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PSMA-directed radioligand therapy (PSMA-RLT) with Lutetium-177 (177Lu-PSMA) as a treatment to metastatic resistant prostate cancer: a systematic review

PT-BR: Radioterapia PSMA-ligante dirigida com Lutécio 177 como um tratamento para câncer de próstata resistente a castração: uma revisão sistemática

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ABSTRACT: Prostate cancer is the second most prevalent in the world and an important cause of mortality in elderly men. Its most severe form is metastatic castration-resistant prostate cancer, difficult to control as it does not respond well to chemotherapy or androgen deprivation. A new treatment, based on PSMA ligands chelated to a Lutetium-177 atom, is a potential therapy for these patients, with evidence that it causes tumor regression. The goal of this systematic review is to evaluate the literature regarding the safety and efficacy of this new therapy.

Keywords: Prostatic Neoplasms; ^{177}Lu-PSMA; Castration-resistant prostate cancer, Efficacy, Neoplasm metastasis, Prostate-specific membrane antigen, Radioligand therapy, Safety, Dosimetry, Nuclear medicine.

RESUMO: O câncer de próstata é o segundo mais prevalente no mundo, sendo uma importante causa de mortalidade dentre homens idosos. Sua forma mais séria é o câncer metastático resistente a terapia hormonal, sendo difícil de controlar pois não responde tanto a quimioterapia quanto a privação de androgénos. Um novo tratamento, baseado em moléculas ligantes de PSMA, quelado ao átomo Lutécio-177, é uma terapia potencial para esse perfil de paciente, com evidências que esta causa regressão tumoral. O objetivo dessa revisão sistemática é avaliar a segurança e eficiência dessa nova terapia baseada na literatura atual.

Palavras-chave: Neoplasias da próstata; ^{177}Lu-PSMA, Câncer de próstata resistente à castração, Eficácia, Metástase neoplásica, Antígeno de membrana específico da próstata, Terapia com radioligantes, Segurança, Dosimetria, Medicina nuclear.

INTRODUCTION

Prostate cancer is the second most prevalent cancer amongst men worldwide[1] as well as in Brazil, with an incidence of 62 new cases/100.000 men across the country[2]. Metastatic resistant prostate cancer (mCRPC) is the most severe and hardest to treat presentation of the disease, as it doesn't respond to surgery and androgen deprivation, and chemotherapy stops eliciting a response in the long run[3]. The failure of conventional therapies to address mCRPC has spurred the development of alternative therapeutic options, such as treatment with enzalutamide, abiraterone acetate, sipuleucel-T, cabazitaxel, as well as Radium-223[4] and other radiopharmaceuticals. Radionuclide ligand therapy (RLT) with Lu-177-labeled PSMA radioligands is a promising treatment for mCRPC.

Prostate-specific membrane antigen (PSMA) is an integral membrane glycoprotein, which is highly expressed in the surface of prostate cancer cells during all tumor

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stages and remains high in mCRPC even after multiple lines of therapy. Because of this, PSMA is considered to be the best-established target antigen in prostate cancer[5]. PSMA small ligands labeled with radioactive atoms such as ^{68}Ga or ^{177}Lu when applied intravenously, can incorporate these atoms in cancer cells by binding to the PSMA glycoproteins on the cell membrane, allowing diagnostic imaging and/or systemic RLT, according to the emission of these radionuclides. As a result of the potential of this new targeted radioligand therapy, several studies have been conducted to evaluate its efficacy and safety[6]. However, because of its status as a relatively recent treatment, the risks and benefits of ^{177}Lu-PSMA RLT are still not entirely known, despite the studies that have already been done.

The goal of this systematic review is to evaluate clinically and scientifically relevant aspects of ^{177}Lu-PSMA therapy, as a way of measuring its safety as well as its effectiveness in patients with mCRPC. Due to the short interval of introduction of this therapy, radiation dose will be considered as a potential marker of future adverse reactions and laboratory markers will be studied together with survival and other clinical indicators.

MATERIALS AND METHODS

Eligibility Criteria

In order to be included in this review, articles had to involve patients with metastatic castration-resistant prostate cancer that received at least one cycle of ^{177}Lu-PSMA-617 therapy. Outcomes were measured primarily based on overall survival (OS), PSA decline, dose of radiation received by the tumor and vital organs, and occurrence of adverse side effects, verified either by laboratory or physical examination.

Search strategy and Study Selection

In order to collect data for this review, we searched the MEDLINE database, using MeSH terms '^{177}Lu-PSMA-617 [Supplementary Concept]' and '^{177}Lu-DKFZ-PSMA-617"[Supplementary Concept]', yielding 89 articles before applying the exclusion criteria. Boolean operators (AND, OR, NOT) were used to improve the search process and to exclude studies based on the following exclusion criteria. Reviews articles, letters, and case reports were excluded. Articles where animal and in-vitro testing were employed rather than human patients were also excluded. Portuguese and English were the preferred languages, with articles available exclusively in another language excluded. Regarding time of publication, no restrictions were applied. The reviewers also read the abstract and the main text briefly in order to discard studies that didn't present relevant information, as well as studies about types of PSMA other than PSMA-617 and PSMA-I&T. This search strategy, which can be summarized in the flowchart below (Figure 1), resulted in a selection of 25 articles.

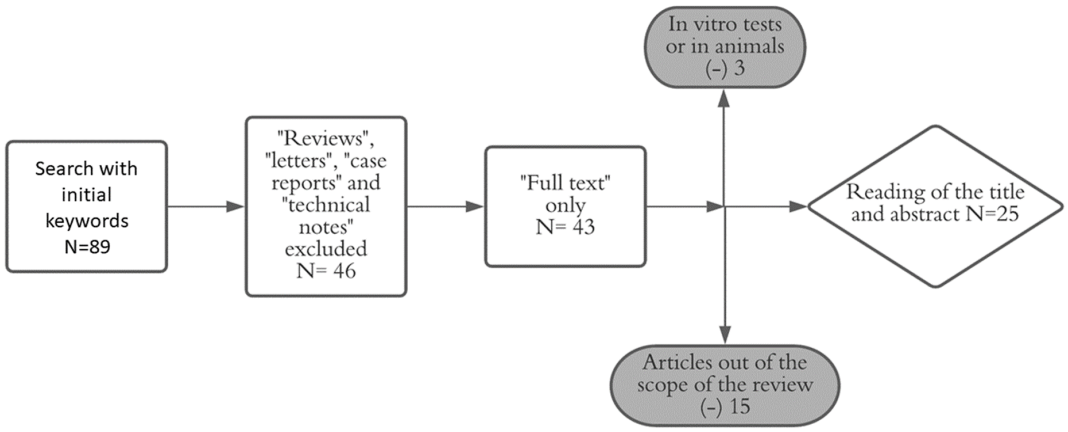

Figure 1. Search strategy flowchart

Risk of Bias assessment

Conflicts of interest and sources of funding: none declared.

Data extraction and statistical analysis

Data regarding effectiveness of treatment, dosimetry and safety concerns was collected from the studies. Effectiveness was measured in terms of overall survival (OS), percentage of patients who experienced >50% PSA decline, as well as the percentage of patients who experienced any PSA decline. Dosimetry analysis was measured in terms of dose of radiation received by the tumor and organs. Safety was evaluated in terms of occurrence of side effects. Data considered important by the reviewers which did not fit these criteria were presented in narrative form.

RESULTS

Literature Search

Initial search using the initial keywords yielded 89 articles. Forty-three were excluded for being reviews, case reports, letters or technical notes. Three were excluded as full text was not available. Three were excluded for being comprised of animal or in-vitro testing. Upon reading of the title and abstract, 15 articles were excluded for being out of the review's scope, with the remaining 25 articles being chosen for this review[6-20].

All articles are fairly recent. They span a period of roughly 5 years with the oldest being published online on July 31, 2015, and the most recent on June 01, 2020. Of the 25 articles, 16 were written by researchers in Germany, where many of the medical centers which pioneered the technique are located; The most recent literature is more geographically diverse. Most of the studies were retrospective rather than prospective, which may be a source of bias in the outcomes reported.

A summary of the characteristics of reviewed articles is available in Table 1.

Table 1. Summary of reviewed articles

Title	Date of publication	Country	Authors	Type of publication	Objective	Conclusions	Therapy
Pre-therapeutic dosimetry of normal organs and tissues of ^{177}Lu-PSMA-617 prostate-specific membrane antigen (PSMA) inhibitor in patients with castration-resistant prostate cancer	31/07/2015	Turkey	Kabasakal L, et al.[20]	Retrospective study	"The aim of the present study was to estimate the pretreatment radiation doses in patients who will undergo radiometabolic therapy using a tracer amount of ^{177}Lu-labeled PSMA ligand."	"Our first results suggested that ^{177}Lu-PSMA-617 therapy seems to be a safe method. The dose-limiting organ seems to be the parotid glands rather than kidneys and bone marrow. The lesion radiation doses are within acceptable ranges; however, there is a substantial individual variance so patient dosimetry seems to be mandatory."	One dose, with ^{177}Lu-PSMA-617 activity ranging from 185 to 210 MBq (4–4.6 nmol of the ligand) with a mean of 192.6± 11.0 MBq (4.1±0.2 nmol of the ligand).
^{177}Lu-Labeled Prostate-Specific Membrane Antigen Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: Safety and Efficacy	21/01/2016	Germany	Baum RP, et al.[19]	Retrospective study	We analyzed the safety and efficacy of the ^{177}Lu-labeled DOTAGA-based PSMA ligand 177Lu-DOTAGA-(I-y)fk(Sub-KuE) (177Lu-PSMA) in a larger cohort of patients with mCRPC. The endpoints of our analysis, which was performed in correlation with kinetics and dosimetry, were safety, objective response, progression-free survival, and overall survival.	^{177}Lu-PSMA radioligand therapy for end-stage progressive mCRPCis safe and effective. The avidity of the tumor target that defined the achievable tumor dose was demonstrated before therapy with 68Ga-PSMA PET/CT and a theranostic approach. PET/CT was applied to monitor the tumor response and to guide decisions about further personalized treatment. This novel therapy achieved objective responses with minimal toxicity in patients whose prostate cancer had progressed despite all standard treatments.	Median dose of 5.76 GBq (range, 3.6–8.7 GBq). Patients underwent 125 cycles of ^{177}Lu-PSMA RLT between May 2013 and June 2015 (1 cycle for 16 patients, 2 cycles for 15 patients, 3 cycles for 17 patients, 4 cycles for 6 patients, and 5 cycles for 2 patients).
Therapeutic response and side effects of repeated radioligand therapy with ^{177}Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer	08/02/2016	Germany	Ahmadzadehfar H, et al.[18]	Retrospective study	"In the current study, we retrospectively analyzed the side effects and response rate in 24 patients who received up to two cycles of therapy with ^{177}Lu-PSMA."	"^{177}Lu-PSMA is a safe treatment option for metastatic PC patients and has a low toxicity profile. A positive response to therapy in terms of decline in PSA occurs in about 70% of patients."	2 cycles of PSMA RLT, mean of 6.0 GBq (range 4.1 – 7.1 GBq)

continue

Table 1. Summary of reviewed articles *continuation*

Title	Date of publication	Country	Authors	Type of publication	Objective	Conclusions	Therapy
Lacrimal Glands May Represent Organs at Risk for Radionuclide Therapy of Prostate Cancer with [^{177}Lu]DKFZ-PSMA-617	26/02/2016	Germany	Hohberg M, et al.[17]	Retrospective study	"The aim of this study was to perform image-based absorbed dose calculation for critical organs during the first cycle of [^{177}Lu]DKFZ-PSMA-617 therapy in a small cohort of patients with metastatic prostate cancer."	Absorbed organ doses of [^{177}Lu]DKFZ-PSMA-617 therapy are not likely to be critical for kidneys, salivary glands, and the nasal mucous membrane. The lacrimal glands may represent the dose-limiting organs. Whole-body scintigraphy appears sufficient for dose estimation, but late measurements are mandatory, if accurate dose calculation is required.	One dose of [^{177}Lu] DKFZ-PSMA-617. 5.52 GBq (SD = 156 MBq), range from 5.28 to 5.77 GBq
Evaluation of radiation safety in ^{177}Lu-PSMA therapy and development of outpatient treatment protocol	18/04/2016	Turkey	Demir M, et al.[14]	Retrospective study	The study aims to measure the safety of an outpatient treatment protocol (a.k.a hospitalization not required). Thus, the study evaluates the radiation dose given off by the patient at different distances from him/her, and the dose absorbed by medical staff and caregivers	"^{177}Lu-PSMA therapy seems to be well tolerated for patients suffering from prostate cancer and it is considered to be an excellent candidate for outpatient protocol. Our study shows that after approximately 5h, the dose rate decreases below the determined threshold of 30 μSv h−1 and after 6h degrades to 20 μSv h−1. In addition, radiation exposure of the caregivers remains below the standard limit of 5 mSv, supporting the possibility of adopting outpatient protocol for this kind of therapy."	1 cycle of 7400MBq
Radioligand Therapy With ^{177}Lu-PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer	01/07/2016	Germany	Rahbar K, et al.[15]	Retrospective study	"The aim of this study was to evaluate tumor response, adverse effects, and survival in patients undergoing radioligand therapy with ^{177}Lu-PSMA-617."	Results from 50 therapies show that radioligand therapy with ^{177}Lu-PSMA-617 is effective and well tolerated and seems to increase overall survival. A future randomized controlled prospective study will be necessary to confirm these results.	2 therapies. Dose at first therapy was 5.92 ± 0.44 GBq. Dose at second therapy was 5.86 ± 0.73 GBq
Delayed response after repeated ^{177}Lu-PSMA-617 radioligand therapy in patients with metastatic castration resistant prostate cancer.	01/09/2016	Germany	Rahbar K, et al.[8]	Retrospective study	The objective was to analyse the PSA response of treatment with 3 cycles of 177Lu-PSMA-617	Data showed a significant response to ^{177}Lu-PSMA-617 treatment, and a delayed response due to a phenomena known as "PSA-flare"	3 cycles of RLT with Lu-PSMA (mean administered activity: 6.016 ± 0.543 GBq) every 8 weeks
Predictors of Response to Radioligand Therapy of Metastatic Castrate-Resistant Prostate Cancer with ^{177}Lu-PSMA-617	01/09/2016	Germany	Ferdinandus J, et al.[13]	Retrospective study	"In this study, we evaluated the effect of different pretherapeutic parameters on the therapeutic response measured by prostate-specific antigen (PSA) 2 mo after RLT."	"A PSA decline of more than 50% was observed significantly more in patients without a regular need for analgesics" Other factors, however, seem to have affected PSA decline if we consider any PSA decline in the analysis. These factors were: a higher platelets count, high C-reactive protein (CRP) level, younger age, higher Gleason score, and a regular need for pain medication, all of which affect PSA decline negatively (i.e. it undermines tumor response). Additionally, there was no correlation between SUV and PSA decrease.	One cycle, average of 6GBq

Table 1. Summary of reviewed articles *continuation*

Title	Date of publication	Country	Authors	Type of publication	Objective	Conclusions	Therapy
Response and Tolerability of a Single Dose of ^{177}Lu-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: A Multicenter Retrospective Analysis	01/09/2016	Germany	Rahbar K, et al.[16]	Retrospective study	The aim of this retrospective study was to evaluate the response to and toxicity of this novel therapeutic option in a large cohort of metastatic castration-resistant prostate cancer (mCRPC) patients,who were treated with a single dose of ^{177}Lu-PSMA-617 as salvage therapy	This retrospective multicenter analysis suggested that radioligand therapy with ^{177}Lu-PSMA-617 is safe and well tolerated and has a considerable effect on PSA level in patients with advanced mCRPC.	1 dose of therapy, mean dose of 5.9±0.5 GBq.
Radiation Dosimetry for ^{177}Lu-PSMA I&T in Metastatic Castration-Resistant Prostate Cancer: Absorbed Dose in Normal Organs and Tumor Lesions	22/09/2016	Germany	Okamoto S, et al.[12]	Retrospective study	"The purpose of this study was to estimate the absorbed doses for ^{177}Lu-PSMA I&T in normal organs and in tumor lesions in a considerable number of patients with mCRPC undergoing up to 4 cycles with a reference activity of 7.4 GBq. In addition, it aimed to investigate the relationship of pretherapeutic SUV of Glu-NH-CO-NH-Lys-(Ahx)-[^{68}Ga(HBEDCC)] (^{68}Ga-PSMA-HBED-CC) PET and subsequently achieved tumor-absorbed dose and tumor response by PET."	"Organ- and tumor-absorbed doses for ^{177}Lu-PSMA I&T for RLT are comparable to recent reports using the same ligand as well as ^{177}Lu-PSMA-DKFZ-617. The kidneys represent the critical organ, with a mean absorbed dose of 0.72 Gy/GBq. Kidney-absorbed dose is relatively similar across different studies and is constant across several cycles in the same patient. When established dose limits from radiation oncology are used, up to 40 GBq of ^{177}Lu-PSMA I&T appear feasible, with limited risk of radiation-induced side effects on normal organs given the average life expectancy for mCRPC patients. The preliminary correlation between pre therapeutic SUV and absorbed tumor dose emphasizes the need for initial PSMA ligand PET imaging for appropriate patient selection. Nevertheless, more data need to be collected from larger series to confirm and validate these initial findings."	"The mean applied activity for all cycles was 7.3 6 0.30 GBq (range, 6.47–7.83 GBq), 7.3 6 0.32 GBq (range, 6.47–7.78 GBq) for the first cycle, 7.3 6 0.34 GBq (range, 6.47–7.73 GBq) for the second cycle, 7.5 6 0.22 GBq (range, 7.30–7.83 GBq) for the third cycle, and 7.3 6 0.24 GBq (range, 6.95–7.60 GBq) for the fourth cycle."
Preliminary experience with dosimetry, response and patient reported outcome after ^{177}Lu-PSMA-617 therapy for metastatic castration-resistant prostate cancer	24/09/2016	Germany	Fendler WP, et al.[11]	Retrospective study	We aimed to evaluate dosimetry, safety and efficacy of ^{177}Lu-PSMA-617 radioligand therapy (RLT) in patients with metastatic castration-resistant prostate cancer (mCRPC).	^{177}Lu-PSMA-617 therapy proved safe and indicated promising response rates for both objective and patient-reported outcomes in our small group of mCRPC patients"	Fifteen patients each received two cycles of 3.7 GBq (n = 5) or 6.0 GBq (n= 10) ^{177}Lu-PSMA-617 at an eight to ten weeks interval.
German Multicenter Study Investigating ^{177}Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients	20/10/2016	Germany	Rahbar K, et al.[6]	Retrospective study	Initiated by the German Society of Nuclear Medicine, a retrospective multicenter data analysis was started in 2015 to evaluate efficacy and safety of ^{177}Lu-PSMA-617 in a large cohort of patients.	The present retrospective multicenter study of ^{177}Lu-PSMA-617 RLT demonstrates favorable safety and high efficacy exceeding those of other third-line systemic therapies in mCRPC patients. Future phase II/III studies are warranted to elucidate the survival benefit of this new therapy in patients with mCRPC.	Total of 248 therapy cycles; 1–4 therapy cycles per patient and an activity range of 2–8 GBq per cycle.

Table 1. Summary of reviewed articles *continuation*

Title	Date of publication	Country	Authors	Type of publication	Objective	Conclusions	Therapy
^{177}Lu-PSMA-617 radioligand therapy and outcome in patients with metastasized castration-resistant prostate cancer	17/06/2017	Germany	Bräuer A, et al.[10]	Retrospective study	The aim of this study was to evaluate the overall survival (OS) and to identify parameters predicting outcome in mCRPC patients treated with ^{177}Lu-PSMA-617.	A PSA decline after the first cycle of ^{177}Lu-PSMA-617 and an initial ALP level <220 U/L were predictors of a longer OS in patients with end-stage mCRPC. An ALP level <220 U/L was additionally associated with a longer PPFS.	159 cycles (median 3 cycles, range 1–7) of ^{177}Lu-PSMA-617 (median dose 6.11 GBq, IQR 5.9–6.3 GBq).
PSMA targeted RLT in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/ or enzalutamide. A retrospective analysis of overall survival	12/10/2017	Germany	Rahbar K, et al.[9]	Retrospective study	"Our aim was to evaluate overall survival and parameters prognosticating longer survival in a large and homogeneous group of patients treated with ^{177}Lu-PSMA-617 radioligand therapy with heavily pretreated advanced metastatic castration resistant prostate cancer."	^{177}Lu-PSMA-617 RLT is a new and effective therapeutic and seems to prolong survival in patients with advanced mCRPC pretreated with chemotherapy, abiraterone and/or enzalutamide. The effect on survival is even greater in patients already responding to the first cycle of the therapy, especially if a PSA decline ≥20.87% occurs.	The median administered dose was 6.1 GBq (IQR 5.9–6.3) and median cumulative injected activity in each patient was 18.8 GBq (IQR 12.9–24.75). A median of three cycles of ^{177}Lu-PSMA-617 RLT were administered (range one to eight cycles).
Relevant tumor sink effect in prostate cancer patients receiving ^{177}Lu-PSMA-617 radioligand therapy	15/12/2017	Germany	Fils C, et al.[7]	Retrospective study	"In this study a correlation between total tumor volume (TTV) and measured kidney dose as well as salivary glands (SG) uptake in ^{177}Lu-PSMA-617 therapy was evaluated."	The inverse correlation between TTV/Kidney and SG uptake("sink effect") supported the hypothesis that in ^{177}Lu-PSMA-617 therapy an individualized treatment activity based on TTV could be beneficiary	First cycle administered activity for each patient for therapy was approximately 6.0 GBq ^{177}Lu-PSMA-617 (range 5.7 – 6.6 GBq; average 6.1 GBq).
Outcome and safety of rechallenge [^{177}Lu]Lu-PSMA-617 in patients with metastatic prostate cancer	01/11/2018	Germany	Yordanova A, et al.[23]	Retrospective study	"We aimed to assess the outcome and safety of rechallenge PSMA-RLT in patients with progressive prostatic cancer who previously benefited from this therapy."	Rechallenge prostate-specific membrane antigen (PSMA) therapy has an acceptable safety profile. The majority of the retreated patients benefited from the rechallenge therapy. Patients who showed a biochemical response achieved a longer OS compared to patients who did not respond. The median OS was significantly longer in patients after rechallenge PSMA-RLT than in patients who received only baseline PSMA-RLT.	A total of 30 patients who were initially treated with a median of 3 cycles (range 1–5) of PSMA-RLT and were eventually retreated after a median of 6 months (range 2–26). Each patient received a median of 3 (range 1–6) rechallenge cycles. The median injected activity was 6.1 GBq per cycle (range 3.8–6.7 GBq), followed by a 1000-ml infusion of 0.9% NaCl solution.
Treatment Outcome, Toxicity, and Predictive Factors for Radioligand Therapy with ^{177}Lu-PSMA-I&T in Metastatic Castration-resistant Prostate Cancer.	01/06/2019	Germany	Heck M, et al.[26]	Retrospective study	"The objective of this study is to report our clinical experience with RLT using ^{177}Lu–labeled PSMA-I&T".	In conclusion, RLT with ^{177}Lu-PSMA-I&T showed mild toxicity and good antitumor activity in a subgroup of latestage mCRPC patients. A PSA decline of 50% under RLT within 12 wk was associated with longer cPFS and OS. A subgroup analysis identified an association of visceral metastasis at baseline and rising LDH with worse treatment outcome. In these patients, alternative treatment options need to be considered.	A total of 100 patients were treated under acompassionate use protocol with a total number of 319 cycles (median two cycles, range 1–6). The ^{177}Lu-PSMA-I&T was given 6–8 weekly with an activity of 7.4 GBq up to six cycles.

Table 1. Summary of reviewed articles *continuation*

Title	Date of publication	Country	Authors	Type of publication	Objective	Conclusions	Therapy
Effect of External Cooling on ^{177}Lu-PSMA Uptake by the Parotid Glands	01/03/2019	Turkey	Yilmaz B, et al.[24]	Prospective study	The current study aimed to show the effect of external cooling with ice packs on ^{177}Lu-PSMA-617 uptake by the parotid glands (PGs).	External cooling does not reduce uptake of ^{177}Lu-PSMA-617 by the PGs.	19 (mean age, 72.9 y; range, 62–81 y). One hour before the initiation of PRLT, 500 mL of intravenous hydration with saline was started. At the same time, frozen ice packs, covered with a dry towel, were affixed over the right PG of each patient. The ice packs were applied without cessation until 4 h after the treatment had ended (;5 h). The ice packs were replaced with fresh ones every 30 min. ^{177}Lu-PSMA-617 (mean, 5.3 6 14.6 GBq; range, 3.7–7.7 GBq), diluted in 100 mL of physiologic saline was administered slowly in an intravenous infusion for over 15–20 min. After termination of the infusion, all patients received intravenous hydration (1,000 mL of 0.9% NaCl;flow, 250 mL/h) for 4 h.
Early Experience of Rechallenge ^{177}Lu-PSMA Radioligand Therapy After an Initial Good Response in Patients with Advanced Prostate Cancer	01/05/2019	Germany	Gafita A, et al.[25]	Retrospective study	Our aim was to retrospectively evaluate the feasibility of rechallenge ^{177}Lu-prostate-specific membrane antigen (^{177}Lu-PSMA) radioligand therapy	In a small patient cohort with an initial excellent response, ^{177}Lu-PSMA rechallenge is still active, with lower efficacy and higher toxicity.	Eight patients underwent a median of 2 (range: 1–4) cycles of rechallenge with ^{177}Lu-PSMA for imaging and therapy
First Experience With ^{177}Lu-PSMA-617 Therapy for Advanced Prostate Cancer in the Netherlands	01/06/2019	Netherlands	van Kalmthout L, et al.[27]	Restrospective study	The present study summarizes the first experience with ^{177}Lu-PSMA-617 (177Lu-PSMA) treatment in metastatic castration-resistant prostate cancer (PCa) in our institution.	"These results confirm the favorable safety and efficacy profile of ^{177}Lu-PSMA, even up to 6 treatment cycles ..."	Thirty patients with advanced PCa received therapy cycles with 6 GBq ^{177}Lu-PSMA (median, 4 cycles; range, 1–6)
Clinical Outcomes of ^{177}Lu-PSMA Radioligand Therapy in Earlier and Later Phases of Metastatic Castration-Resistant Prostate Cancer Grouped by Previous Taxane Chemotherapy	01/07/2019	Australia	Barber TW, et al.[28]	Retrospective study	This retrospective study evaluates clinical outcomes of ^{177}Lu-PRLT in earlier and later phases of mCRPC grouped by previous taxane chemotherapy.	^{177}Lu-PRLT is a promising therapy in mCRPC with encouraging outcomes and minimal associated toxicity seen in both our T-naıve and heavily pretreated patient cohorts.	A total of 167 patients were included: 83 were T-pretreated and 84 were T-naive. The entire patient cohort received a median of 3 ^{177}Lu-PRLT cycles (range, 1–10), with an average of 6.3 GBq/cycle (range, 3.6–8.6 GBq) and a median total administered activity of 16.2 GBq (range, 3.9–56.5 GBq)
Efficacy and Safety of ^{177}Lu-PSMA-617 Radioligand Therapy in Metastatic Castration-Resistant Prostate Cancer Patients.	01/01/2020	India	Yadav MP, et al.[29]	Prospective study	The aim of this study was to evaluate the efficacy and safety of ^{177}Lu-PSMA-617 radioligand therapy in metastatic castration-resistant prostate cancer (mCRPC).	^{177}Lu-PSMA-617 radionuclide therapy is a safe and effective approach to the treatment of mCRPC patients	Patients received 1 to 7 cycles of RLT, median activity administered per cycle was 3.7 to 8 GBq

Table 1. Summary of reviewed articles *continuation*

Title	Date of publication	Country	Authors	Type of publication	Objective	Conclusions	Therapy
Posttherapeutic Critical Organ Dosimetry of Extensive ^{177}Lu-PSMA Inhibitor Therapy With Metastatic Castration-Resistant Prostate Cancer: One Center Results	01/04/2020	Turkey	Özkan A, et al.[30]	Retrospective study	"...to estimate the absorbed radiation doses for critical organs (eg, kidneys, parotid glands, submandibular glands, and lacrimal glands) of patients treated with 4 to 6 cycles by ^{177}Lu-PSMA inhibitor RLT, retrospectively, and to evaluate the findings extensively in order to determine the critical organ radiation-absorbed limitations and the number of prospective RLT."	"Patient-specific dosimetry is very important in radionuclide therapy being a deterministic factor on the target organ risks and optimal therapy doses. However, for patient groups, which have short/ very short survival rates, increased tolerated dose limits might be necessary. As seen in this study, in extensive ^{177}Lu-PSMA inhibitor RLT, some of the exceeding dose limits for target organs would not cause a serious medical problem in a 14 to 40 months' time course."	Patients received 4 to 6 cycles of RLT. The mean ^{177}Lu-PSMA activity injected to the patients was 6.48 ± 0.55 GBq (175 ± 15 mCi)
TheraP: A randomised phase II trial of ^{177}Lu-PSMA-617 (LuPSMA) theranostic versus cabazitaxel in metastatic castration resistant prostate cancer (mCRPC) progressing after docetaxel: Initial results (ANZUP protocol 1603).	01/05/2020	Australia	Hofman MS, et al.[31]	Clinical trial	To assess the activity and safety of cabazitaxel chemotherapy vs that of treatment with ^{177}Lu-PSMA-617, a novel radiolabelled small molecule that binds with high affinity to prostate-specific membrane antigen (PSMA), in men with metastatic castration-resistant prostate cancer (mCRPC) who have received prior docetaxel treatment	In men with docetaxel-treated mCRPC, LuPSMA was more active (PSA50-RR) than cabazitaxel with relatively fewer G3-4 AEs and PSA-PFS favoring LuPSMA.	Men with mCRPC, and imaging with ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT that confirmed high PSMA-expression and no sites of FDG-positive/PSMA-negative disease, were randomly assigned (1:1) to LuPSMA (6-8GBq q6weeks up to 6 cycles) vs cabazitaxel (20mg/m2 q3weeks up to 10 cycles)
Long-Term Follow-up and Outcomes of Retreatment in an Expanded 50-Patient Single-Center Phase II Prospective Trial of ^{177}Lu-PSMA-617 Theranostics in Metastatic Castration-Resistant Prostate Cancer.	01/06/2020	Australia	Violet J, et al.[32]	Clinical trial	To report the "longer-term outcomes (of the LuPSMA trial) , including a 20-patient extension cohort and outcomes of subsequent systemic treatments after completion of trial therapy"	"This expanded 50-patient cohort of men with extensive prior therapy confirms our earlier report of high response rates, low toxicity, and improved quality of life with ^{177}Lu-PSMA radioligand therapy. On progression, rechallenge ^{177}Lu-PSMA demonstrated higher response rates than other systemic therapies"	Fifty patients with PSMA-avid metastatic castration-resistant prostate cancer who had progressed after standard therapies received up to 4 cycles of ^{177}Lu-PSMA every 6 weeks. The mean administered radioactivity was 7.5 GBq/cycle

Primary Outcomes

Dosimetry

Most of the articles evaluated apply approximately 6.0 GBq of radiation overall for ^{177}Lu-PSMA-617 therapy. One of the most important aspects of dosimetry is in determining the maximum dose that can be applied to patients in radiotherapy without causing excessive radiation exposure to healthy organs. Based on dosimetric data for radiation absorbed by healthy organs (Table 2), the treatment practices adopted seem to be safe and below the threshold for toxicity. Average dose absorbed by each individual kidney ranged from 0.5-0.88 Gy/GBq, while salivary glands received an average of 0.55-1.34 Gy/GBq. There are no permanent clinical complications in these two organs as a consequence of RLT (see safety section for more details)[16]. The lacrimal glands are major absorbers of radiation, with absorbed dose ranging from 2.28 - 3.8 Gy/GBq[12,18], but this doesn't seem to translate into clinical consequences, given the relatively low occurrence of xerophthalmia.

Table 2. Dosimetry

Author	Median absorbed dose (whole body)	Mean absorbed dose (Kidneys)	Mean absorbed dose (Salivary Glands)	Mean absorbed dose (Lacrimal Glands)	Mean absorbed Dose (Bone marrow)	Mean absorbed Dose (Tumor)
Fendler WP[11]	n/a	(right/left 0.6±0.2/0.5±0.3 Gy/GBq).	(1.0±0.6Gy/GBq)	n/a	(0.002 ±0.005Gy/GBq)	6.1±4.9 Gy/GBq
Okamoto S[12]	0.06 ± 0.03 (0.06 Sv/GBq).	0.72 ± 0.21 (0.72 Gy/GBq)	0.55 ± 0.14 (0.55 Gy/GBq)	3.8 ± 1.4 (3.8Gy/GBq)	n/a	3.2 ± 2.6Gy/GBq
Hohberg M[17]	63.0 (μGy/MBq)	0.53 (mGy/ MBq)	0.72(mGy/MBq)	2.82 mGy/MBq	n/a	n/a
Baum RP[19]	0.02±0.01 (mGy/MBq)	0.8±0.4 (mGy/ MBq)	1.3±2.3 (mGy/ MBq) (Parotid glands)	n/a	n/a	3.3±14 (mGy/ MBq)
Kabasakal L[20]	n/a	0.88±0.40 mGy	1.17±0.31 mGy (Parotid glands)	n/a	n/a	n/a
Yilmaz B[24]	One dose of 177Lu-PSMA-617 (mean activity of 5.3 ± 14.6 GBq; range, 3.7–7.7 GBq),					
Özkan A[30]	Patients received 4 to 6 cycles of RLT. The mean 177Lu-PSMA activity injected to the patients was 6.48 ± 0.55 GBq (175 ± 15 mCi)	n/a	0.7 ± 0.24 Gy/ GBq	1.34 ± 0.78 Gy/ GBq (Parotid glands) // 0.94 ± 0.45 Gy/ GBq (Submandibular glands)	2.28 ± 1.29 Gy/ GBq	n/a

Safety

Generally speaking, there are few severe side effects of treatment with ^{177}Lu-PSMA-617. The most frequently reported one was mild to moderate xerostomia, usually reversible[6,15,16,18,19,26,27,29,30]. This can be explained by radiopharmaceutical uptake by salivary glands, as pointed out in dosimetry. Other reported side effects include mild xerophthalmia[10], fatigue[10,18,26,27,29] and nausea that responds well to medication[11,15,18,29]. ^{177}Lu-PSMA-617 did not lead to more severe forms of nephrotoxicity (grades 3-4), as measured by creatinine blood levels and glomerular filtration rate[10,26,27,29,30], despite the kidney being one of the organs which most receives radiation.

Severe (grade 3-4) adverse hematological events were reported, such as leucopenia[6,10,26-28], thrombocytopenia[6,10,26,28,29], and, the most frequent one, anemia[6,10,26-29] .This is most likely a consequence of the disease, as rates of such events are higher amongst patients treated with placebo, chemotherapy or immunotherapy[6]. Preliminary results of the TheraP clinical trial comparing RLT with cabazitaxel treatment reveal a higher occurrence of grade III/IV adverse events in the cabazitaxel cohort (49% vs. 32%) and discontinuation due to treatment toxicity (3% vs. 1%) compared to RLT-treated patients[31]. Further evidence that treatment with ^{177}Lu-PSMA-617 doesn't seem to increase the occurrence of adverse hematological events is the fact that there is no statistically significant change in white blood cell count, hemoglobin and platelet after cycles of RLT[15,16,19]. Some studies reported gastrointestinal symptoms, such as diarrhea or vomiting[26,29].

Most studies are retrospective and don't have control groups with which the frequency and severity of side effects can be compared with, which limits their predictive power. However, as exposed in the paragraph above, one clinical trial resulted in ^{177}Lu-PSMA-617 RLT having fewer side effects than cabazitaxel treatment[31] .It is difficult to know whether long term treatment with ^{177}Lu-PSMA-617 can lead to more severe side effects, as the lifespan of both treated and untreated mCRPC patients is short, though one cohort of 50 patients with an extended follow-up period of 31.4 months (median) showed long-term toxicity results consistent with those achieved in the remaining literature[32].

Efficacy

Treatment with ^{177}Lu-PSMA-617 is significantly correlated with a decrease in PSA levels[9-11,15,16,18,19,26-29,31] and tumor regression, that, according to preliminary data from the TheraP clinical trial, is superior to the result obtained from a cabazitaxel-treated control group (66% vs. 37% of patients with PSA decline >50%, $p<0.001$). The percentage of patients who experienced any PSA decline ranged from 64%-91% between studies. The percentage of patients who experienced PSA decline >50% ranged from 31%-60%. This spread can be in part attributed to the difference in the number of RLT cycles, as there is

a positive correlation between the number of cycles and PSA decline[15]. Percentage of patients which experienced any PSA decline ranged from 59%-67% and percentage of patients which experienced PSA decline >50% ranged from 31%-33% when only the first cycle of therapy is taken into consideration[9,15,16,29] and from 68.2%-79.1% and 41.6%-60% respectively after 2 cycles of RLT[11,15,18].

^{177}Lu-PSMA-617 therapy is correlated with improved OS (Overall Survival) and cPFS (clinical progression-free survival). Comparison of patients receiving the treatment with a historic cohort of patients receiving only BSC (Best supportive care) revealed that the median OS of the patients treated with ^{177}Lu-PSMA-617 therapy was 29.4 weeks long, while the median OS of the BSC cohort was only 19.7 weeks long[15]. Similarly, another study suggests that ^{177}Lu-PSMA-617 RLT results in a 2.5 month increase in OS compared to placebo[29]. OS is also significantly correlated with change in PSA levels, with a PSA decline after the first cycle being associated with improved OS[9,10,26].In one study, multivariate analysis showed that PSA decline of over 50% is a predictor of improved OS and cPFS[(4)].

Rechallenge therapy

^{177}Lu-PSMA rechallenge therapy is defined RLT undertaken in patients that initially had an effective response after treatment with ^{177}Lu-PSMA RLT and experienced disease progression afterwards. Since ^{177}Lu-PSMA RLT is a last-line therapeutic in advanced PC, only a few other recourses can be employed (e.g. chemotherapy with cabazitaxel). However, there is evidence of high response rates, low toxicity and improved quality life after a second course of RLT in these patients, compared to other systemic therapies[32].

Two retrospective studies in 2018[23,25] and a phase II single-center prospective trial from 2020[32] attempted to measure toxicity, image response, PSA response, progression-free survival, overall survival[23,25,32] and patient-reported health-related quality of life[32].

All studies concluded that rechallenge therapy was beneficial, resulting in an increase in median OS compared to the group that only received one RLT course (p value <0,001), as well as a PSA decline of over 50% compared to pre-treatment levels in 25%[23], 37,5%[25] and 64%[5] of patients. In one study, PSA decline of at least 50% was significantly associated with longer OS and progression free survival[32]. Median OS was significantly shorter after a second course of treatment, demonstrating high response rates but less durable responses in this set of patients[32].

All studies used the Common Toxicity Criteria (CTC) to evaluate toxicity. There was only one report of grade 4 toxicity, and several grade 1-3 reports. However, when compared to systemic chemotherapy, rechallenge RLT had better chemical and quality of life outcomes, with less bone pain severity and interference in daily activities, as well as significant global health improvement[32].

These results indicate the enormous potential of ^{177}Lu-PSMA-617 in the rechallenge setting. While treatment response is less durable when compared to the initial treatment, it nevertheless yields high response rates, increase in quality of life and less toxicity when compared to other treatments[32].

DISCUSSION

All studies agree on the fact that treatment with ^{177}Lu-PSMA-617 leads to a reduction in PSA levels in most patients, though the exact percentage can vary between studies (64%-91%). Treatment is also correlated with significant PSA declines, with outcomes of decline >50% ranging from 31% - 60% of patients. While PSA kinetics is an imperfect surrogate for tumor progression or regression in low-risk men[21], there is indeed evidence that ^{177}Lu-PSMA-617 treatment improves OS significantly[22], meaning it can be a very effective weapon in treating prostate cancer.

While dosimetry data reveals that kidneys, salivary glands, and lacrimal glands absorb radiation, reported side effects such as xerostomia or xerophthalmia are generally uncommon and have mild to moderate intensity. There are few side effects exclusively attributable to ^{177}Lu-PSMA-617, mostly mild. It should be noted, however, that the way the studies were designed doesn't allow for the evaluation of long term health effects of exposure to ^{177}Lu-PSMA-617, as in most cases only up to three or four cycles of RLT were allowed. It is difficult to know whether this limited exposure can have long-term effects that persist for years, as mCRPC patients have short lifespans, though one study showed no toxic effects 2.5 years after treatment other than those already reported in the studies with shorter follow-ups. Knowing the extent or existence of such effects is crucial if ^{177}Lu-PSMA-617 therapy is to be expanded to patients with less advanced tumors in the future.

Because all patients studied have metastatic castration-resistant prostate cancer, there isn't direct evidence that treatment with ^{177}Lu-PSMA-617 can be used in patients with less advanced tumors, or how it can be compared with other treatments - such as androgen deprivation or chemotherapy. If ^{177}Lu-PSMA-617 is to be used in patients with other forms of prostate cancer, it is necessary to evaluate how it holds up with a different patient profile and how it can be used in combination with other therapies, for the patients that have this option.

There are important limitations to the studies available in the literature so far that impair our ability to understand the consequences of treatment with ^{177}Lu-PSMA-617. Unlike most treatments, which traditionally undergo phase I, II and III clinical trials before being put into the market, ^{177}Lu-PSMA-617 was initially offered as compassionate treatment for patients with mCRPC, who currently don't have any other robust therapeutic options

to choose from. Data collected from patients was then retrospectively analyzed to obtain information on efficacy and safety. As most studies analyzed were retrospective, quality of data suffers as a consequence. Even more importantly, a number of studies didn't include control groups. Preliminary data from the TheraP clinical trial shows ^{177}Lu-PSMA-617 to be more effective and less toxic than the cabazitaxel control group, a very encouraging result that is nevertheless still incomplete as of February 2021[31]. Therefore, while promising, ^{177}Lu-PSMA-617 can only become an accepted therapy once it goes through controlled clinical trials.

Two phase III trials are currently being conducted, the TheraP trial (https://clinicaltrials.gov/ct2/show/NCT03392428) comparing ^{177}Lu-PSMA617 Versus Cabazitaxel in Progressive mCRPC, and the VISION trial (https://clinicaltrials.gov/ct2/show/NCT03511664) assessing overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ^{177}Lu-PSMA-617 in addition to best supportive/best standard of care versus patients treated with best supportive/best standard of care alone.

CONCLUSION

^{177}Lu-PSMA-617 therapy has few side effects and is effective in slowing down tumor progression in patients with metastatic castration-resistant prostate cancer. However, these results should be validated by controlled clinical trials

Author's participation: All the work was done under the supervision of the professor *Marcelo Tatit Sapienza*, MD Phd. The authors *Lucca Paolo Hsu Helmich* and *Marcelo Augusto Magalhães de Arruda* leaded the selection of the articles, but all authors had participation in the discussion of eligibility criteria. Both *Lucca Paolo Hsu Helmich* and *Marcelo Augusto Magalhães de Arruda* read all the articles and did the extraction and selection of the information contained in the articles. The tables were made by *Lucca Paolo Hsu Helmich* and *Marcelo Augusto Magalhães de Arruda* and discussed with the other authors until it was in its final form. After the extraction of the data and discussion of the results the article was written in its final form by the authors *Lucca Paolo Hsu Helmich* and *Marcelo Augusto Magalhães de Arruda* and revised by the professor Marcelo Tatit Sapienza.

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