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Molecular Imaging and Theranostics—A Multidisciplinary Approach

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Prostate cancer is a major global health care challenge. Due to the recent relevant improvements in the diagnosis, imaging and treatment, management of these patients is becoming extremely complex. However, new multiple diagnostic procedures and treatment options, tailored on the single patient, require a multidisciplinary effort. Molecular imaging is gaining importance in the decision making process of prostate cancer patients, playing a key role in the majority of clinical setting, including staging, restaging during biochemical recurrence and castration-resistant stage. Moreover recent significant advances are changing the management of these patients impacting on the choice of therapeutic strategy. In particular, prostate-specific membrane antigen PET imaging is assuming the role of the gatekeeper addressing patients to the correct treatment option and also, in the advanced stages, selecting patients potentially suitable for targeted α- or β-therapy bridging to the fascinating concept of theranostic. Even if radioligand therapy found its first clinical application in 1946, in the last few years several α- or β-radionuclide prostate-specific membrane antigen-labeled for targeted therapy have been proposed where other treatment options do not show a significant impact on survival. The theranostic field is experiencing a rapid growth in prostate cancer giving to nuclear medicine a central role that has to be confirmed by further prospective studies.
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Introduction

Prostate cancer (PCa) is the most frequently diagnosed cancer other than skin cancer and the second leading cause of death from cancer in men in Western countries.[1] Therefore, care for men with PCa is a major global health care challenge. Due to the recent relevant improvements in the diagnosis, imaging, and treatment of PCa, management of these patients is becoming extremely complex. Multiple diagnostic procedures and treatment options, tailored on the single patient, require a multidisciplinary network ideally consisting of pathologists, urologists, radiologists, nuclear medicine physicians, radiation oncologists, medical physics experts, oncologists and palliative care physicians. Multidisciplinary team (MDT) discussions have been shown to be associated with improved adherence to guidelines supported by the literature.[2] In this review, we introduce the role of molecular imaging and theranostic concept from a multidisciplinary point of view, summarizing the currently available data, and also describing ways on how to implement nuclear medicine techniques for diagnosis and treatment of PCa.

PSMA, A Star Is Born

Since 2012, year of the first PET images obtained with ^{68}Ga-labeled HBED-CC conjugate of the prostate-specific membrane antigen (PSMA),[3] a multitude of trials are assessing this promising tracer with theranostics potential. PSMA is a cell surface protein, which is increasingly expressed in PCa compared to other tissues providing a promising target for specific imaging and therapy due to its transmembrane location and internalization after ligand binding.[4]

Molecular Imaging

In the last two decades, molecular imaging is gaining importance in the decision making process and management of PCa patients, playing a key role in the majority of clinical setting of

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PCa, in particular during staging of disease, biochemical recurrence (BCR) detection, and evaluation of castration-resistant PCa patients (CRPC). Herein, we discuss main implications of molecular imaging in these clinical stages.

Staging

Local Staging

Several imaging techniques are progressively improving for PCa staging. Transrectal ultrasound does not show significant accuracy for local staging[5] whereas the employment of color/power Doppler and contrast−enhancement has determined an improvement in tumor detection, without a significant increase in the staging accuracy.[6,7] Multiparametric MRI (mpMRI), that allow noninvasive imaging evaluation of the anatomy, angiogenesis, and cell density of the prostate, has been the cornerstone for some years in this setting of disease, and it is being crucial for decision making, for example, selection of patients suitable for nerve-sparing surgical approaches.[5,8,9] Thus, European Association of Urology (EAU)-European Society for Radiotherapy & Oncology-International Society of Geriatric Oncology guidelines suggest to perform mpMRI in high-risk PCa patients, together with cross-sectional abdominal pelvic imaging and bone scanning for metastatic screening, and eventually in intermediate-risk PCa patients.[5] A five−point score on each MRI sequence was developed (Pi-RADS score) to overcome the lack of standardization in the expression of results and to permit a more virtuous teamwork between radiologists and urologists.[10] In the world of molecular imaging, PET/CT seems to have a confined role for intraprostatic detection of PCa regardless of the radiopharmaceutical employed. Interestingly, the application of new hybrid PET/MRI tomographs with PSMA-based compounds could increase sensitivity and specificity for evaluation of primary PCa.[11,12]

Systemic Staging

Concerning nodal and distant staging, a systemic assessment for high-risk and intermediate-risk patients is mandatory before treatment. The relatively poor performance of CT and MRI for the detection of nodal spread of disease is well established. Moreover, CT and bone scan (BS) show a low sensitivity for bone assessment, even in high-risk patients. Whole-body molecular imaging allows investigating all tissues and organs (Fig. 1) and PET/CT with choline and PSMA has been applied for systemic staging of PCa. In a meta-analysis choline PET/CT demonstrated a superior sensitivity, specificity, and positive prognostic value (PPV) compared to CT and MRI in the same patient population.[13] However, in the PSMA era, several studies are running on paying specific attention to the nodal and distant staging. In an Australian study, van Leeuwen et al prospectively evaluated ^{68}Ga-PSMA-11 PET/CT in a cohort of 30 patients with intermediate- or high-risk PCa.[14] On a patient-based analysis, PSMA PET/CT showed a sensitivity of 64% for the detection of nodal disease, its specificity was 95% and negative prognostic value (NPV) was 82%. On a region-based analysis, the sensitivity was 56%, the specificity was 98%, and the NPV was 94%. Interestingly, the mean size of missed lymph nodes was only 2.7 mm. Both PET/CT and PET/MRI were applied using ^{68}Ga-PSMA-11 in a retrospective study conducted by Maurer et al[15] in a population of 130 patients using histopathology as the gold standard. On a patient-based analysis, the sensitivity, specificity, and accuracy of ^{68}Ga-PSMA-11 PET were 65.9%, 98.9%, and 88.5%, respectively, while those of morphologic imaging (CT or MRI) were 43.9%, 85.4%, and 72.3%, respectively. On template-based analysis, the sensitivity, specificity, and accuracy of ^{68}Ga-PSMA-11 PET were 68.3%, 99.1%, and 95.2%, and those of morphologic imaging were 27.3%, 97.1%, and 87.6%, respectively. To date, the role of PSMA PET has not been extensively investigated for bone metastasis, whereas ^{18}F-SodiumFluoride (NaF) PET/CT and BS are usually largely employed for bone staging of disease.

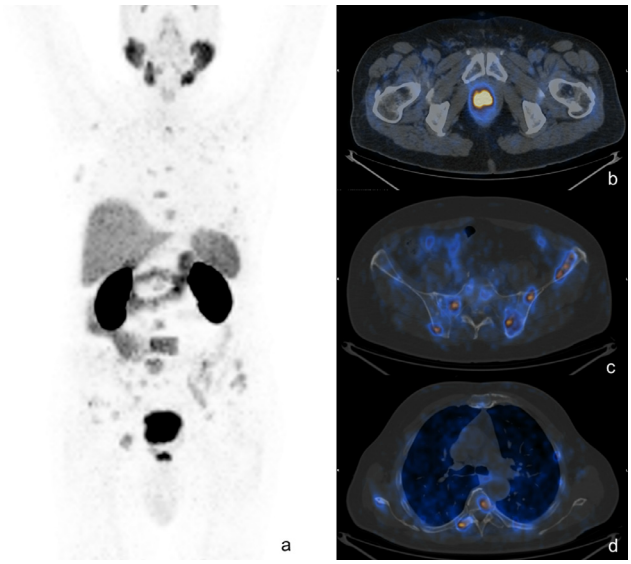

Figure 1 68Ga-PSMA-11 PET/CT of 79-year-old male with prostate cancer (GS = 5 + 5 in 6 of 14 cores; iPSA = 96 ng/mL) presenting for initial staging, found to have intense PSMA uptake in the prostate gland (SUV_{max} = 23.9) and multiple diffuse bone lesions. mpMRI was not performed. After 68Ga-PSMA-11 PET/CT was excluded from radical surgery and started hormonal manipulation. PET MIP image is shown in image a. Axial PET/CT images are shown in images b-d.

Taking into consideration these assumptions, new hybrid PET/MRI tomographs combined with the injection of PSMA-based compounds for the detection and characterization of the intraprostatic lesions are showing promising results. PSMA PET/CT and PET/MRI have demonstrated a better accuracy if compared to morphologic imaging (CT or MRI) in the detection of nodal involvement of disease. In this setting of disease, a solid alliance between nuclear medicine physicians and radiologists is mandatory for an optimal interpretation of hybrid images and consequently an accurate and precious report helping urologist in decision making process.

Biochemical Recurrence

The clinical setting of PCa patients experiencing BCR is challenging because, depending on imaging results, clinicians

have to address patients to the correct therapy including salvage radiation therapy (S-RT), salvage lymph nodal dissection, androgen deprivation therapy, or chemotherapy. It is clear this intricate scenario needs the cooperation of several experts participating in an MDT. By the EAU, the BCR in patients who have undergone prostatectomy is defined an initial PSA value of at least 0.2 ng/mL followed by a subsequent confirmatory PSA value of 0.2 ng/mL or more.[16] In patients who have undergone definitive primary radiation therapy (EBRT), BCR is defined as a rise of 2 ng/mL or more above the nadir PSA level.[17] Overall, BCR after primary therapy is a frequent event. In fact, within 10 years, 20%-40% of patients undergoing radical prostatectomy (RP) and 30%-50% of patients undergoing EBRT will experience BCR.[18,19] The most common locations of recurrence are within the prostate gland, the surgical bed after prostatectomy, the regional nodal spread, and the bone metastases.[20] Although nomograms, taking into account PSA levels, PSA doubling time, Gleason score, and TNM stage, may predict the potential localization, in this scenario, the imaging contribution is crucial in order to detect the correct site of disease and consequently address patients to the adequate therapy. However, anatomic imaging with CT and MRI alone, mostly basing on morphologic characteristics, has limited sensitivity, in particular for the detection of nodal metastases. In this setting, molecular imaging can increase the accuracy of PCa disease detection compared to morphologic imaging alone, guiding clinicians in the choice of the most tailored salvage therapy.[21,22] Several PET radiotracers, exploring different functional aspects, have been proposed in the last decades in the investigation of PCa patients experiencing BCR, such as, acetate, choline, fluciclovine, and more recently PSMA.[22-25] As demonstrated by Stephenson and Tendulkar,[26,27] the S-RT performed at low PSA levels (0.50 ng/mL or lower) determines more favorable outcomes. Therefore, 2017 EAU guidelines advise performing S-RT in patients experiencing BCR after RP as early as reasonably possible. This is a crucial point in the choice of the appropriate molecular imaging technique. In the wide landscape of radiotracers mentioned above, many studies demonstrated that PSMA-11 PET/CT has a higher detection rate in the lower range of PSA levels of BCR, in particular if compared to direct competitors such as choline or fluciclovine PET/CT.[28-34] In a recent published paper, Visschere et al systematically reviewed the literature to determine the role of imaging in PCa patients in BCR at very low PSA levels and taking into account all possible imaging modalities such as transrectal ultrasound, CT, BS, mpMRI, whole body MRI, Prostascint SPECT, ^{99m}Tc PSMA SPECT, PET imaging including ^{18}F-FDG, ^{11}C-choline, ^{11}C-acetate, ^{18}F-choline, ^{18}F-fluciclovine, ^{68}Ga-PSMA-11, ^{18}F-DCFPyL, ^{18}F-DCFBC, and PET/MRI. Among these, mpMRI seems to be superior for detecting local relapse, but it must to be integrated by a PET imaging evaluation of nodal and distant metastasis. Overall, ^{68}Ga-PSMA-11 PET/CT showed the higher detection rates than any other imaging modality, especially in the range of low PSA values (<0.5 ng/mL)[35] (Fig. 2). Based on these results, a future increasing use of hybrid PET/MRI imaging using PSMA-labeled radiotracers is likely, establishing a deeper relationship between radiologists and nuclear medicine physicians.[36] PSMA-labeled tracers are rapidly gaining interest and increasingly being performed worldwide, even if in many countries they are not yet gained marketing authorization. In the immediate future, because of the long half-life, ^{18}F-labeled PSMA tracers will probably have a wider acceptance among PET centers not equipped with an on-site cyclotron or a ^{68}Ge/^{68}Ga generator. Moreover, PSMA imaging seems to have a role on radiotherapy planning and several studies report a potential impact on RT field change ranging from 19% to 87% of patients using ^{68}Ga-PSMA-11 PET/CT.[37-44] Albisinni et al, in a retrospective study of 131 PCa patients, demonstrated that ^{68}Ga−PSMA-11 PET/CT determines a modification of planned therapeutic strategy in 76% of patients experiencing BCR. These modifications mainly regarded active surveillance, hormonal manipulations, stereotaxic radiotherapy, and salvage treatments.[41] Another fascinating approach seems to be the radio-guided surgery (RGS) in PCa patients, consisting in a preoperative PSMA-labeled SPECT imaging and subsequent surgical guidance in the detection of unusually sited or small PCa metastases using gamma probes.[45] ^{111}Indium-based and ^{99m}Technetium-based tracers have been proposed to perform PSMA-RGS. The possibility to achieve a quick and direct confirmation of metastases removal by analyzing ex vivo the tissue removed through the gamma probe is the main advantage of this procedure. Rauscher et al showed data of 31 consecutive patients with localized recurrent PC undergoing RGS.[46] They observed a PSA decline of >50% and >90% in 76.7% and in 53.3% of patients, respectively. A PSA value

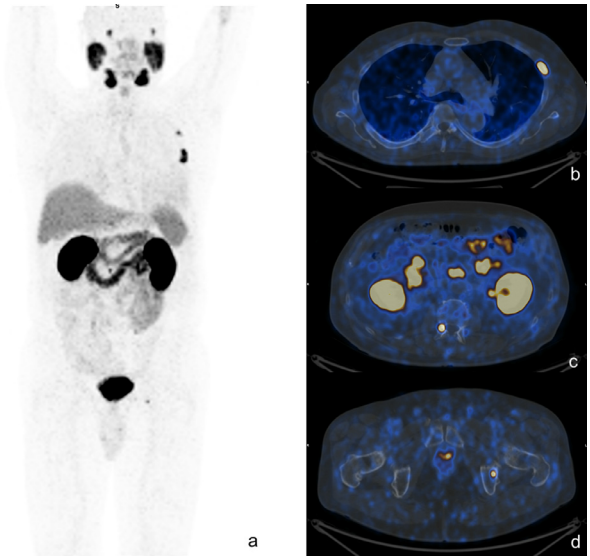

Figure 2 68Ga-PSMA-11 PET/CT of 81-year-old male treated in March 2017 with radical prostatectomy and pelvic lymph-node dissection for high-risk prostate cancer GS = 4 + 5, pT3 pN0, iPSA = 7.47 ng/mL. PSA nadir = 0.03 ng/mL. Biochemical recurrence occurred in February 2018 with PSA = 0.2 ng/mL and 68Ga-PSMA-11 PET/CT was performed in April 2018 revealing the presence of four bone lesions: left ischium (SUV_{max} = 11.6), L2, III, and IV left ribs (SUV_{max} = 20.9). PET MIP image is shown in image a. Axial PET/CT images are shown in images b-d.

<0.2 ng/mL was reached in 60% of patients. Maurer et al in a retrospective study on 31 PCa patients with BCR after primary RP found a sensitivity of 83.6% and an accuracy of 93.0% using ^{99m}Tc-PSMA-I&S.[45] The presented data on RGS are encouraging but need to be confirmed by larger prospective studies. As shown above, molecular imaging advances in the field of PCa, and in particular in the setting of BCR, requires to be well integrated in the multidisciplinary algorithm of PCa patients care system that is becoming extremely intricate.

Castration-Resistant Prostate Cancer

In patients with CRPC mortality rate exceeds 50% and more than 90% of metastatic CRPC (mCRPC) patients present bone metastases. Until 2010, docetaxel was the only agent with proven survival benefit for CRPC. The development of cabazitaxel, abiraterone acetate, enzalutamide, radium-223, and sipuleucel-T has increased the number of treatment options. Nevertheless, there is currently a lack of consensus regarding the timing and sequencing of the available treatment options.[16] Additionally, we should consider side effects and cost-effectiveness ratio of these treatment options. This clinical context is challenging for both oncologists and patients, thus more accurate imaging procedures are needed for better staging and improved assessment of disease response in CRPC. Conventional cross-sectional imaging by either CT or MRI and BS is still the recommended staging modalities. Nevertheless, the introduction of PSMA PET for patients with CRPC as a staging modality may provide higher sensitivity and specificity compared to morphologic imaging and BS, but also raises many questions. First, a higher sensitivity would result in a shift from men who were previously found to have nonmetastatic castration resistant according to BS into a mCRPC disease state, which would significantly influence treatment decision making, resulting in earlier treatment and, second, exclude certain treatment options (Fig. 3). The definition of response to treatment and disease progression are also new challenges and predictive biomarkers are absent. Recent advances in radionuclide therapy, strictly related with PET and SPECT molecular imaging, are leading a major revolution in the highly complex world of CRPC and a highly specialized and experienced MDT of physicians is crucial to determine the best therapeutic algorithm for each individual patient.

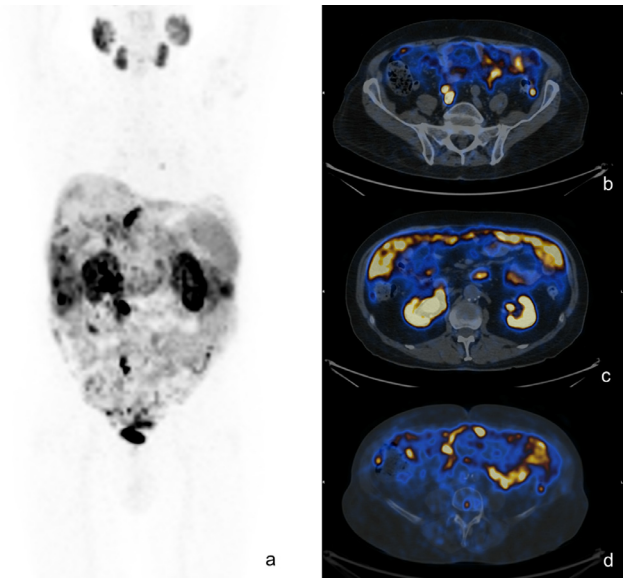

Figure 3 68Ga-PSMA-11 PET/CT of 77-year-old male treated in 2013 with radical prostatectomy and pelvic lymph-node dissection for prostate cancer GS = 5 + 4; pT3b pN0, iPSA = 4.0 ng/mL, and subsequent adjuvant radiotherapy and 6 months of androgen deprivation therapy. Biochemical recurrence occurred in November 2015 with PSA = 0.67 ng/mL. A first 68Ga-PSMA-11 PET/CT was performed in April 2017 with a PSA = 111 ng/mL and a PSA doubling time = 2.5 months revealing the presence of peritoneal carcinosis with high PSMA uptake and positive retroperitoneal and right internal mammary lymph nodes. Subsequently, the patient started Docetaxel with an increase in PSA levels after five cycles, up to 200 ng/mL in July 2017. A second 68Ga-PSMA-11 PET/CT was performed (images a-d) confirming the presence of a diffuse peritoneal carcinosis (SUV_{max} = 35), retroperitoneal, and right internal mammary lymph nodes and showing the appearance of a new bone lesion of the lumbar spine (SUV_{max} = 5.3). Therefore, the patient was addressed to Cabazitaxel. Axial PET/CT images are shown in images b-d.

Theranostic Concept

Background of Radioligand Therapy

The Hellenic and fascinating term "theranostic" found its first clinical application in 1946, when Seidlin et al reported the therapeutic potential of ^{131}I for patients who have metastasized thyroid cancer.[47] Thereafter, the first phase 1 study using ^{90}Y-CYT-356 monoclonal antibody that binds to the intracellular domain of PSMA to treat patients with CRPC was published in 1996.[48] However, hematologic toxicity was significant using monoclonal antibodies, most probably because they are large molecules with poor permeability in solid tumors and slow clearance from the circulation, thus exposing the normal bone marrow to prolonged radiation doses. Thus, Maresca et al described in 2009 a series of small-molecule inhibitors of PSMA[49] and the first small-molecule inhibitor used for radioligand therapy in men was MIP-1095.[50] Currently, the β-emitting radioisotope ^{177}Lutetium has gained popularity as one of the therapeutic radionuclide of choice due to its most favorable physical properties and the feasibility of post-treatment scintigraphic assessment and dosimetry thanks to its low-energy γ-rays emission. The first prospective phase 2 trial using ^{177}Lu-PSMA-617 was published in 2018 by Hofman et al.[51] In patients with diffuse bone marrow involvement, especially after extensive previous chemotherapy, or resistance toward therapy with ^{177}Lu-PSMA ligands, PSMA compounds labeled with the α-emitter ^{225}Actinium have been tested since 2016 with encouraging results. Recently ^{90}Yttrium-PSMA-617 was proposed for

patients with bulky lesions, but limited bone involvement.[52] The rationale is the higher penetration depth in water of ^{90}Y (mean range approximately 3 mm for ^{90}Y vs 0.6 mm for ^{177}Lu) and the potential benefit of increased cross-fire effects in large lesions. Many studies are currently on-going, exploring the feasibility, safety, and efficacy of several radionuclides in a therapeutic intent with the prospective of establish which is the optimal treatment of choice on a pattern of spread basis, for example, an α-emitter in patients with diffuse bone marrow involvement of disease (Fig. 4).

Efficacy of Radioligand Therapy

So far, significant clinical results have been achieved with the subsequent use of radiolabeled PSMA ligands in the treatment of CRPC. Afshar-Oromieh et al reported 34 mCRPC men treated with ^{131}I-MIP-1095 with 23 patients receiving a second and three patients a third dose.[53] The best therapeutic effect was achieved by the first therapy and any PSA response was found in 94% of patients and ≥50% PSA decline was achieved in 71%. Regarding radioligand therapy (RLT) with ^{177}Lu-PSMA, a systematic review including a total of 20 studies on PSMA-based radionuclide therapy in mCRPC was performed by von Eyben et al.[54] In the subgroup of patients treated with ^{177}Lu-617 or ^{177}Lu-I&T (12 articles) a ≥50% PSA decline was described in 44%. In the first prospective phase II study including 30 CRPC patients, Hofman et al[51] reported any PSA decline in 97% and a >50% PSA decline in 57% of patients. On the other hand Kratochwil et al[55] found a PSA response of any degree in 87% of patients and a >50% PSA decline in 63% in a retrospective study including 38 patients with at least 8 weeks of survival after RLT.

Safety of Radioligand Therapy

The safety of RLT with ^{131}I-MIP-1095 was evaluated in a cohort of 34 patients. With regard to hematological toxicity, after the first cycle of therapy, grade 1-2 leukopenia occurred in 38%, whereas no significant thrombocytopenia was observed in 82% of patients, while salivary glands toxicity, grade 1-2 xerostomia was reported in 88%.[53] The safety of ^{177}Lu-PSMA RLT has been evaluated by multiple groups and the largest body of evidence comes from a retrospective multicenter trial including 12 clinics from Germany in which 145 patients with mCRPC received a median of two RLT cycles (range 1-4).[56] Grade 3-4 anemia occurred in 10% of patients and grade 3-4 thrombocytopenia in 4%, while mild to moderate xerostomia was reported for 8% of patients by the participating centers. In the prospective study on ^{177}Lu-PSMA RLT published by the Australian group,[51] grade 3-4 thrombocytopenia occurred in 13% of patients while the most common toxic effects related were grade 1 dry mouth in 87%, grade 1-2 transient nausea in 50% and grade 1-2 fatigue in 50%. Regarding α-particle emitters, Kratochwil et al[55] found xerostomia being the main reason why patients discontinued therapy or refused additional administration (13% of patients) while the relevance of hematologic changes was small. Regardless the differences of the various radiopharmaceuticals, the risk of development of hematotoxicity

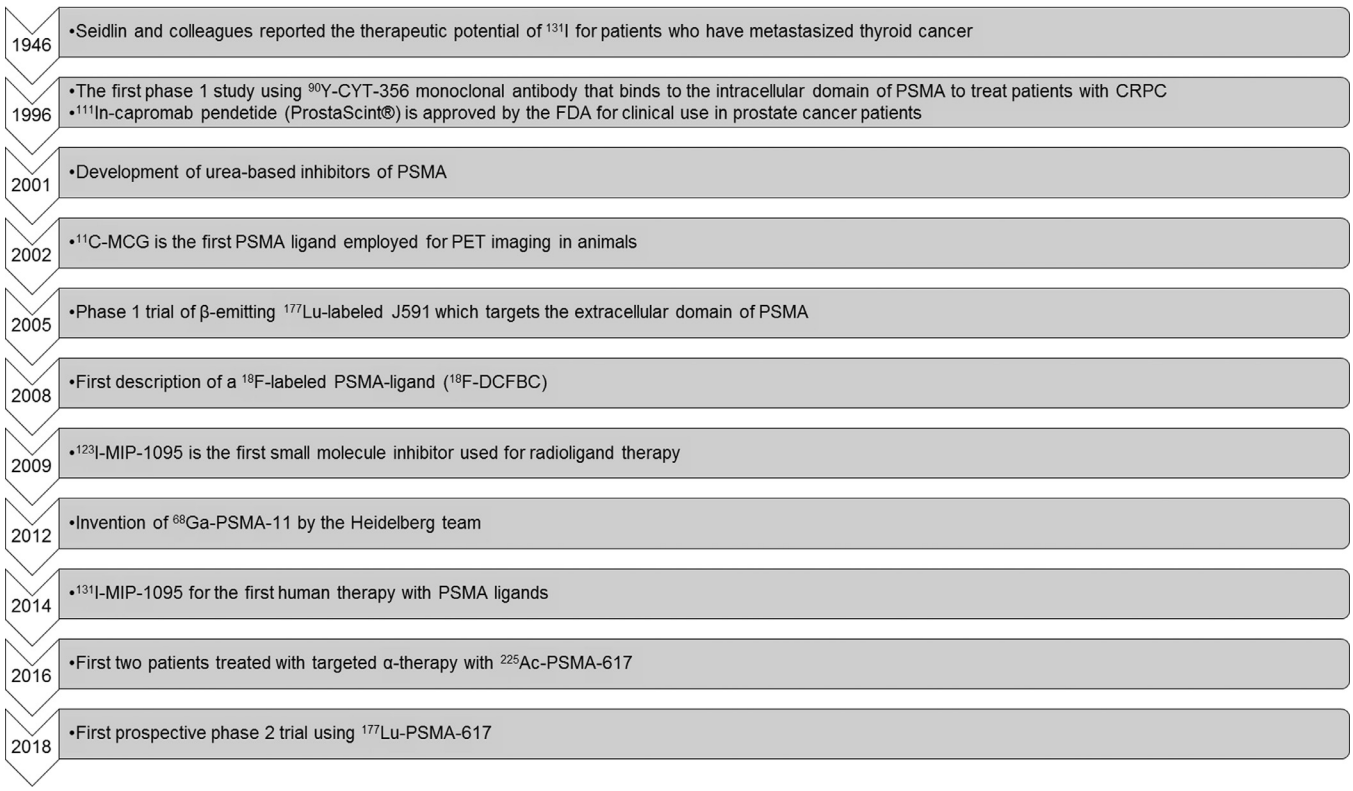

Figure 4 Theranostic concept time line.

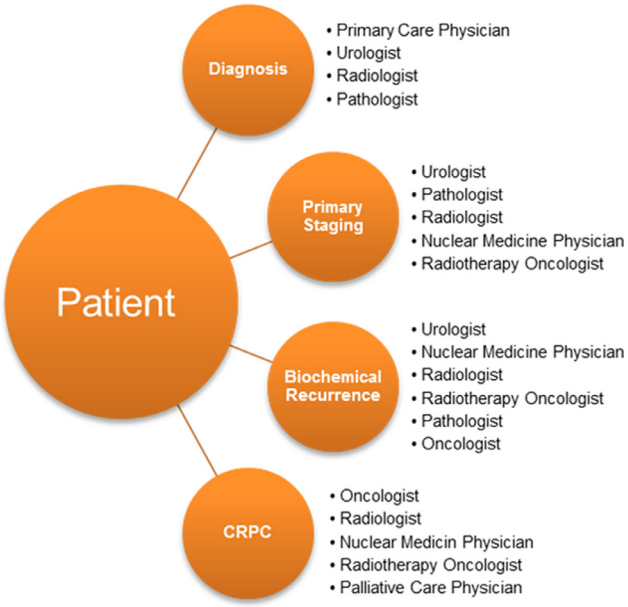

Figure 5 Multidisciplinary network in prostate cancer care.

is increased in extensively pretreated CRPC patients. Especially patients with extensive bone marrow involvement and previous chemotherapies may respond with higher bone marrow toxicity. Fractionation of activities could be a way to avoid severe hematotoxicity in the next future. In a theranostics intent, pretherapeutic PSMA imaging (SPECT/CT or PET/CT or PET/MRI) is mandatory to confirm and to quantify the PSMA expression for selecting patients who most likely will benefit from PSMA-directed RLT. To date, PSMA imaging plays the role of the gatekeeper for any patients potentially suitable for targeted α- or β-therapy. Taking advantage of different physical properties of α- and β-emitter molecules, PSMA imaging potentially could become the mainstay of late stage CRPC patients guiding physicians to choose either a β-emitter or an α-emitter for a patient tailored approach on the basis of the pattern of tumor spread as suggested by Heidelberg researchers.[55] Future challenges include the integration of RLT with other anticancer drugs (eg, immune checkpoint inhibitors, DNA damage repair pathway inhibitors, or T-cell-based immunotherapy) for a synergic approach in cancer treatment.

Practical Considerations

For a safe translation into the clinical routine, RLT has to be performed according to the local legal and ethical requirements. The treating physicians and nurses, as well as the involved radiochemists and medical physics experts, have to comply with appropriate general radiation safety standards. Individual patient-specific therapy planning includes dosimetric studies and corresponding dose calculations by medical physicists to ensure safety and efficacy of the treatment. For dosimetry, biokinetic data need to be collected, such as blood sampling and sequential scanning for quantitative imaging. Even this aspect requires a strict cooperation between different professionals to achieve the optimal treatment result.

Conclusion

An MDT approach to PCa care guarantees a higher probability for the PCa patient to receive adequate care including all possible diagnostic and therapeutic strategies, balancing advantages and related side effects. The future of PCa patients depends on a successful multidisciplinary collaboration between experienced physicians of all relevant disciplines, which should lead to important advantages in all the phases and aspects of PCa management (Fig. 5). In this context, nuclear medicine may become protagonist in several stages of disease as long as it steps forward into the clinical world of PCa care together with radiology, urology, oncology, radiation oncology, and pharmacology. Further prospective studies are warranted to better understand the role of molecular imaging and theranostic in PCa patients.

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