Review Article

The Clinical Management of Patients with Recurrent Prostate Cancer: Integrative Review

ABSTRACT

SAMPLE ABSTRACT: The ^{68}Ga-PSMA PET/CT precision increase in the Biochemical Recurrence (BR) cell detection brings new challenges in the patients clinical management, specially on RT. Although the RT treatment is a well established practice in 70% of the Prostate Cancer (PCa) patients, 30% to 40% of them show BR after the local Radiotherapy (RT). However, therapeutic innovations, modern imaging techniques and molecular characteristics advances are raising the survival time of recurrent PCa patients. Using target molecules and radiotracers combinations, it was possible to get promising results with radiopharmaceutical therapy directed to PMSA.

Aims: This study aims to analyze the new challenges in the clinical management of patients with recurrent PCa through the advent of ^{68}Ga-PSMA PET/CT imaging.

Study design: The bibliographic research of the published articles was realized on the electronic databases: PubMed. The article inclusion criteria, previously defined to the review were: articles in portuguese, spanish or english, between 2016 and 2023, with the abstract and full works online. Articles that were not related were excluded.

Place and Duration of Study: between 2016 and 2023.

Methodology: The method used was an integrative literature review, through the search for publications in journals indexed in the PubMed databases. 44 articles were identified, from which 30 were removed: 22 being diagnostic studies and 9 being equipment quality control studies. 14 works were selected for the final sample of the study. All of them using ^{68}Ga-PSMA PET/CT in the patient clinical management submitted to RT and 8 identified using other means.

Results: According to the European Association of Urology, BCR is the second of ten controversial areas in the management of patients with advanced PCa. Currently, the binding of the Gallium-68 radiotracer to the prostate-specific membrane antigen (PSMA) for Positron Emission Tomography (PET/CT 68Ga-PSMA) imaging in patients may allow for a more rational selection of subsequent ideal therapy, although PSMA is not overexpressed in all PCa cases. The use of ^{68}Ga-PSMA PET/CT and RT has shown promise in several studies for recurrent PCa. It is indeed emerging to increase sensitivity and change the treatment landscape. This is an active area of research that has a significant impact on the clinical management of patients, spanning from conventional techniques to advanced Stereotactic Body Radiotherapy (SBRT).

Conclusion: The presented data on this study collaborate with the 68Ga-PSMA PET/CT on the recurrent PCa patients, specially on the selection on to the target molecular therapy. It has become an active investigation, presenting new challenges on the conventional and Hypofractionated (HF) RT on SBRT techniques to the PCa treatment. As research and technology continue to advance, the use of PSMA and other specific markers for diagnosis and treatment is likely to become more refined and widespread. The use of ^{177}Lu-PSMA suggests that molecular targeted therapy is a promising area of development, potentially offering more effective and less invasive treatments for prostate cancer.

Keywords: Stereotactic Body Radiotherapy, Prostate neoplasms, PET-CT, PSA

1. INTRODUCTION

Using target molecules and radiotracers combinations, it was possible to get promising results with radiopharmaceutical therapy directed to PMSA in initial studies, according to Kratochwil et al.[1].

According to the American Cancer Society, 223.043 new cases of Prostate Cancer (PCa) were diagnosed in 2020 in the US. In Brazil, 65.840 new cases were expected by year between 2020 and 2022.In 2019, the Advanced Prostate Cancer Consensus Conference (APCCC) noted that the PCa biochemical recurrence (BR) after local therapy was the second most common. One of the ten controversial areas of advanced PCa patient management [2].

Although the RT treatment is a well established practice in 70% of the PCa patients, 30% to 40% of them show BR after the local RT [3]. However, therapeutic innovations, modern imaging techniques and molecular characteristics advances are raising the survival time of recurrent PCapatients [2].

The ^{68}Ga-PSMA PET/CT precision increase in the BR cell detection brings new challenges in the patients clinical management, specially on RT. The ^{68}Ga-PSMA PET/CT is a specific procedure, realized on nuclear medicine services using a radioactive tracker, positron emitter, linked to a molecule that has affinity with a specific structure, abundant on PCa cells [4].

The biggest advantage of the ^{68}Ga use on organic synthesis is its chemical characteristic of linking with chelating compounds. This property facilitates its annexation in complex molecules, like the peptides and the PMSA, which is a type II transmembrane and a protein that appears on most PCa clinically important. Its appearance increases in high risk tumors, metastatic and resistant to hormone therapy [5].

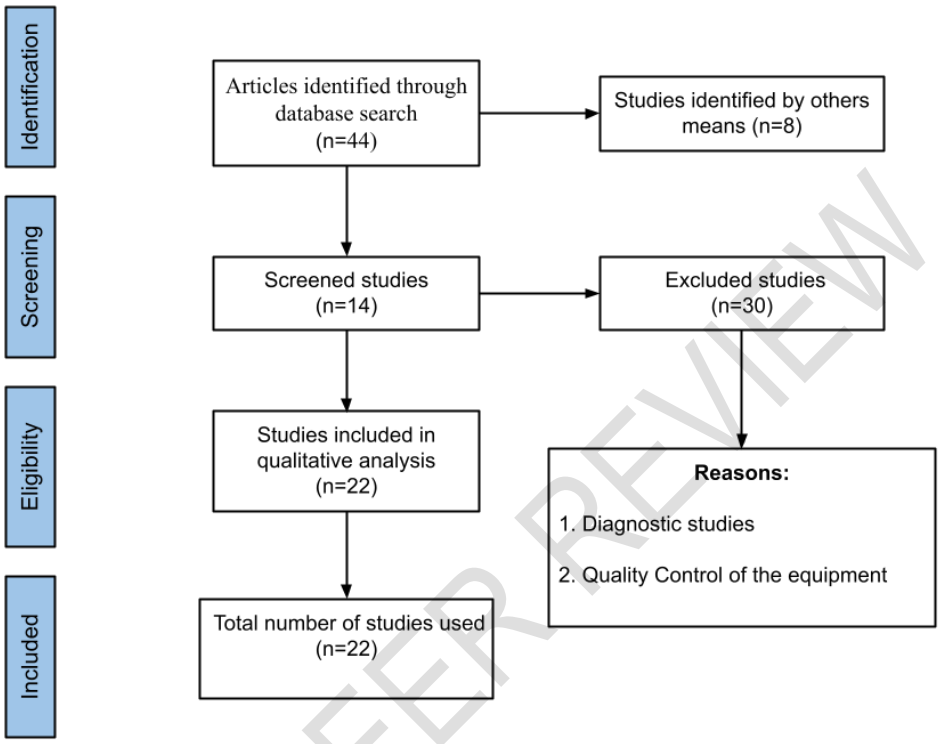
However, the appearance is little expressed in benign prostatic tissue or hyperplasic [6].

To the radiation oncologist, the challenge is to incorporate this technology efficiently in modern RT planning, as with the Stereotactic Body Radiation Therapy (SBRT) with hypofractionation treatments [3]. From an integrative review, the objective of this study is to analyze the scientific evidence on the use of ^{68}Ga-PSMA PET/CT in recurrent PCa patients submitted to SBRT.

2. MATERIALS AND METHODS

This review followed the steps suggested in the literature [7]. That being: selecting the main question, defining the criteria and eligibility (inclusion and exclusion), definition of the studies relevant information, evaluation of the findings, interpretation and synthesis of the found information. The bibliographic research of the published articles was realized on the electronic databases: PubMed. The article inclusion criteria, previously defined to the review were: articles in portuguese, spanish or english, between 2016 and 2023, with the abstract and full works online. Articles that were not related were excluded. The keywords “Stereotactic Body Radiotherapy”, “Prostate neoplasms", “*PET-CT", “PSA" were* connected by the boolean connector *“AND”*. 44 articles were identified, from which 30 were removed: 22 being diagnostic studies and 9 being equipment quality control studies. 14 works were selected for the final sample of the study. All of them using ^{68}Ga-PSMA PET/CT in the patient clinical management submitted to RT and 8 identified using other means. The search and selection process can be seen on Figure 1.

Fig. 1. Integrative review searching mechanism.



Source: Adapted from Page, et al. [8].

From the adaptation of an evaluation instrument [9], the article's synthesis was made. The data gathering searched for the following information: publication year; article title; author names; published periodic; utilized instruments e results found. This study analyzed the scientific productions on the evaluation of new challenges on the recurrent PCa patients submitted to RT with ^{68}Ga-PSMA PET/CT clinical management.

3. RESULTS

The research realized using the specified keywords resulted in a total of 17 scientific articles related to the chosen theme, which were selected to the study based on an initial review of its titles and abstracts.

On Table 1, are identified the data to extract the useful information needed for this investigation.

Table 1. Presentation of the selected articles from the specified identification to each article, as well as title, authors, year, conclusions.

n°	Author	Article Title	Conclusion
1	Kratochwil et al.[1]	Joint EANM/SNMMI procedure guideline for the use of ^{177}Lu-labeled PSMA-targeted radioligand-therapy (^{177}Lu-PSMA-RLT)	The objective of this study is to help the nuclear medicine professionals on the adequate patient for the treatment; on the treatment procedure realization and to comprehend the therapy consequences. Clinical follow-up, possible collateral effects management and response evaluation.
2	Gillessenet al.[2]	Management of Patients with Advanced Prostate Cancer: Report of the Advanced Prostate Cancer Consensus	Can help clinicians navigate controversial areas of advanced prostate management for which high-level evidence is sparse.
3	Bouchelouchee t al.[3]	PSMA PET and radionuclide therapy in prostate cancer	This PSMA “image and treat” strategy with radiolabeled PSMA ligands, has the potential to improve the treatment outcome of patients with PCa. PSMA as a target for imaging and therapy is paving the way for personalized medicine in PCa.
4	Afshar et al. [4]	Diagnostic performance of ^{68}Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients	Tumor detection is clearly associated with PSA level and ADT. Only a tendency for an association without statistical significance was found between higher GSC and a higher probability of a pathological PET/CT scan.
5	Slaoui et al. [5]	Pelvic salvage (SBRT) radiotherapy based on ^{68}Ga-PSMA PET/CT: About a case	^{68}Ga-PSMA PET/CT might be an interesting tool for early detection and RT guidance of small recurrences after radical prostatectomy for prostate cancer, delaying the use of systemic therapy.
6	Violet et al. [6]	Dosimetry of ^{177}Lu-PSMA-617 in Metastatic Castration-Resistant Prostate Cancer: Correlations Between Pretherapeutic Imaging and Whole-Body Tumor Dosimetry with Treatment Outcomes	Significant correlations between aspects of screening ^{68}Ga-PET/CT and tumor and normal tissue dose were observed, providing a rationale for patient-specific dosing.
7	Hope et al. [10]	Impact of ^{68}Ga-PSMA-11 PET on management in patients with biochemically recurrent prostate cancer	PET with ^{68}Ga-PSMA-11 resulted in a big change in the management in 53% of the biochemical recurrent patients. More studies are needed to investigate if the strategies of management based on PSMA result in better results for the patients.
8	Schwenck et al. [11]	Comparison of ^{68}Ga-labelled PSMA-11 and ^{11}C-choline in the detection of prostate cancer metastases by PET/CT	PET using ^{68}Ga-PSMA-11 showed a higher detection rate than ^{11}C-choline PET for lymph nodes as well as bone lesions.
9	Wondergem et al. [12]	Early lesion detection with ^{18}F-DCFPyL PET/CT in 248 patients with biochemically recurrent prostate cancer	The PET/CT ^{18}F-DCFPyL offers precocious detection of injuries in patients with BCR, even in PSA levels <0.5 ng/ml.

10	Couñago et al. [13]	Importance of ^{68}Ga-PSMA PET/CT in hospital practice. View of the radiation oncologist. PET/TC con ^{68}Ga-PSMA, importanciaen la prácticahospitalaria. Visión del oncólogoradioterápico	It may be said that the ^{68}Ga-PSMA PET/CT has become a decisive element to the decision making of the PCa, and its use has been established on the practical clinical routine in many European countries. However, the use of the PSMA as a target therapeutic with the ^{177}Lu-PSMA-617 has been shown to be very promising.
11	Lukka et al. [14]	Patient Reported Outcomes in NRG Oncology RTOG 0938, Evaluating Two Ultra Hypofractionated Regimens for Prostate Cancer	Based on the alterations on the intestinal and urinary tracts e on the toxicity (sharp and late), the regimen of 5 to 12 fractions are well tolerated. This ultra fractionated need to be compared with the current regimen of standard radiotherapy.
12	Marzec et al. [16]	^{68}Ga-PSMA-PET/CT-directed IGRT/SBRT for oligometastases of recurrent prostate cancer after initial surgery	The range between 0.1 and 0.2ng/ml was associated to the survival rate enhancement associated to Distance Metastasis Free Survival (DMFS) and could be used as a substitute for oligo metastasis after initial prostatectomy. Short term effects from the ablative Radiotherapy based in ^{68}Ga-PSMA-PET/CT showed an acceptable toxicity profile and favored biochemical response.
13	Patel et al. [18]	Stereotactic body radiotherapy for bone oligometastatic disease in prostate cancer	Hormone-sensitive patients showed the greatest benefit, with results similar to that published for oligometastatic pelvic nodal disease treated with SBRT.
14	Calais et al. [19]	^{68}Ga-PSMA-11 PET/CT Mapping of Prostate Cancer Biochemical Recurrence After Radical Prostatectomy in 270 Patients with a PSA Level of Less Than 1.0 ng/mL: Impact on Salvage Radiotherapy Planning	Post hoc analysis of ^{68}Ga-PSMA-11 PET/CT implied a major impact on SRT planning in 52 of 270 patients (19%) with PCa early BCR (PSA < 1.0 ng/mL).
15	de Bleser [20]	Metastasis-directed Therapy in Treating Nodal Oligo Recurrent Prostate Cancer: A Multi-institutional Analysis Comparing the Outcome, Toxicity of Stereotactic Body Radiotherapy, Elective Nodal Radiotherapy.	It is important to state that both SBRT and ENRT remain investigational approaches.
16	Júnior et al. [21]	Experiência de um ano com PET/CT ^{68}Ga-PSMA: aplicações e resultadosnarecidivabioquímica do câncerprostático.	The study shows the initial experience of PET/CT with ^{68}Ga-PSMA in a brazilian clinic during the time period of a year.
17	Scobioala et al. [22]	A treatment planning study comparing IMRT techniques and cyber knife for stereotactic body radiotherapy of low-risk prostate carcinoma	The CK (CyberKnife) provided lower homogeneity in the target volume, but higher values for most of the conformity indices compared to the IMRT (intensity-modulated).

Source: author's own construction (2023).

3.1. Biochemical Recurrance (BR) after local radiotherapy

The BR after local treatment of PCa, happens in about 30% to 40% patients and may represent isolated local failure or metastatic, routinely detected by the augment of the

specific prostatic antigen (PSA) and may be associated with a worst oncological quality [10,11].

The European Association of Urology (EAU), don't recommend a specific limit on the PSA as a limiar to recurrent PCa, but to evaluate the risk factors of each case and ponder on the other investigation results for the patient management to the subsequent treatment [2]. The prognostic factors are: time from the surgery to the BR, i. e., time of PSA duplication and local characteristics of the disease (surgical margin) [2].

However, the inherent limitation to the traditionally image methods as computed tomography (CT) and bone scintigraphy (BS), critical to the disease identification out of the planned field of surgery or radiotherapy that take to the PSA persistency and may influence in these patients management, as a delay on the subsequent treatment [2,3,12].

The incorporation of the ^{68}Ga-PSMA PET/CT exams have been used in recurrent recurring PCa patients, i. e., showed promising results in comparison to the conventional imaging techniques and may permit a more rational selection of subsequent therapy, although the PSMA isn't linked to all PCa [2,13].

The management of recurring PCa patients after the local therapy administration with healing intention is changing with the introduction of new and more sensible PSA tests and new imaging methods, particularly PET/CT associated with PSMA [2].

3.2. ^{68}Ga-PSMA PET/CT Imaging

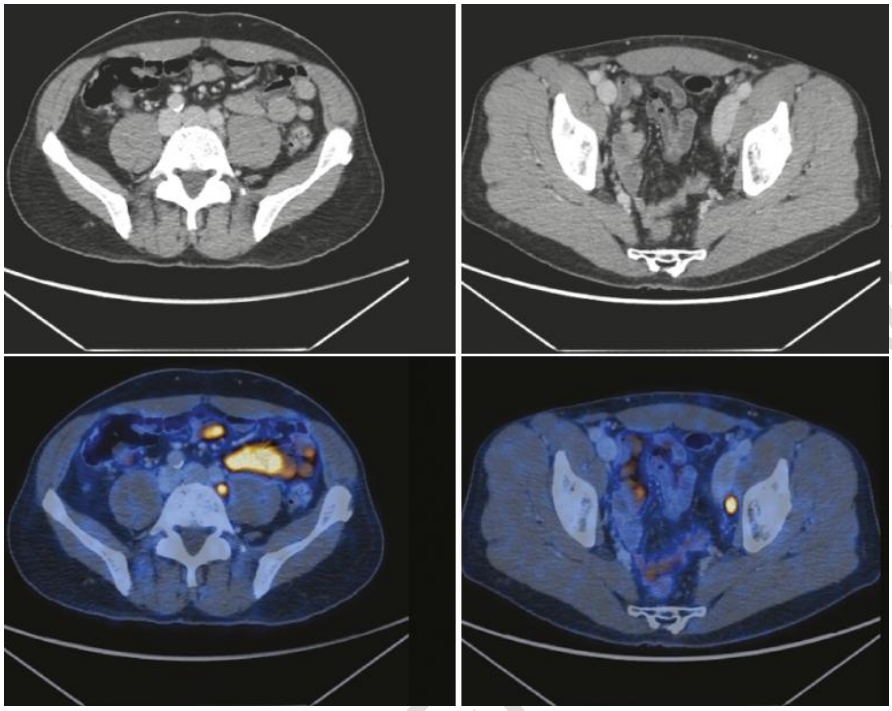
The incorporation in the Prostate Specific Membrane Antigen (PSMA), a transmembrane glycoprotein expressed in PCa patients, on the ^{68}Ga radioisotope used in nuclear medicine ^{68}Ga-PSMA PET/CT has been helping to the target volume definitions on the RT planning of recurrent PCa[3].

The technique consists of a study realized 60 minutes after the administration of ^{68}Ga-PSMA, being acquired from the legs to the head, without the administration of the iodized contrast. After that the PET images are fused with anatomical images in the workstation [13].

Precise ^{68}Ga-PSMA PET/CT imaging may help in the regional or distant tumor residues identification, allowing a more rational selection of ideal therapy [19].

Many studies converge in the PET use to complete what is seen in CT or MRI, identifying subvolumes (dependent metabolic activity) called biological targets, as shown in the Figure 2, (functional subvolume contour) in the lymph nodes and prostate region, with this, the PET imaging help identifying the correct RT technique with the SBRT [15].

Fig. 2.Images of ^{68}Ga-PSMA PET/CT showing hypercaptation of the radiopharmaceutical on the pelvic obturator and left external iliac lymph nodes, confirmed as metastasis.



Source: Júnior, Prado, et al.[21]

In a review study, Couñagoet al.[13], the main articles on the ^{68}Ga-PSMA PET/CT in PCa patients were analyzed and its potential impact on the RT treatments. This raising in diagnosis precision represents a potential impact on the patient management, specially on RT [15].

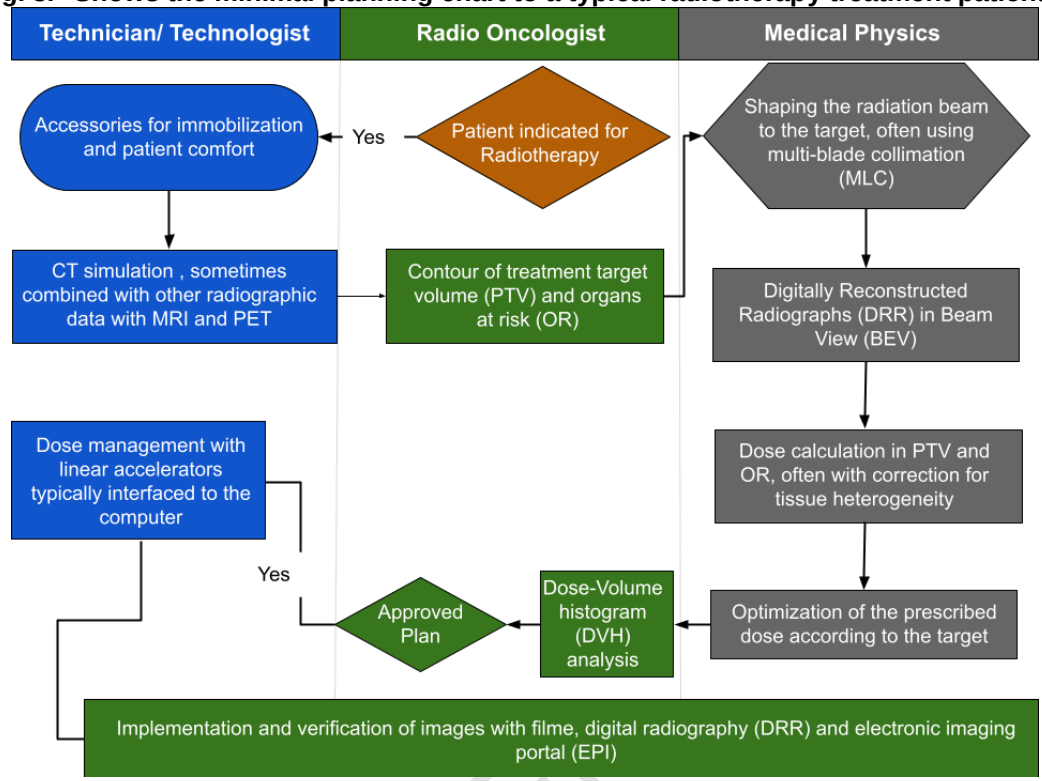
3.3. Radiotherapy

The last years Radiotherapy technological advances, stood out in the computerized therapy planning systems (TPS), multileaf collimators (MLC) and linear accelerators culminating in the high tech implementation and radiation use accuracy, however, modern RT needs a multi disciplinary and multi professional practice [5,15].

The target volume border lining to PCarescue RT after radical prostatectomy are usually made without the visual recurrent disease, i. e., it doesn't have a Gross Tumor Volume (GTV), with it, the radio oncologist defines the Clinical Tumor Volume (CTV), according to Figure 3, based on the Radiation Therapy Oncology Group (RTOG) laws, that includes the prostate layering and pelvic lymphatic drainage chains, usually marked on the TC imaging TPS [15].

A RTOG clinical study is being conducted in comparing the Hypofractionated (HF) RT on SBRT treatment regimen with more usual PCa treatment techniques [4,14].

Fig. 3. Shows the minimal planning chart to a typical radiotherapy treatment patient



Source: author's own construction (2023).

Early HF regimen PCa RT (daily doses of 2.5 Gy to 3.5 Gy) showed better local disease control, as similar toxicity levels to healthy tissues than usual treatments (2 Gy daily dose) [22].

Techniques with higher fraction radiation doses have become one of the main challenges in the modern RT, especially in repeated irradiation in recurrent PCa patients [16].

Nowadays there's a consensus in the dose escalation use in PCa treatments with low to medium risk patients (Table 2). The new RT techniques may potentially use high doses per fraction, allowing high conformity treatment plans and reducing the administered dose on the healthy tissues [15,22].

Table 2 shows the dose escalation per fraction on different RT techniques on PCa patient management.

Table 2. General characteristics of PCa RT on different clinical practice techniques

Characteristics	**Conventional**	**HF**[e]		**Ultra-HF**
Techniques	**3DCRT**[a]	**IMRT**[b]	**VMAT**[c]	**SBRT**[d]
Dose/fraction	2 Gy	3 Gy	3 Gy	7 - 7.25 Gy
Fraction number	35-38	20	20	5

Total Dose	70-76 Gy	60 Gy	60 Gy	35-36.25 Gy
Treatment volume	(GTV+CTV) PTV	(GTV/CTV) ITV	(GTV/CTV) ITV[f]	(GTV/CTV) ITV
Border	Centimeters	Millimeters	Millimeters[g]	Millimeters

Source: Adapted from Morikawa [15]. [a]The 3DCRT technique has been the basis of the newer and preciser techniques like IMRT, IGRT; [b]The IMRT technique allows a modulation on the radiation beam, i. e., permitting a dose intensity variation in a single radiation field, using moving multileaf or blocks collimators; [c]Volumetric Modulated Arc Therapy (VMAT) could be considered a type of IMRT executed in an arc shape, both can have variations in MLC speed and position and in dose rate and gantry speed, needing stricter control systems. VMAT was the one with the bigger evolution and originated to the currently used technologies of RT clinical practices. [d]The Stereotactic Body Radiation Therapy (SBRT) uses the 3DCRT, IMRT and IGRT, associated with the high dose delivery per fraction (HF) and high precision. [e]HF is getting a popularity increase, it can reduce the treatment time a lot with higher doses per fraction and less total doses. [f]Prostate limit definition with ultrasound guided metallic seeds to assure the placement during the daily applications. [g]The size and position variation on the PTV (GTV/CTV) in the respiratory cycle may be checked with 4D tomography or three tomography sequences combined obtained in inspiration, expiration and free breathing, generating a intern layering to the GTV/CTV called Internal Target Volume (ITV).

3.4. Target Molecular Therapy

PSMA is overexpressed in most clinically significant cases of this cancer, making it a key target for both diagnostic and therapeutic purposes. One of the main applications discussed is molecular imaging using PET/CT with radiolinked antibodies or inhibitors, with 68Ga-PSMA as a common choice [7]. Additionally, the mention of ^{177}Lu-PSMA hints at its use in targeted molecular therapy [1,6].

Typically, the request for targeted molecular therapy with ^{177}Lu-PSMA is performed by a medical oncologist or urologist, but ideally by an interdisciplinary decision. The nuclear physician is responsible for administering this therapy and subsequent follow-up of the patient, in close liaison with the medical team involved in the treatment of that patient [1].

Candidates for targeted molecular therapy are patients with metastatic castration-resistant, PSMA-positive prostate cancer who have progressed under at least one new androgen axis drug and at least one taxane or docetaxel regimen, or candidates for cabazitaxel therapy [1].

3.2 Discussions

The essential role of PSMA in prostate cancer diagnosis. Its overexpression in the majority of clinically significant cases makes it an attractive target for molecular imaging. Using radiolinked antibodies or inhibitors, particularly ^{68}Ga-PSMA in PET/CT scans, allows for precise and specific imaging of PSMA expression in the tumor. This approach aids in early and accurate detection, providing valuable information for patient management.

The ^{68}Ga-PSMA PET/CT patients obtained images submitted to radiation oncologist orientation in high tech RT applications are showing to be promising in many recurrent PCa studies [5].

The ^{68}Ga-PSMA PET/CT use is a new diagnosis modality getting its spot in the light, because of its excellent PCa lymph nodes and metastatic organs detection diagnosis, as in the main tumor detection, changing in at least 50% of the BR patients. ^{68}Ga-PSMA PET/CT has shown to detect metastasis even in low PSA patients [3,17].

Clinical randomized tests associating modern and high precision RT techniques confirmed that higher doses result in a better PSA control [17].

To Calais et al. [19], the SBRT is useful in prostate cancer irradiation, given the favorable biological PCa properties. This technique has been one of the more active investigation areas, because of the high incidence rate of the disease, and may be a treatment option in patients with limited metastasis numbers, what may take to an important paradigm change in the therapeutic gain when compared to the conventional fractionation [3,4,14].

A clinical study of the RTOG is being conducted to compare SBRT techniques in HF and conventional PCa therapies [19].

According to Morikawa [15], the high technology treatment planning is a typical result of a sequence optimization process, where each objective defined by the user is configured separately, in a predetermined order. With it representative set of clinical objectives is necessary, as:

- Having at least 95% PTV covered on the prescribed dose;
- Limiting the urethral volume that receives 120% of the dose to 0.1 ml (according to ATD brachytherapy with the UCSF experience);
- Minimize the rectum and bladder volume with 75% of the prescribed dose;
- Avoid hot spots in the healthy tissues; and
- Maximize the target volume dose.

Although prospective randomized control tests are necessary to determine the patient survival rate, real SBRT benefits on recurrent PCa and in determining the prognostic indicators [20].

According to Patel et al. [18], SBRT use is a well tolerated therapy in bone oligo metastatic prostate cancer. The results found in 2015 are comparable to the older published works on the lymph node diseases with SBRT, suggesting that the bone metastasis might benefit with the SBRT.

4. CONCLUSION

The data presented in this study collaborate with ^{68}Ga-PSMA PET/CT in patients with recurrent PCa, especially for the selection of target molecular therapy. It has become an active research, presenting new challenges in conventional and HF techniques in SBRT for the treatment of PCa.

Radiation oncologists have a limitation in detecting recurrence, noting that CT, MRI and BS imaging techniques have not yet solved this problem, so for the time being, the PSA value remains a decisive parameter in treatment. It is therefore a question of surgery, as specified by the RTOG, where 80% of recurrences are found. Procedure guides must be drawn up to determine the best course of action for the patient.

By assessing the expression of PSMA in a patient's tumor, medical professionals can make informed decisions about the most appropriate treatment strategy. This individualized approach is a significant advance in cancer care, as it tailors therapy to the specific characteristics of each patient's cancer.

As research and technology continue to advance, the use of PSMA and other specific markers for diagnosis and treatment is likely to become more refined and widespread. The use of ^{177}Lu-PSMA suggests that molecular targeted therapy is a promising area of development, potentially offering more effective and less invasive treatments for prostate cancer.

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