abiraterone, enzalutamide) confirming the activity of Lu177-PSMA RLT was performed in 2018. This study revealed a ≥50% PSA decline in 57% of the patients as well as a significant improvement in their quality of life (Hofman et al., 2018). In November 2019, Violet et al published the long-term outcomes of an expanded cohort. The authors reported a statistically significant longer OS of 18.4 months in patients who had a PSA decline ≥50% with a median OS of 13.3 months(Violet et al., 2020).

There is no question, that randomized and prospective data collection is needed to define the effect of this new therapy. Since prostate cancer has a high prevalence in our societies, the pharmaceutical industry will perform the necessary phase III trials to define the relative value of this new therapy. The recruitment of patients in the currently performed phase III study “vision” by Novartis (NCT03511664) has been completed and the results were published in the NEJM in June 2021.The study showed that radioligand therapy with ^{177}Lu-PSMA-617 prolonged imaging-based progression-free survival and overall survival when added to standard care in patients with advanced PSMA-positive metastatic castration-resistant prostate cancer (Sartor et al., 2021). These exciting results are confirming observations made in studies like ours and represent then necessary basis for future approval of the PSMA radioligand therapy by FDA and EMA. It will be very interesting to learn in future studies about the direct comparison of theranostics and conventional therapy in patients with early disease stages under controlled study conditions. Further prospective research is needed to define details of therapeutic protocols in order to optimize the pharmacokinetics of ligands as well as dosimetry in order to exploit the full potential of therapeutic effects.

The Hofman group presented at ASCO 2020 preliminary results of a first randomized Phase-2-trial (TheraP), which compares ^{177}Lu-PSMA to cabazitaxel in 200 men with mCRPC upon progression to docetaxel (Michael S Hofman, 2020).

In this study an improved biochemical response rate of ^{177}Lu-PSMA as compared to cabazitaxel in patients progressing after docetaxel (PSA decline ≥50% achieved in 66% vs. 37%) is described.

At a median follow-up of 13 months, treatment with ^{177}Lu-PSMA significantly improved biochemical PFS as compared to cabazitaxel

In addition, the combination of various therapeutic approaches at various stages of disease may be of interest to offer patients with PC options based on their individual disease profile. Finally, prospective studies are needed to apply RLT very early in the disease process, since prostate cancer is radiosensitive and may be especially responsive at the very early time points of disease.

The low number of side effects are a special characteristic of ^{177}Lu-RLT. Among the various adverse events analyzed in the meta-analysis by Yadav et al. the most common one was anemia in 23% of the patients, which was described in 14 of the 17 papers (Yadav et al., 2019). Our analysis showed that 43% of the patients developed anemia in the course of therapy of which 36% were grade 1-2 and only 7% grade 3. No grade 4 anemia was seen. The previous studies with the biggest patient cohort showed grade 3-4 anemia in 4-10 % of the patients. Thrombocytopenia was assessed in 12 studies with a median of 15% (0%- 47%). In our analysis only 1% had grade 4 and 4% of the patients grade 3 thrombocytopenia. In total thrombocytopenia has been seen in 25% of the patients.

Concluding, ^{177}-PSMA I&T RLT shows a low profile of toxicities compared to other treatment options as chemotherapy.

Discussing the hematologic toxicity, the bias of aggressive pre-treatments and the advanced stage of disease always has to be taken into consideration. The most common non-hematological toxicities were xerostomia (18%) and fatigue (16%). Those numbers lie within the median published in other papers.

Even though there is no standard treatment protocol and different doses of radiation were used, the toxicities published about the ^{177}Lutetium RLT appears to be lower than chemotherapy with comparable results in treatment efficacy (von Eyben et al., 2018). This supports the discussion of a start of the Lutetium RLT at an earlier stage of disease. However, in patients with longer life-expectancy potential, late toxicity to the

kidneys as a critical organ for PSMA-targeted RLT has not yet been investigated (Zechmann et al., 2014).

7.2 Future outlook

As discussed above the completion of clinical prospective clinical trials are needed to confirm the first observations of published retrospective data analysis in clinically selected cases. Besides the need of clinical evidence numerous questions remain associated with the further development of RLT. These challenges can be divided in technical and biological aspects.

As radioligand therapy relies on the use of radioactive substances, which are highly regulated and primarily reserved for the diagnostic use in nuclear medicine, a well-organized and efficient interdisciplinary teamwork has to be created. In future the theranostic therapy approach will have to bridge interdisciplinary boundaries by forming disease-oriented teams working closely together in the manner of already existing tumor boards. This approach could improve the patient selection and create the most appropriate therapy. Few US and many more European and Australian centers are operating this way but need to disseminate well executed interdisciplinary teamwork uniformly is essential nowadays even more with the complexity of newly developed treatment strategies.

The other big technical challenge is the limited and globally varying availability of radioisotopes and their sources. A coordinated industrial scale-up process is hoped to help overcome this barrier. And will provide sufficient production of available radioisotopes.

There has been no Phase I or Phase II studies reported for the definition of the most adequate dose of ^{177}Lutetium-PSMA. Most studies use the activity dose based on historic experience with radiotherapy in neuroendocrine tumors. In addition, economic consideration and reimbursement may limit the applied amount of radioactivity. A prospective dose-escalation study together with accurate dosimetry is needed to define the most appropriate dose regimen.

Besides those technical considerations there remain many biological questions. In most reported therapy series, the response rate was very heterogeneous. Besides technical factors this may also reflect heterogenous biological response to the radiation therapy. Future studies need to focus on biological characteristics of tumor tissue

relating in-vitro tissue analysis with clinical outcome. This analysis may also include genetic analyses of various tumor biopsy samples in the treated patients populations. Future application of RLT in earlier stages of disease may produce a more homogeneous response-rate. The large number of pre-treatments with various drugs may affect the response rate to our RLT.

An interesting future question will be if ^{177}Lutetium-PSMA may be suitable as first line therapy in patients with newly detected prostate cancer. Several trials addressing the described questions are currently on the way.

7.2.1 Combination therapy

The possible combination of non-radioactive therapies with theranostics agents may evoke synergistic effects and increase the clinical acceptance and treatment outcome. Table 12 displays some of the current trials evaluating combinations of RLT with androgen receptor blockage, inhibition of DNA repair, chemotherapy and combination with radiolabeled antibodies.

Also the combination of external beam radiation therapy with integrating radiotheranostics has shown promising avenue for further studies in preclinical trials and data (Dietrich et al., 2015).

As the clinical experience with RLT grows, the future applications and indications of theranostics will be defined and hopefully result in better therapeutic results in patients with PC in all stages.

Table 12: Ongoing clinical Trials on RLT combination with other therapies

Combination of RLT with:	**Trial**	**Topic**	**Design**
Androgen receptor blockage	EnzaP NCT04419402	Combination of enzalutamide and 177Lutetium PSMA vs. enzalutamide alone	Randomized Phase II Trial
Inhibitors of DNA damage repair	NCT03874884	Combination of ^{177}Lu-PSMA and Olaparib	Dose-escalation Phase I Trial
Immune checkpoint inhibitors	PRINCE trial NCT03658447	Combination of pembrolizumab and ^{177}Lu-PSMA	Phase Ib/II Trial
Chemotherapy	UpFrontPSMA study NCT04343885	^{177}Lu-PSMA delivered 6 weeks apart followed by 6 cycles of docetaxel vs. docetaxel alone	Randomized Phase II Trial
With different RLTs	NCT03545165	^{177}Lu-PSMA-617 combined with the antibody-based ^{177}Lu-J591	Phase I Trial

8 Summary

The aim of this doctoral thesis was to retrospectively analyze the first experience regarding toxicity, efficacy and safety with this new therapeutic approach of RLT with ^{177}LU-PSMA-I&T at the Klinikum rechts der Isar of TUM.

In patients with late stage mCRPC the admitted RLT with ^{177}LU-PSMA-I&T showed a good antitumor activity with very mild toxicity profile. The treatment was well tolerated and there were no treatment-related grade 3-4 nonhematological adverse-events observed. The most common grade 1-2 non hematological adverse events xerostomia, fatigue, loss of appetite and diarrhea.

Grade 3-4 hematological adverse-events were only nine patients with anemia, six patients with neutropenia and four patients with thrombocytopenia.

The numbers of patients achieving a maximum PSA decline of >30%, >50% and >90% were 47, 38 and 11 respectively.

A PSA decline of > 50% in the first 12 weeks of RLT was associated with a prolonged OS and cPFS. A more detailed subgroup analysis showed an association of the presence of visceral metastases at baseline and rising LDH with worse treatment outcome. For those patients an alternative treatment option should be considered.

The clinical benefit of ^{177}Lu-RLT over other treatment options as well as better results when initiated at an earlier stage of disease will be further evaluated by several prospective trials which are currently enrolling.

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