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Abstract

Background: The study aimed to overview radiopharmaceuticals used for the nuclear medicine (NM) imaging of prostate cancer (Pca) since the first mentions in the literature up to recent reports, with the special focus on positron emission tomography-computed tomography (PET-CT) radiotracers.

Materials and methods: We found over 3500 articles discussing the role of PET-CT in Pca patients' management published within 1990–2023. We summarized the past and present interests of the Authors when the Pca diagnostic imaging and the use of radiotracers in Pca diagnosis are considered. Eventually, we have compared the radiotracers' introduction in the literature with the United States (U.S.) Food and Drug Administration (FDA) approval timeline.

Results: The most mentions by the Authors were made of the following PET-CT study compounds: 2-[^{18}F]fluoroethyl-choline ([^{18}F]FECh), gallium-^{68}-labelled prostate-specific membrane antigen using peptide-11, ([^{68}Ga]Ga-PSMA-11), carbon-^{11}-labelled acetic acid ([^{11}C]acetate), and the anti-1-amino-3–[^{18}F]-fluorocyclobutane-1-carboxylic acid (*anti*-3-[^{18}F]FACBC, Axumin®), as well as the non-tumour-specific 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG). The most recent studies analysis showed an increasing interest of the Authors not

only in a relatively new Pca-specific [^{68}Ga]Ga-PSMA-11, but also in a widely used non-specific [^{18}F]FDG.

Conclusions: The literature analysis results lead to the conclusion that Pca remains a constant focus of the NM drug development with particularly high interest in PET-CT-dedicated radiotracers.

Key words: oncology; prostate cancer; prostatic neoplasms; PSMA; radiopharmaceutical; positron emission tomography

Introduction

The methods of choice in the prostate cancer (Pca) early diagnosis are the transrectal ultrasonography (TRUS) and the prostate-specific antigen (PSA) level evaluation. Most often, the Pca patients are referred to further diagnostic management using advanced imaging techniques, i.e., contrast-enhanced computed tomography (ceCT), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT-CT) and the positron emission tomography-computed tomography (PET-CT) [1–5]. The main limitation of the available imaging methods is usually too low spatial resolution of the obtained scans for the small-size primary tumour or metastatic lymph nodes detection. When the nuclear medicine (NM) techniques are considered, the additional limitation may be the availability of some of the radiotracers.

NM techniques can be used for the detection of Pca primary, staging, restaging and therapy planning. According to the literature [1–8], NM methods of imaging can be used, i.e., in early detection of the primary tumour, evaluation of the suspected recurrent disease (suggested by an increase of the serum PSA), and the Pca metastatic bone lesions evaluation. In this study, we performed the comprehensive literature analysis to present both general applications and the timeline of introducing most mentioned radiotracers used for Pca evaluation, focusing mainly on PET-dedicated radiopharmaceuticals, as more commonly described by the Authors.

The study aimed to overview radiopharmaceuticals used for the PET-CT imaging of Pca since its introduction by the literature, through the United States (U.S.) Food and Drug Administration (FDA) approval, up to the recent reports.

Materials and methods

The study was designed per the principles of the Declaration of Helsinki. The study was performed upon the Poznan University of Medical Sciences Bioethical Committee approval of the project this article is a part of (date of approval: 19.05.2022, no. KB/387/22).

We have analysed the English-language full-text manuscripts related to the Pca evaluation, using the *National Library of Medicine* (NLM) resources, covering over 30 years of research. We chose NLM to obtain results from variety of databases (including: PubMed). Based on our research, prior to 1990, the availability of literature resources was limited. Therefore, we analysed the articles published in 1990–2023 available in all databases connected to the NLM. While researching NLM for over a year, we have built the searching scheme using all databases linked to NLM, following the Medical Subject Headings (MeSH) thesaurus, and MeSH major topics logarithm. After research, we have checked the relevance of the articles to the Pca diagnosis objective, avoiding doubled studies (similar studies performed by the same group of authors, providing comparable results and conclusions). Furthermore, after a detailed analysis of the papers' objectives, we excluded those, which were not relevant for the particular steps of the analysis. First, we considered the general Authors' interests in Pca patients management, building the advanced searching scheme upon the general overview results (topics researched by the authors interested in MeSH major topic of "prostate cancer", translated by the MeSH thesaurus to "prostatic neoplasms"). Based on the research results, we checked more detailed keywords [i.e., magnetic resonance imaging (MRI), PET, radiotracer], and organised the results based on the number of reports related to the Pca. Eventually, we focused on the most researched issues. In this study, the obtained results reflect the observations regarding the researchers' interests and most-mentioned aspects of the Pca diagnosis, methods of imaging, and radiotracers. The final analysis focused strictly on radiopharmaceuticals used in Pca diagnosis, as well as recent trends in publishing (most researched topics up to the month of August, 2023, including Theranostics to define the most up-to-date topics related to the NM field). In this study, we focused on PET-CT-dedicated radiotracers as SPECT-CT compounds have been less widely researched compared with radiopharmaceuticals used for PET-CT studies based on research results.

We have compared the timeline of the first available full-text reports regarding the use of PET-dedicated radiopharmaceuticals compared with the FDA's approval. We chose FDA as the biggest body approving medications, representing a wide jurisdiction, and authority over approving radiotracers.

The literature diagram analysed and included in the research is shown in Figure 1.

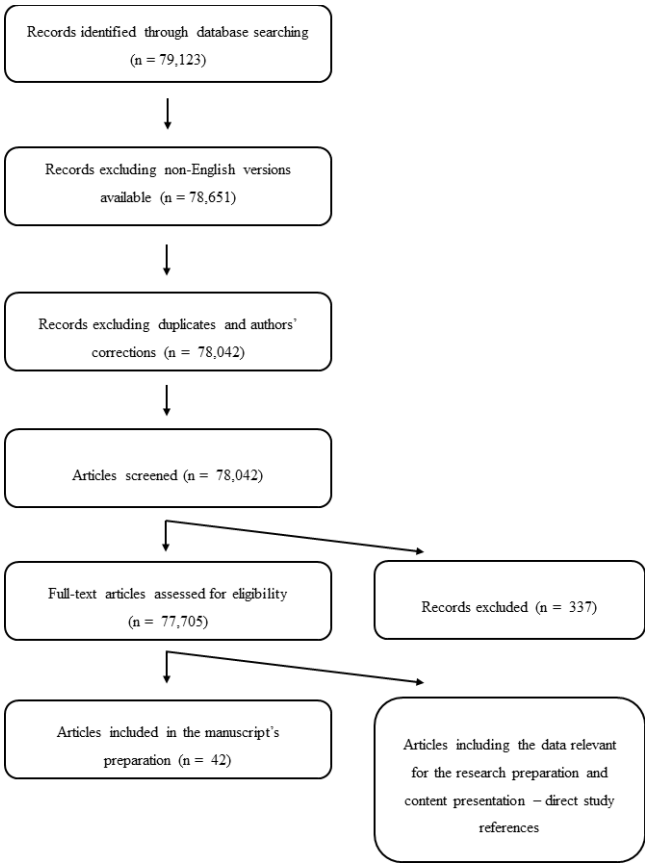

Figure 1. The literature search diagram. n — number of records

Results

The NLM database analysis — overview

According to the scientific database resources, the interest in Pca diagnosis seems to increase over time. When the NM is considered, the growing number of reports can be directly connected to the radiopharmaceuticals development and the necessity to establish their most appropriate applications. Depending on research keywords used, we have found approximately 2,000 to nearly 80,000 scientific papers published within 1990–2023, focusing on a variety of aspects of Pca diagnosis. Up to, approximately, 2019, the leading manuscripts' subjects were local and worldwide Pca epidemiologic reports, recommendations, and the best practice documents, indicating general principles of chosen methods of imaging protocols, including early diagnosis of Pca, and the use of specific methods of imaging. Table 1. presents examples of the most researched objectives related to the Pca diagnosis.

Table 1. The examples of the *National Library of Medicine* (NLM) research results depending on the searching scheme (1990–2023)

Pca diagnosis — examples of most researched issues		
Searching scheme	**Number of articles**	**Main objectives**
"prostate cancer" AND "diagnosis"	77,705	Reports, recommendations, screening
"prostate cancer" AND "oncology"	26,790	Reports, recommendations, status of the Pca worldwide
"prostate cancer" AND "early diagnosis"	11,413	Biomarkers, novelties in Pca diagnosis
"prostate cancer" AND "imaging"	10,962	Reports, recommendations
"prostate cancer" AND "MRI"	9,590	Recommendations, methods of imaging comparison
"prostate cancer" AND "PET"	3,701	Reports, recommendations, different radiotracers used for Pca diagnosis, PSMA, disadvantages of using [^{18}F]FDG
"prostate cancer" AND "TRUS"	1,982	Recommendations, methods of imaging comparison

Pca — prostate cancer; MRI — magnetic resonance imaging; PET — positron emission tomography; PSMA – prostate-specific membrane antigen, [^{18}F]FDG — 2-deoxy-2-[^{18}F]fluoro-D-glucose; TRUS — transrectal ultrasonography

Since 2019, the Authors' areas of interest have shifted from comparison of NM diagnostic imaging methods and general recommendations for Pca patients' management, to drug development, introduction of new radiopharmaceuticals, and, eventually, Pca Theranostics performance. The leading objective of the Authors' considerations was to indicate the most sensitive and specific method of imaging for Pca detection, staging, and restaging, which involves the choice of a radiotracer. It seems worth mentioning that most of the analysed studies focused on the specific, usually newly developed or clinically tested, compounds' utilities in Pca evaluation rather than comparative analysis of the different radiotracers' usefulness.

Radiopharmaceuticals used for Pca diagnosis: thirty years of research

We found 3701 full-text articles discussing the role of PET-CT study in Pca diagnosis. Among these reports, over 3500 focused on the utilities of the study using a variety of radiotracers. The most studied were - according to the number of papers – the PET-CT study using the 2-[^{18}F]fluoroethyl-choline ([^{18}F]FECh) and the gallium-^{68} PSMA-11 ([^{68}Ga]Ga-PSMA-11). The literature mentioned several other PET-dedicated radiotracers, including the carbon-^{11}-labelled acetic acid or choline ([^{11}C]acetate, [^{11}C]choline), fluorine-^{18}-labelled acetate analogue ([1^{8}F]FAc), anti-1-amino-3–^{18}F-fluorocyclobutane-1-carboxylic acid (*anti*-3-[^{18}F]FACBC, *Axumin*®), [^{18}F]PSMA-007, as well as, the non-tumour-specific 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG; Tab. 2).

Table 2. The use of radiopharmaceuticals in prostate cancer (Pca) patients' management (1990–2023)

Radiopharmaceuticals in Pca diagnosis — most researched issues		
Searching scheme	**Number of articles**	**Pca diagnosis — leading subject**
"prostate cancer"AND "[^{18}F]FECh"	983	The role of [^{18}F]FECh PET-CT in metastatic castrate-resistant Pca, [^{18}F]FDG *vs.* [^{18}F]FECh comparison, bone metastases evaluation
"prostate cancer" AND "[^{68}Ga]Ga-PSMA-11"	721	Early and recurrent Pca diagnosis
"prostate cancer" AND "[^{18}F]FDG"	623	Comparison with different radiotracers, rediscovering the utilities of [^{18}F]FDG in Pca diagnosis
"prostate cancer" AND "[^{18}F]PSMA-1007"	481	Recurrent Pca diagnosis
"prostate cancer" AND "[^{11}C]choline"	425	Recurrent Pca diagnosis
"prostate cancer" AND "[^{11}C]acetate"	193	Comparison with different radiotracers, early and recurrent Pca diagnosis
"prostate cancer" AND "*anti*-3-[^{18}F]FACBC"	98	Pca early detection

[^{18}F]FECh — 2-[^{18}F]fluoroethyl-choline; [^{68}Ga]Ga-PSMA-11 — gallium-^{68}prostate-specific membrane antigen-11; [^{18}F]FDG — 2-deoxy-2-[^{18}F]fluoro-D-glucose; [^{18}F]PSMA-1007 — fluorine-18 prostate-specific membrane antigen-1007, [^{11}C]choline — carbon-11-labelled choline; [^{11}C]acetate — carbon-11-labelled acetic acid, anti-3-[^{18}F]FACBC — anti-1-amino-3–[^{18}F]-fluorocyclobutane-1-carboxylic acid

One of the most sensitive and specific method of Pca diagnosis is the PSA level measurement, used both for screening and recurrent Pca detection [3, 4]. Therefore, the connection between PSA level and the radiopharmaceuticals' uptake level measured with the PET-dedicated parameter maximal standardized value uptake (SUVmax) obtained in PET-CT study using variety of radiopharmaceuticals has been frequently discussed by the Authors [4]. However, prior to 2019, the articles involved mainly the [^{18}F]FECh studies. The recent literature focuses on the applications of the newest and most promising compounds, such as [^{68}Ga]Ga-PSMA-11, and Pca's Theranostics supported by NM resources (radiopharmaceuticals and techniques). Within 2022-2023, the leading subject concerning Pca patients' management was the use of lutetium-^{177} PSMA-617 ([^{177}Lu]Lu-PSMA-617, Pluvicto^{TM}) or actinium-^{225} PSMA-617 ([^{225}Ac]Ac-PSMA-617) in Theranostics rather than distinguishing different characteristics of radiopharmaceuticals or their usefulness in Pca staging and restaging. The summary presented in this study does not include all radiotracers, but those most mentioned in the literature . Some of the potentially useful compounds, i.e., those used for Pca PET-CT diagnosis (eg., [^{18}F]PSMA-1007), androgen receptors expression PET-CT imaging radiopharmaceuticals (i.e. fluoro-5α-dihydrotestosterone, [^{18}F]-FDHT), or SPECT-dedicated compounds labelled with the technetium-99-metastable ([^{99m}Tc]Tc; eg. [^{99m}Tc]Tc-PSMA-T4) used for Pca diagnosis, have not been widely discussed in this study due to a relatively low number of available reports describing their utilities [9–11].

From first reports and FDA approval to clinical practice

Aside from the radiopharmaceuticals' overview, we have analysed literature making the first mention of each radiotracer's application in Pca patients' evaluation in comparison with the FDA approval timeline. Over the course of years, the Authors presented a potential utility of multiple radiotracers for Pca diagnosis. However, the extensive research has led to just a few FDA approvals of use in Pca patients, namely the labelled-choline compounds (FDA-approved in 2012) and anti-3-[^{18}F]FACBC (FDA-approved in 2016) have been recognized as highly useful in Pca detection and monitoring, especially considering the metastatic bone lesions regardless of the histologic structure of the lesion [6–8, 12, 13].

Undoubtedly, one of the most available and most commonly used radiotracers in oncology is [^{18}F]FDG, approved by the FDA in 2000.

The utilities of the radiopharmaceutical [^{18}F]FDG in the Pca patients' diagnosis have been studied since 1994. Some of the Authors [14] focused on the advantages and limitations of using [^{18}F]FDG in evaluating primary Pca tumours, suggesting its potential utilities in detecting poorly differentiated Pca. Since 2021, the Authors have mainly described the usefulness of the [^{18}F]FDG PET-CT method in advanced stage of Pca assessment [15]. The advantage of the technique seems to be a relatively high availability of the [^{18}F]FDG when compared with the Pca-specific radiotracers.

Following 2000, the Authors [16-18] focused on describing opportunities of using anti-[^{18}F]FACBC, [^{18}F]FECh, [^{11}C]acetate (FDA-approved in 2012) in primary and recurrent Pca, especially in castrate-resistant Pca patients. Furthermore, Authors [19] proposed using [^{11}C]choline as potentially superior to the available radiopharmaceuticals in detecting biochemical Pca recurrence to provide appropriate treatment in patients in whom a lymph nodes relapse has been detected. In the last three years, however, the Authors have mainly discussed the utilities of [^{68}Ga]Ga-PSMA-11 (approved by FDA in 2020) in Pca evaluation with just a few analyses comparing the ^{68}Ga-labelled tracers and other, widely investigated compounds. Eventually, the novelty in literature seems to be the non-FDA-approved [^{18}F]PSMA-1007 (Fig. 2 and 3).

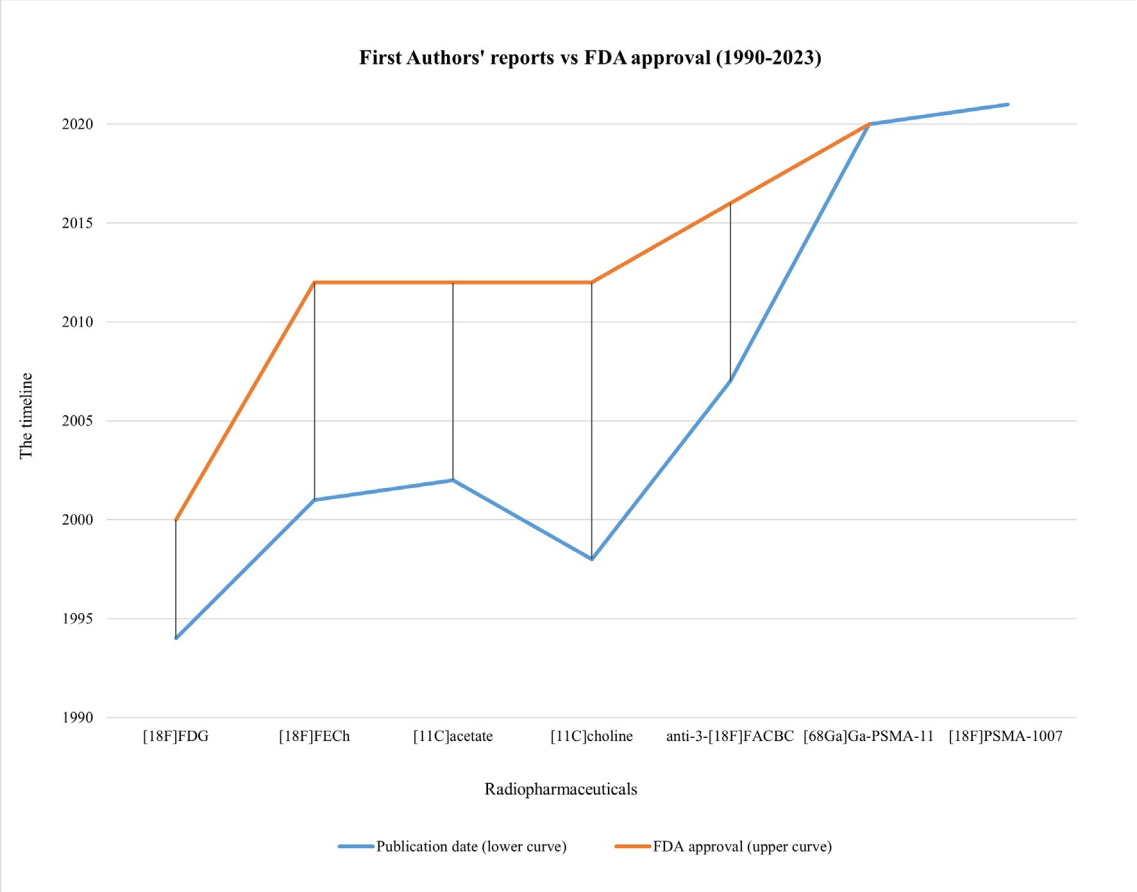

Figure 2. The timeline of radiopharmaceuticals that are most researched in prostate cancer (Pca) diagnosis: the first available literature mention versus Food and Drug Administration (FDA) approval (1990–2023). [^{18}F]FDG — 2-deoxy-2-[^{18}F]fluoro-D-glucose; [^{18}F]FECh — 2-[^{18}F]fluoroethyl-choline; [^{11}C]acetate — carbon-11-labelled acetic acid; [^{11}C]choline — carbon-11- labelled choline; anti-3-[^{18}F]FACBC — anti-1-amino-3–[^{18}F]-fluorocyclobutane-1-carboxylic acid; [^{68}Ga]Ga-PSMA-11 — gallium-68 prostate-specific membrane antigen-11, [^{18}F]PSMA-1007 — fluorine-18 prostate-specific membrane antigen-1007

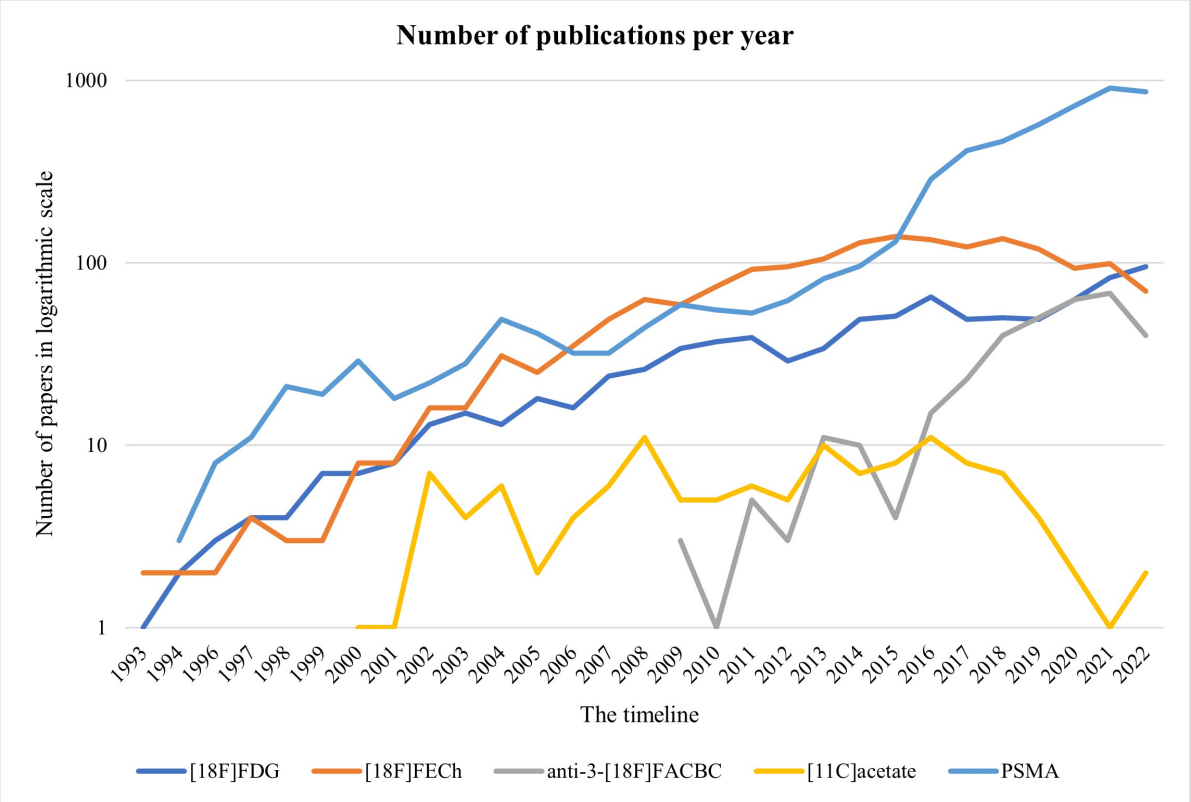

Figure 3. Radiopharmaceuticals most researched in the literature (1990-2023). [^{18}F]FDG — 2-deoxy-2-[^{18}F]fluoro-D-glucose; [^{18}F]FECh — 2-[^{18}F]fluoroethyl-choline; anti-3-[^{18}F]FACBC — anti-1-amino-3–[^{18}F]-fluorocyclobutane-1-carboxylic acid; [^{11}C]acetate — carbon-11-labelled acetic acid; PSMA — radiotracers targeting prostate-specific membrane antigen — positive lesions

According to the literature review, the Authors studied multiple tracers to indicate the most suitable radiopharmaceutical for sensitive and specific Pca diagnosis, focusing on each compound in a specific moment of the publishing timeline. Within the last couple of years, the [^{68}Ga]Ga-PSMA-11 has gained recognition as being an incredibly valuable tracer and, therefore, widely discussed by the Authors. [^{11}C]acetate seems to be the least researched among all above-mentioned compounds due to its relatively low availability. In this study, we observed the highest number of [^{18}F]FDG, [^{18}F]FECh, anti-3-[^{18}F]FACBC, [^{11}C]acetate, and [^{68}Ga]Ga-PSMA-11 studies published in 2022, 2015, 2021, 2002, 2021, respectively. A very recent literature research shows, however, the increased interest in [^{18}F]FDG studies, despite wide investigations conducted by the Authors in the past.

Pca diagnosis — methods and radiopharmaceuticals: summary

According to Authors [20-26], the early detection of the primary tumour in Pca might be performed using various imaging modalities and should be started from evaluating the PSA level. Very often, the investigators have mentioned the TRUS examination, which has been considered as the method of choice in the Pca patients' diagnosis, especially for the screening purposes. The predominantly mentioned methods of imaging were the contrast-enhanced MRI and the PET-CT study using the radiopharmaceuticals [^{18}F]FDG, [^{18}F]FECh, and the [^{68}Ga]Ga-PSMA-11. The usefulness of the above-mentioned techniques has been described several times in case of the primary and recurrent Pca detection, as well as in the metastatic lesions' evaluation [20–26].

The evaluation of the metastatic bone lesions has been considered as the substantial element in the Pca patients' diagnosis and critical for establishing the therapeutic protocol. Among the NM methods of imaging, it is the PET-CT study using the radiotracers [^{68}Ga]Ga-PSMA-11 and the [^{18}F]FECh that was found to be the most relevant. According to some of the reports [27, 28], the technetium-^{99m}-labelled (^{99m}Tc) methylene diphosphonate (MDP) planar bone scintigraphy (BS), [^{18}F]FDG PET-CT, and [^{18}F]FECh PET-CT methods can be successfully used in patients with advanced Pca, as well as in early staging before the treatment. Nevertheless, it seems important to mention the superiority of the three-dimensional PET-CT method to planar BS, providing the data limited to the bones' involvement. The Authors [5,9,10,29] mentioned also the possibility to perform PET-CT using ^{18}F-labelled sodium fluoride ([^{18}F]NaF), as well as SPECT-CT studies using the ^{99m}Tc-based ligands, such as [^{99m}Tc]Tc-PSMA-T4, [^{99m}Tc]Tc-MIP-1404 SPECT-CT, as potentially valuable in Pca evaluation.

According to Authors [30–32], approximately 30% of Pca patients treated with external beam radiotherapy can develop a biochemical failure which may result in distant metastases. The Authors [30] suggested the benefits of using multiple methods of imaging, i.e., BS, CT, and the MRI in each patient, which increases the possibility to detect metastatic lesions in soft tissue, lymph nodes and skeletal system, which might be of value especially in case of biochemical failure development [30]. Most often, the reports indicated the PET-CT study as the most effective imaging tool in initial and recurrent Pca assessment, especially when using the specific radiopharmaceuticals. The widely used [^{18}F]FDG PET-CT examination has been recognized as inaccurate to diagnose the initial Pca due to non-specific properties of the radiotracer [^{18}F]FDG, but useful in case of advanced and recurrent Pca diagnosis (i.e. high Gleason score patients [33]).

Authors [31] showed that not only the actual radiotracer, but also the isotope selection is highly important due to half-time period and specific tracer's characteristics. For

example, [^{18}F]FECh due to a relatively long half-time of ^{18}F (app. 110 minutes, min) ensures the possibility to perform both early and delayed scanning. Nevertheless, the compound tends to concentrate in the urine bladder, causing high radioactivity level, which limits the possibility to assess the prostate gland and the local tissues if the scanning will not be precisely designed. [^{11}C]acetate PET-CT and [^{18}F]FAc PET-CT seem to be more sensitive and specific than the [^{18}F]FECh PET-CT method in early Pca diagnosis. The short ^{11}C half- life (20 min) might be considered as disadvantage of the technique, however the lack of accumulation in the kidneys makes the [^{11}C]acetate a highly valuable radiotracer [32]. The ^{68}Gaoffers longer half-life of 68 min which seems more convenient for the onsite use of the radioisotope, however, limits the possibility to perform the delayed scanning as well as the radiocompounds' transportation to different centres. The use of ^{68}Ga-labelled radiotracers' provide the possibility to obtain a high tumour-to-tissue ratio within an hour post injection with no cerebral cortex or heart uptake and low lung and thymus accumulation, which seems to be a great advantage of this radiotracer while the observed renal excretion is the limitation of the study using ^{68}Ga-labelled radiotracers [23]. The Authors [31, 32, 34] found that performing the PET-CT examinations using the labelled amino-acids (i.e. anti-3-[^{18}F]FACBC) and the nucleosides (^{18}F-fluoro-methyl-arabinofuranosyl-uracilas, [^{18}F]FMAU) is helpful in the initial and recurrent Pca diagnosis [31, 32, 34]. [^{18}F]PSMA-1007 ([^{18}F]PSMA-7) is a radiopharmaceutical newly introduced into clinical trials, used for the PET-CT scanning purposes is the [35–39], which has been mentioned as improving the Pca patients' diagnostic management, especially in the early detection of the recurrent tumours in Pca patients who underwent radical prostatectomy.

Discussion

According to the literature [3, 4, 42], the PSA level is the most relevant Pca biomarker used for screening purposes. Among the useful methods of imaging, the Authors [1–4, 25, 26, 28] mention several imaging methods, including TRUS, MRI, BS, SPECT-CT, and PET-CT using a variety of radiotracers. The most mentioned methods of imaging regardless of the stage of Pca are the MRI examination, BS, and the PET-CT study using the radiotracers [^{68}Ga]Ga-PSMA- 11, [^{18}F]FECh, and [^{11}C]acetate. [^{18}F]FDG PET-CT scanning is the most commonly performed method of choice worldwide in different oncological diseases management; however, the non-specific properties of the radiotracer [^{18}F]FDG limit the ability to differentiate between the benign and malignant lesions in the prostate gland [31]. Moreover, the high [^{18}F]FDG concentration in the urine bladder is a limitation of the [^{18}F]FDG PET-CT method. Some of the ^{18}F-labelled radiotracers are considered less useful in case of early Pca diagnosis than, e.g., ^{11}C-labelled ligands, i.e., [^{11}C]acetate versus [^{18}F]FAc, due to a high accumulation [^{18}F]FAc [31] in urine of. Some of the Authors [31] reported

promising results of the [^{11}C]acetate PET- CT scanning, however the tracer's accessibility is limited. The novelty in the Pca patients' diagnostic management is the possibility to use the [^{99m}Tc]Tc-PSMA-T4 and [^{99m}Tc]Tc-MIP- 1404 [9,10,29]. The [^{99m}Tc]Tc-PSMA-T4 SPECT-CT might be helpful in Pca evaluation, i.e. in case of limited PET-CT scanners accessibility, despite lower spatial resolution of the method. [^{18}F]PSMA-1007 is another radiotracer currently mentioned in the literature [30–32, 35], which has been considered to improve the management of Pca patients. The main limitation of the widely described [^{68}Ga]Ga-PSMA-11 is that the radioisotope is excreted by the kidneys, which enhances the urine radioactivity and requires protracted examinations. The Authors [34] suggest that replacing the isotope ^{68}Ga with ^{18}F, and using PSMA-11 instead of PSMA-1007, by modifying biochemical properties of the radiotracer, remove the limitations of the [^{68}Ga]Ga-PSMA-11 PET-CT method and, therefore, improve the Pca diagnosis, especially in the recurrent Pca patients who underwent radical prostatectomy [34]. Similarly, the *anti*-3- [^{18}F]FACBC does not accumulate in the urine bladder as early as other radiotracers [6–8, 12, 13].

Over the course of years, the Authors have studied several radiotracers in order to establish the most appropriate compound for Pca evaluation using the PET-CT method. One of the most interesting observations regarding radiotracers used for Pca diagnosis is the role of [^{18}F]FDG. Once considered useful, then neglected in the literature as non-tumour- specific enough for the advanced Pca evaluation, has been recently rediscovered by the Authors' due to the limited availability of more advanced compounds, i.e., [^{18}F]FECh. The [^{18}F]FECh has been considered more useful than [^{18}F]FDG and developed as the first prostate- specific radiopharmaceutical. However, some of the reports [40-42] mention a limited usefulness of [^{18}F]FECh PET-CT in small lesions evaluation due to a low spatial resolution of the study, in pre-treatment tumour evaluation due to observed uptake of [^{18}F]FECh in glandular tissue, and benign hyperplasia assessment. Moreover, some of the Authors [28] suggest that [^{18}F]FECh PET-CT and [^{99m}Tc]Tc-MDP BS can be considered complimentary methods of Pca metastatic bone lesions evaluation. The [^{11}C]acetate has been recognized as highly valuable in the initial Pca detection and staging but, simultaneously, unavailable for most of the departments. The potentially most useful radiotracer is [^{68}Ga]Ga-PSMA-11, offering (up to 100% [2]), distant Pca metastases detection (over 80% [2,17,32]. In this study, we found that the number of articles considering the use of the [^{18}F]FDG, and [^{68}Ga]Ga-PSMA-11 constantly increases, while [^{11}C]acetate research remains comparable over time. At the same time, the number of reports on labelled-choline compounds and *anti*-3-[^{18}F]FACBC dropped in 2018 and 2020, and continues to decrease.

The imprecise count of articles is the main study limitation. It seems impossible to obtain a precise number and tendencies in publishing when Pca NM diagnosis is considered. Therefore, materials presented in this study shall be considered an estimated summary of the

Authors' interest in presenting diagnostic solutions and considerations related to radiotracers over the course of the last thirty years. Furthermore, neglecting PET-MRI study applications in Pca diagnosis could be considered the study limitation. Omitting the above-mentioned technique in the presented considerations results from the lack of sufficiently documented reports confirming possible usefulness of the method in Pca evaluation. Finally, not all radiotracers useful for Pca' have been described in the study as we have focused on the ones most mentioned by the Authors, omitting those which demand much more studies to be considered useful, according to the availability of literature sources.

Despite the development of oncological diagnostic methods and successful Pca screening, fast and precise Pca detection seems challenging. This results in a great interest of professionals researching the most effective diagnostic management tools. NM offers various possibilities due to accessible radiopharmaceuticals' range. Nevertheless, it seems impossible to indicate one specific radiotracer of choice which would be both optimal and available enough to – in conjugation with the technique — ensure the best diagnostic pathway, suitable for all clinical indications. Over the course of years, researchers have focused on evaluating various radiopharmaceuticals ensuring the highest specificity of the imaging method in Pca staging and restaging, therapy planning and recurrence detection.

Conclusions

The analysis of over 30 years of several Authors' considerations regarding the most suitable radiopharmaceuticals for Pca diagnosis leads to the conclusion that Pca remains a constant focus of the NM drug development. However, despite the extensive research of the specific compounds' utilities in Pca diagnosis, leading to FDA's approving their use in Pca evaluation in daily clinical practice, the analysis of the most recent studies showed an increasing interest of the Authors in both Pca-specific [^{68}Ga]Ga-PSMA-11, and non-tumour-specific [^{18}F]FDG studies.

Conflict of interest

Authors declare no conflict of interest.

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Disclosure

All Authors of this manuscript have approved the whole article content.

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