ANTICANCER RESEARCH *44*: 2297-2305 (2024)
doi:10.21873/anticanres.17037

Review

Systematic Review of the First 40 Cases of ^{177}Lu-PSMA Therapy in the Treatment of Non-prostatic Cancer

HAIM GOLAN[1], KUDRATBEK K. TURSUNOV[2] and OLGA VOLKOV[3]

[1]*Theranostics and Molecular Imaging, Isotopia Molecular Imaging Ltd., Tel Aviv, Israel;*
[2]*Traumatology and Orthopedics, Andijan State Medical Institute, Andijan, Uzbekistan;*
[3]*Nuclear Medicine Institute, Sheba Medical Center, Ramat Gan, Israel*

Abstract. *Background/Aim: The current systematic review aimed to collect and analyze all available published and unpublished cases in which prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (^{177}Lu-PSMA) was used to treat non-prostatic cancer. Materials and Methods: Literature search and evidence acquisition through contacts with organizations that use ^{177}Lu-PSMA were employed. PubMed/Medline, SCOPUS, and ScienceDirect searches were performed following PRISMA recommendations. The search strategy was to screen all articles describing ^{177}Lu-PSMA radioligand therapy published to date with the key word "^{177}Lu-PSMA". These articles were collected and screened for non-prostatic cancer cases. Quality assessment was performed using the GRADE criteria. Results: A total of 713 articles were screened, and the search revealed 15 eligible records. Forty patients with a mean age of 51.2±18.5 years were treated with ^{177}Lu-PSMA for non-prostatic cancer. Of them, 30 cases were published, and 10 were found in medical institution records. Cancers of the salivary glands were most often targeted (13/40), followed by various brain cancer types (8/40), and osteosarcoma (6/40). The authors used previously established protocols for castration-resistant prostate cancer with the dose per cycle as 6.0-7.4 GBq and the number of cycles between one and four. Toxicity was estimated as low, and 21 out of 28 patients with reported outcomes survived to the time of the publication. Conclusion: PSMA-targeted radioligand therapy was infrequently used to treat different non-prostatic cancer types in various target organs. These pioneering efforts indicate that ^{177}Lu-PSMA can be used to treat non-prostatic cancer with PSMA expression. The toxicity of such treatment was low, and the outcome was relatively good.*

Correspondence to: Haim Golan (ORCID: 0000-0002-6054-5120), MD, 25 Nehar Hayarden, Kiryat Ono, 5545052, Israel. Tel: +972 537346145, Fax: +972 39300667, e-mail: hmgolan@gmail.com

Key Words: PSMA-targeted radioligand therapy, ^{177}Lu-PSMA, non-prostatic cancer, systematic review.

The role of prostate-specific membrane antigen (PSMA) theranostics is well-known regarding prostate cancer. Non-prostatic diseases exhibiting PSMA uptake on positron-emission tomography (PET) are becoming more common as the number of scans performed increases. Recognizing those tumors exhibiting PSMA expression is essential since the theranostics approach might also be applied for them. The topic of this systematic review was developed in four phases.

Phase 1: PSMA was discovered. This 750-residue integral membrane glycoprotein known as glutamate carboxypeptidase II, which acts as a transmembrane zinc metalloenzyme, was purified in 1979, received its serological definition in 1981-82, and was immunohistochemically localized in 1983 (1-4). Finally, its role was established as "a new antigenic marker in epithelial prostatic cells and serum of prostatic cancer patients" in 1987, and it became widely known as PSMA (5).

Phase 2 began in 1999 and ended about 2008 (6-11). During these years, researchers realized that PSMA is not 'prostate-specific'. PSMA was found in the epithelium of the prostate, urinary bladder, kidneys, liver, esophagus, stomach, small intestine, colon, testicular seminiferous tubules, hippocampal neurons and astrocytes, ependyma, and the adrenal gland. Moreover, PSMA was found in females in the ovary stroma, breast, and fallopian tubes (11). Among specific benign tissues, PSMA was detected in prostate secretory-acinar epithelium, duodenal columnar epithelium, proximal renal tubular epithelium, colonic ganglion cells, and breast epithelium (6). Among specific tumors besides prostatic, PSMA presence was detected in renal cells, transitional cells of the urinary bladder, testicular embryonal, neuroendocrine, breast, and pancreatic duct carcinomas, glioblastoma multiforme, malignant

melanoma, soft tissue sarcoma, colonic adenocarcinoma, and osteosarcoma (6, 7, 9, 12). In addition to PSMA, prostate-specific antigen (PSA) was also found in different tissues in men and women (13-15). PSA is secreted into the blood, and its serum concentration is easy-detectable. That is why PSA produced by epithelial prostatic cells was suggested as a possible biomarker in non-prostatic cancers (16).

Phase 3: The most effective non-surgical treatment modality for prostate cancer (prostatic carcinoma) was established. Such intervention was needed for castration-resistant prostate cancer and metastatic castration-resistant prostate cancer. PSMA-targeted radioligand therapy was suggested for this purpose. β-Particle-emitting lutetium-177-labeled PSMA inhibitor (^{177}Lu-PSMA) with its variations ^{177}Lu-PSMA-617 (vipivotide tetraxetan), ^{177}Lu-PSMA-I&T (zadavotide guraxetan), and some others were offered as a new molecular nuclear radiotherapy agent. It was tested *in vivo* in 2011 (17) and adopted in 2013 (18). After that, seven systematic reviews and meta-analyses, all dedicated to the role of ^{177}Lu-PSMA in the treatment of castration-resistant prostate cancer, were published from 2016 to 2021 (19-25). In summary, ^{177}Lu-PSMA radioligand therapy appeared to be relatively effective even for patients with metastases, prolonged overall survival and progression-free survival periods and demonstrated a low toxicity rate.

Phase 4 is the topic of the current review. It was assumed that if ^{177}Lu-PSMA radioligand therapy was effective in treating prostate cancer, it might be equally effective in the treatment of other cancers in which PSMA is also expressed. It was hypothesized that soft-tissue and bone cancers with strong neovascular PSMA expression may be treated with PSMA-targeted radioligand therapy (26).

Following PICOS (patients, intervention, comparison, outcomes, study design) criteria (27), the current systematic review aimed to answer the following questions: How many patients, if any, with non-prostatic cancer have been treated with PSMA-targeted radioligand therapy to date? How was PSMA expression in non-prostatic tumors detected and evaluated? What types of tumors were involved, and what organs were targeted? What treatment protocols were used (dose, number of cycles, and duration of the treatment)? What results were achieved regarding treatment response, outcome, and treatment-toxicity-related complications?

Materials and Methods

Search strategy. The Authors aimed to collect as many cases as possible, published and unpublished, in which ^{177}Lu-PSMA radioligand therapy was applied to non-prostatic cancer. Therefore, we employed literature search, conference presentations search, and evidence acquisition through contacts with organizations (hospitals, medical centers, and theranostic centers) which were using ^{177}Lu-PSMA radioligand therapy.

Literature search and selection criteria. The current review applied recommendations presented by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (28). We performed PubMed/Medline, SCOPUS, and ScienceDirect searches, including publications in English and other languages, and with no restrictions on the years of publication. The search strategy was relatively simple because not many articles describing ^{177}Lu-PSMA radioligand therapy have been published to date, and we only used "^{177}Lu-PSMA" as a key word. All these articles were collected. The report exclusion procedure was done in several steps. First, all publications regarding prostate cancer were excluded. Secondly, all review and meta-analysis articles were excluded. Finally, all animal studies and articles describing ^{177}Lu-PSMA technicalities without involvement of patients were also excluded. The remaining publications were investigated for ^{177}Lu-PSMA radioligand therapy for non-prostatic cancer. Meta-analysis was not performed due to the level of evidence (IV-V) of the included studies, as determined following the 2011 Oxford Centre for Evidence-Based Medicine guidelines (29). Two reviewers searched for publications up to 1 January 2024.

We planned to assess the treatment response as a binary outcome based on serum PSA decline of ≥50% as the primary variable and any level of PSMA decrease/increase as additional binary outcomes if these variables were reported in the studies. In some cases, additional information was requested from the corresponding authors of the selected publications.

Radioligand therapy-related toxicities were assessed with the Common Terminology Criteria for Adverse Events (CTCAE) grading system (30) and divided into two groups: Low-grade toxicities (CTCAE 1/2) and high-grade toxicities (CTCAE 3/4) (Grade 5: death). If the analyzed publications did not report toxicities with the CTCAE grading system, we estimated the CTCAE grade using clinical information, the description of the complication, and other related information provided in the publication. The term 'not reported' was used if the toxicity information was not provided. A comparison of ^{177}Lu-PSMA-I&T and ^{177}Lu-PSMA-617 was not performed because it was already demonstrated that these two variations do not statistically significantly differ when applied to therapy (20).

Assessment of risk bias and quality appraisal. The selected studies did not describe prospective studies and randomized trials, and the risk of bias assessment was performed with limitations applicable to case reports. Two independent investigators (HG and OV) used the criteria of the GRADE guidelines to assess the individual quality of selected studies that involved a high-moderate-low-very low definition scale (31). All discrepancies were resolved by consensus with KKT serving as a judge. The quality appraisal of the relevant articles was performed and is reported. Assessment of risk bias was performed with the help of the Cochrane classification (32). Levels of evidence were assessed according to the Oxford Centre for Evidence-Based Medicine guidelines (29).

Additional evidence acquisition. Conference proceedings were searched for oral or poster presentations reporting ^{177}Lu-PSMA therapy of non-prostatic tumors which were not further published in academic articles. In addition, the Authors personally contacted known medical organizations in which ^{177}Lu-PSMA was used. While all of them were involved in treating castration-resistant prostate cancer, the inquiry concerned ^{177}Lu-PSMA application to non-prostatic cases. The institutions were asked to provide the information to cover the above-mentioned research questions: Non-

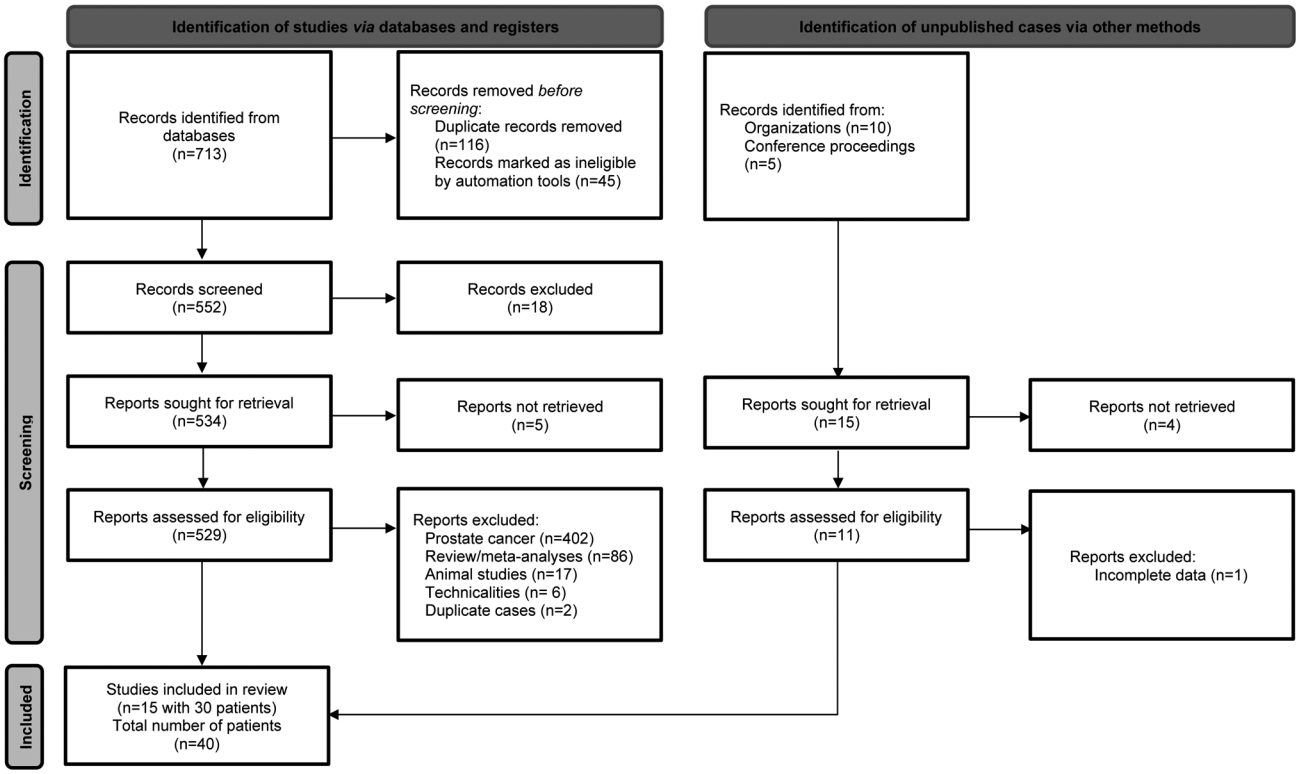

Figure 1. *PRISMA flow diagram of the current study.*

prostatic tumor ^{177}Lu-PSMA therapy – yes/no; how many patients (age, sex); pretreatment diagnostics (PSMA expression in a given tumor case; serum PSA in ng/ml); types of tumors treated and target organs; the treatment protocol (dose, cycles, and duration); the treatment response (serum PSA decline of ≥50% – yes/no); and follow-up (outcome, survival, and toxicity-related complications according to CTCAE, version 5).

Results

The main findings, quality appraisal, and bias. We screened 713 articles, and the literature search gave 15 records that met our eligibility criteria. Figure 1 shows the PRISMA flow diagram. Table I shows a summary of the studies and unpublished cases included in the review. The quality appraisal of the relevant articles is presented in Table II. The first case of PSMA-targeted radioligand therapy for non-prostatic cancer was reported in 2017 (33) but was duplicated in a later publication. These 15 publications described 30 patients (34-48). Four were described twice, and one duplicate was excluded (33). We added 10 unpublished cases which were obtained directly from medical institutions to the review. The examined studies spanned the period from 2017 to 2023 and were carried out in Europe and Asia. Researchers from the USA, the UK, Canada, and Australia apparently did not participate in these pioneering efforts.

The absolute majority of the articles presented case reports or case series (13/15; 19 patients) and were classified as level V (cases) or IV (case series) evidence. There were two retrospective studies (11 patients), and no prospective study was retrieved. The overall quality of the selected reports included was moderate to low with demographic data (83.5%), types and stages of treated tumors (100.0%), ^{177}Lu-PSMA therapy protocol (100.0%), toxicity estimations (83.5%), and outcome (50.0%) reported. For case reports or retrospective studies, the quality of studies was graded as "low" as per the GRADE criteria (31). Most of the studies were case reports that described "first-time" events, and the selection bias was minimized. Moreover, the issue of consecutive vs. randomization was unimportant because two retrospective studies reported consecutive series of patients. However, outcomes were not reported for 15 patients, and risk of bias due to missing outcome data was estimated as serious according to Cochrane classification (32). The quality of unpublished cases and conference presentations was high because they were selected on the basis of all the above-mentioned variables and their presentation was supervised by us. Evaluating the contribution of possible covariates in the heterogeneity was impossible because the selected articles indicated 16 different types of tumors in 11

Table I. *Summary of the studies and unpublished cases included in the review. The studies are in chronological order.*

No.	First author (Ref)	Year	Country	Study type	Patients, n	Age, years	Sex	Tumor	Organ
1	Tolkach (34)	2018	Germany	Case report	1	38	F	Breast carcinoma	Breast
2	Has Simsek (35)	2019	Turkey	Case report	1	67	M	AdCC	Salivary gland
3	Assadi (36)	2019	Iran	Case report	1	42	M	RrDTC	Thyroid gland
4	Kunikowska (37)	2020	Poland	Case report	1	54	M	GBM	Brain
5	Kumar (38)	2020	India	Case report	1	37	M	GBM	Brain
6	de Vries (39)	2020	Netherlands	Case series	2	50, 65	F, F	PTC	Thyroid gland
7	Hirmas (40)	2021	Germany	Case report	2	NR	NR	HCC	Liver
8	Has Simsek (41)	2021	Turkey	Case report	1	46	M	MTMGCT	Testicle
9	Klein Nulent (42)	2021	Netherlands	Retrospective	6	32-74	3 M/3 F	AdCC/ACC	Salivary gland
10	Truckenmueller (43)	2022	Germany	Case series	3	59/NR	M/NR	1 WG/2 MA	Brain
11	Zhang (44)	2023	Germany	Case report	1	61	M	Renal cell carcinoma	Kidney
12	Civan (45)	2023	Germany	Retrospective	5	NR	M/F	4 AdCC/1 ACC	Salivary gland
13	Terroir (46)	2023	France	Case report	1	56	M	Metastatic carcinoma	Salivary gland
14	Naeem (47)	2023	Pakistan	Case report	1	69	M	Renal cell carcinoma	Kidney
15	Graef (48)	2023	Germany	Case series	3	58-70	M/F	Glioma	Brain
16	Conference case 1	2020	Ukraine		1	29	M	OSCC	Oral cavity
17	Unpublished case 1	2020	Uzbekistan		1	20	F	Osteosarcoma	Bone (femur)
18	Conference case 2	2021	Ukraine		1	57	M	OSCC	Oral cavity
19	Unpublished case 2	2021	Uzbekistan		1	61	F	Osteosarcoma	Bone (femur)
20	Unpublished case 3	2021	Uzbekistan		1	30	M	Osteosarcoma	Bone (tibia)
21	Unpublished case 4	2022	Uzbekistan		1	19	M	Osteosarcoma	Bone (femur)
22	Unpublished case 5	2022	Uzbekistan		1	63	M	Osteosarcoma	Bone (tibia)
23	Unpublished case 6	2022	Uzbekistan		1	60	F	Osteosarcoma	Bone (femur)
24	Conference case 3	2023	Israel		1	68	M	AdCC of tongue	Tongue
25	Conference case 4	2023	Israel		1	71	M	Cutaneous melanoma	Skin

ACC: Acinic cell carcinoma; AdCC: adenoid cystic carcinoma; GBM: glioblastoma multiforme; HCC: hepatocellular carcinoma; MA: mutant astrocytoma; MTMGCT: metastatic testicular mixed germ cell tumor; NR: not reported; OSCC: oral squamous cell carcinoma; PTC: papillary thyroid carcinoma; RrDTC: radioiodine-refractory differentiated thyroid cancer; WG: wild-type glioblastoma.

organs (Table I). Having 40 cases with 16 different tumor types made a sound statistical analysis impossible.

Specific results. Answering our five review questions, we received the following results:

A total of 40 patients within the age range from 19 to 74 years (mean 51.2±18.5 years), 24 males, 12 females, and four with unreported sex, were reported to have been treated with ^{177}Lu-PSMA for non-prostatic cancer. Of them, 30 cases were published, and 10 were found in medical institution records or were presented at conferences (Table I).

PSMA expression in non-prostatic tumors was reported as immunohistochemical expression in all studies selected, either as a statement of the fact (14 publications) or with an indication of the expression percentage (one publication) and ranged from 5% to 95%. Eight unpublished cases presented PSMA expression as immunohistochemical expression, which ranged from 5% to 50%, and nine unpublished cases presented serum PSA concentration, which ranged from 1.1 to 23.2 ng/ml.

Despite the small number of cases, the reports indicated numerous target organs and types of cancer (Table I). Cancers including acinic cell carcinoma, adenoid cystic carcinoma, glioblastoma multiforme, hepatocellular carcinoma, mutant astrocytoma, metastatic testicular mixed germ-cell tumor, oral squamous cell carcinoma, osteosarcoma, papillary thyroid carcinoma, radioiodine-refractory differentiated thyroid cancer, melanoma, and wild-type glioblastoma were targeted. The breast, bones, kidneys, oral cavity, salivary glands, tongue, skin, thyroid gland, brain, testicles, and the liver were involved. Various cancers of the salivary glands were most often targeted (13/40), followed by various brain cancer types (8/40), and osteosarcoma of long bones (6/40).

The treatment protocols were based on previously established protocols for castration-resistant prostate cancer, with the dose per cycle as 6.0-7.4 GBq in most cases and the number of cycles between one and four (Table III). The duration of the treatment varied from 4 to 11 weeks when more than one cycle was used.

Unfortunately, none of the 15 publications indicated the presence/absence of serum PSA decline of ≥50% (Table III). Among the 10 unpublished cases, such decline was detected in seven, while the serum PSA decline did not reach 50% in three cases. Among 35 cases with reported toxicity estimation, the reaction of only one patient was estimated as

Table II. *Systematic review of the first 40 cases of the ^{177}Lu-PSMA therapy in the treatment of non-prostatic cancer. Studies included with quality appraisal.*

First author	Year	Evidence level	Age	Sex	Tumor type	Location	Diagnostics	Treatment	Toxicity	Outcome
Tolkach (34)	2018	V	Yes	Yes	Yes	Yes	Incomplete*	Yes	Yes	NR
Has Simsek (35)	2019	V	Yes	Yes	Yes	Yes	Incomplete	Yes	Yes	NR
Assadi (36)	2019	V	Yes	Yes	Yes	Yes	Incomplete	Yes	NR	Yes
Kunikowska (37)	2020	V	Yes	Yes	Yes	Yes	Incomplete	Yes	NR	NR
Kumar (38)	2020	V	Yes	Yes	Yes	Yes	Incomplete	Yes	Yes	NR
de Vries (39)	2020	V	Yes	Yes	Yes	Yes	Incomplete	Yes	Yes	Yes
Hirmas (40)	2021	V	NR	NR	Yes	Yes	Incomplete	Yes	NR	NR
Has Simsek (41)	2021	V	Yes	Yes	Yes	Yes	Incomplete	Yes	Yes	Yes
Klein Nulent (42)	2021	III	Yes	Yes	Yes	Yes	Incomplete	Yes	Yes	Yes
Truckenmueller (43)	2022	IV	Yes	Yes	Yes	Yes	Incomplete	Yes	Yes	Yes
Zhang (44)	2023	V	Yes	Yes	Yes	Yes	Incomplete	Yes	Yes	NR
Civan (45)	2023	III	NR	Yes	Yes	Yes	Incomplete	Yes	Yes	NR
Terroir (46)	2023	V	Yes	Yes	Yes	Yes	Incomplete	Yes	Yes	Yes
Naeem (47)	2023	V	Yes	Yes	Yes	Yes	Incomplete	Yes	Yes	Yes
Graef (48)	2023	IV	Yes	Yes	Yes	Yes	Incomplete	Yes	Yes	NR

NR: Not reported. *Incomplete – the authors determined PSMA expression by immunohistochemistry but not serum prostate-specific antigen concentration.

high toxicity, and for the other 34 patients, toxicity was low. The outcome was reported for only 28 patients out of 40. Of them, seven patients died, with a survival range between 2 weeks and 9 months, but no sound estimation is possible because various cancer types were involved. The remaining 12 patients survived to the time of publication or retrieval, with a follow-up period from 15 weeks to 3 years.

Discussion

We aimed to collect all available published, conference-reported, or unpublished cases in which PSMA-targeted radioligand therapy was used to treat non-prostatic cancer. Only a few patients have been treated so far, and these pioneering efforts represent preliminary results. These results indicated that i) yes, ^{177}Lu-PSMA can be used for the treatment of non-prostatic cancer, ii) the toxicity of such treatment is low, and iii) the outcome is relatively good (21 out of 28 patients survived).

Most of the specialists in theranostics who tried ^{177}Lu-PSMA for the treatment of non-prostatic cancer used already well-established and tested protocols and guidelines recommended for treating castration-resistant prostate cancer (49, 50). Therefore, while pioneering, these efforts were relatively safe from the beginning. These protocols and guidelines are constantly improving; the last update was published in 2023 (51). We anticipate more novel applications of ^{177}Lu-PSMA in the future. Specifically for osteosarcoma, no cases were reported in publications, and we obtained data only for unpublished cases. Nevertheless, there are numerous indications in the emerging literature that expression of PSMA in osteosarcoma cases is frequent and well-detectable (52-55). Further efforts to treat osteosarcoma with ^{177}Lu-PSMA may be expected.

The proper selection of patients suitable for treatment will be the main effort if ^{177}Lu-PSMA treatment of non-prostatic cancer intensifies. As we mentioned above, the authors of all cases included in this review detected PSMA immuno-histochemical expression as a part of the selection procedure, but they did not measure serum PSA concentration. This variable is essential, and we believe that PSA concentration expressed (in ng/ml) should be measured as a part of the pretreatment decision-making process. For castration-resistant prostate cancer and especially for metastatic castration-resistant prostate cancer, these concentrations vary widely from 0.1 to 3,121.6 ng/ml (56). For patients with prostate cancer, PSA ≥1.75 ng/ml was suggested to be the optimal value for identifying positive ^{18}F-fluorocholine-PET/CT findings (57). Further research will be needed to establish similar indicators for non-prostatic cancer (16). After that, the selection process of patients with non-prostatic cancer suitable for ^{177}Lu-PSMA treatment will need to be optimized. Further development of this treatment modality for non-prostatic cancer may be expected.

Study limitations. All cases included in this review were small-group or case report studies related to patients with non-prostatic cancer. Further prospective investigations are required to validate our findings in a larger number of patients with various PSMA-expressing cancer types.

In conclusion, PSMA-targeted radioligand therapy was used to treat different non-prostatic cancer types and target other organs in 40 cases. These pioneering efforts indicated that ^{177}Lu-PSMA can be used to treat non-prostatic cancer with PSMA expression. The toxicity of such treatment was low, and the outcome was relatively good.

Table III. *Characteristics of the applied ^{177}Lu-PSMA radioligand treatment, outcome, and toxicity.*

No.	First author	Cases	PSA, ng/ml	PSMA IHC	DPC, GBq	No of cycles	IBC, weeks	PSA decline >50%	Toxicity	Survival/ status
1	Tolkach (34)	1	NR	+	7.5	2	NR	NR	Low	NR
2	Has Simsek (35)	1	NR	+	7.5	1	-	NR	Low	NR
3	Assadi (36)	1	NR	+	7.4	1	-	NR	NR	2 Weeks
4	Kunikowska (37)	1	NR	+	8.39	1	-	NR	NR	NR
5	Kumar (38)	1	NR	+	3.7	3	4	NR	Low	NR
6	de Vries (39)	1/2	NR	+	6.0	2	6	NR	Low	>1 Year
		2/2	NR	+	6.0	2	11	NR	NR	>6 Months
7	Hirmas (40)	1/2	NR	+	5.9	1	-	NR	NR	NR
		2/2	NR	+	6.2	1	-	NR	NR	NR
8	Has Simsek (41)	1	NR	+	6.03	2	6	NR	Low	>1 Year
9	Klein Nulent (42)	1/6	NR	5%	6.0-7.4	4	6-8	NR	Low	7 Months
		2/6	NR	30%	6.0-7.4	4	6-8	NR	Low	>3 years
		3/6	NR	NR	6.0-7.4	2	6	NR	High	3 Months
		4/6	NR	30%	6.0	1	-	NR	Low	5 Months
		5/6	NR	95%	6.0-7.4	2	6	NR	Low	6 Months
		6/6	NR	30%	6.0-7.4	2	6	NR	Low	9 Months
10	Truckenmueller (43)	1/3	NR	++	6.03	2	10	NR	Low	>15 Weeks
		2/3	NR	++	6.03	2	11	NR	Low	>15 Weeks
		3/3	NR	++	6.03	2	9	NR	Low	>15 Weeks
11	Zhang (44)	1	NR	+	6.0	1	-	NR	Low	NR
12	Civan (45)	1-3/5	NR	+	6.03	1	-	NR	Low	NR
		4-5/5	NR	+	6.03	2	9	NR	Low	NR
13	Terroir (46)	1	NR	+	6.08	4	6	NR	Low	Alive
14	Naeem (47)	1	NR	+	6.0-7.0	3	8	NR	Low	>2 Years
15	Graef (48)	3	NR	++	6.03	1	-	NR	Low	NR
16	OSCC 1	1	13.6	40%	6.03	2	8	Yes	Low	Alive
17	Osteosarcoma 1	1	2.4	5%	6.03	2	6	No	Low	Alive
18	OSCC 2	1	8.6	20%	6.03	4	6	Yes	Low	Alive
19	Osteosarcoma 2	1	11.3	20%	6.03	4	6	Yes	Low	Alive
20	Osteosarcoma 3	1	1.1	5%	6.03	4	8	Yes	Low	>1 Year
21	Osteosarcoma 4	1	18.7	30%	6.03	4	6	No	Low	Alive
22	Osteosarcoma 5	1	23.2	50%	6.03	4	6	No	Low	Alive
23	Osteosarcoma 6	1	10.5	30%	6.03	4	6	Yes	Low	Alive
24	AdCC of tongue	1	NR	+	6.9-7.6	3	Varied*	NR	Low	Alive
25	Cutaneous melanoma	1	8.2	+	6.3	1	-	Yes	Low	3 Months

AdCC: Adenoid cystic carcinoma; DPC: dose per cycle; IBC: interval between cycles (weeks); IHC: immunohistochemical; NR: not reported; OSCC: oral squamous cell carcinoma. *The first cycle was received in August 2022, the second cycle in September 2022, but the third cycle was received in August 2023.

Data Availability

While a systematic review article, the full dataset is presented in the current submission.

Conflicts of Interest

The Authors have no relevant financial or non-financial interests to disclose.

Authors' Contributions

HG: Conceptualization; methodology; investigation – literature search, screening process, selection, analysis; data curation; writing - review and editing; supervision. KKT: Investigation - literature search, screening process, selection; search for unpublished cases. OV: Investigation – literature search, screening process, selection, analysis; validation; writing – original draft. All Authors approved the final version of the article.

Acknowledgements

The Authors thank Dr. Yael Eshet from Sheba Medical Center, Israel, and Liliia Nehuliaieva, Andrei Krupynskyi Lviv Medical Academy, Lviv, Ukraine, each of whom detected and presented two unpublished cases.

References

1 Wang MC, Valenzuela LA, Murphy GP, Chu TM: Purification of a human prostate specific antigen. Invest Urol 17(2): 159-163, 1979.

2 Webb KS, Ware JL, Parks SF, Paulson DF: A serologic approach to the definition of human prostatic carcinoma antigens. Prostate 2(4): 369-380, 1981. DOI: 10.1002/pros.2990020405

3 Frankel AE, Rouse RV, Herzenberg LA: Human prostate specific and shared differentiation antigens defined by monoclonal antibodies. Proc Natl Acad Sci USA 79(3): 903-907, 1982. DOI: 10.1073/pnas.79.3.903

4 Wright GL Jr, Beckett ML, Starling JJ, Schellhammer PF, Sieg SM, Ladaga LE, Poleskic S: Immunohistochemical localization of prostate carcinoma-associated antigens. Cancer Res 43(11): 5509-5516, 1983.

5 Horoszewicz JS, Kawinski, E, Murphy GP: Monoclonal antibodies to a new antigenic marker in epithelial prostatic cells and serum of prostatic cancer patients. Anticancer Res 7: 927-936, 1987.

6 Chang SS, Reuter VE, Heston WD, Bander NH, Grauer LS, Gaudin PB: Five different anti-prostate-specific membrane antigen (PSMA) antibodies confirm PSMA expression in tumor-associated neovasculature. Cancer Res 59(13): 3192-3198, 1999.

7 Dumas F, Gala JL, Berteau P, Brasseur F, Eschwège P, Paradis V, Lacour B, Philippe M, Loric S: Molecular expression of PSMA mRNA and protein in primary renal tumors. Int J Cancer 80(6): 799-803, 1999. DOI: 10.1002/(sici)1097-0215(19990315)80:6<799::aid-ijc1>3.0.co;2-u

8 Sokoloff R, Norton K, Gasior C, Marker K, Grauer L: A dual-monoclonal sandwich assay for prostate-specific membrane antigen: Levels in tissues, seminal fluid and urine. Prostate 43(2): 150-157, 2000. DOI: 10.1002/(sici)1097-0045(20000501)43:2<150::aid-pros10>3.0.co;2-b

9 Chang SS, Reuter VE, Heston W, Gaudin PB: Metastatic renal cell carcinoma neovasculature expresses prostate-specific membrane antigen. Urology 57(4): 801-805, 2001. DOI: 10.1016/s0090-4295(00)01094-3

10 Liu YY, Brent GA: Thyroid hormone-dependent gene expression in differentiated embryonic stem cells and embryonal carcinoma cells: identification of novel thyroid hormone target genes by deoxyribonucleic acid microarray analysis. Endocrinology 146(2): 776-783, 2005. DOI: 10.1210/en.2004-1177

11 Kinoshita Y, Kuratsukuri K, Landas S, Imaida K, Rovito PM Jr, Wang CY, Haas GP: Expression of prostate-specific membrane antigen in normal and malignant human tissues. World J Surg 30(4): 628-636, 2006. DOI: 10.1007/s00268-005-0544-5

12 Zeng C, Ke ZF, Yang Z, Wang Z, Yang SC, Luo CQ, Wang LT: Prostate-specific membrane antigen: a new potential prognostic marker of osteosarcoma. Med Oncol 29(3): 2234-2239, 2012. DOI: 10.1007/s12032-011-0089-4

13 Cunha AC, Weigle B, Kiessling A, Bachmann M, Rieber EP: Tissue-specificity of prostate specific antigens: Comparative analysis of transcript levels in prostate and non-prostatic tissues. Cancer Lett 236(2): 229-238, 2006. DOI: 10.1016/j.canlet.2005.05.021

14 Chen JC, Ho CL, Tsai HW, Tzai TS, Liu HS, Chow NH, Yang WH, Cheng HL: Immunohistochemical detection of prostate-specific antigen expression in primary urothelial carcinoma of the urinary bladder. Anticancer Res 28(6B): 4149-4154, 2008.

15 Seipel AH, Samaratunga H, Delahunt B, Wiklund P, Clements M, Egevad L: Immunohistochemistry of ductal adenocarcinoma of the prostate and adenocarcinomas of non-prostatic origin: a comparative study. APMIS 124(4): 263-270, 2016. DOI: 10.1111/apm.12504

16 Pérez-Ibave DC, Burciaga-Flores CH, Elizondo-Riojas MÁ: Prostate-specific antigen (PSA) as a possible biomarker in non-prostatic cancer: A review. Cancer Epidemiol 54: 48-55, 2018. DOI: 10.1016/j.canep.2018.03.009

17 Behe M, Alt K, Deininger F, Bühler P, Wetterauer U, Weber WA, Elsässer-Beile U, Wolf P: In vivo testing of ^{177}Lu-labelled anti-PSMA antibody as a new radioimmunotherapeutic agent against prostate cancer. In Vivo 25(1): 55-59, 2011.

18 Tagawa ST, Milowsky MI, Morris M, Vallabhajosula S, Christos P, Akhtar NH, Osborne J, Goldsmith SJ, Larson S, Taskar NP, Scher HI, Bander NH, Nanus DM: Phase II study of Lutetium-177-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for metastatic castration-resistant prostate cancer. Clin Cancer Res 19(18): 5182-5191, 2013. DOI: 10.1158/1078-0432.CCR-13-0231

19 Zhang H, Xin P, Zhang YX: Efficacy and safety of the ^{177}Lu-PSMA-617 therapy in the treatment of metastatic castration-resistant prostate cancer: A meta-analysis. Zhonghua Nan Ke Xue 27(1): 63-69, 2021.

20 Sadaghiani MS, Sheikhbahaei S, Werner RA, Pienta KJ, Pomper MG, Solnes LB, Gorin MA, Wang NY, Rowe SP: A systematic review and meta-analysis of the effectiveness and toxicities of Lutetium-177-labeled prostate-specific membrane antigen-targeted radioligand therapy in metastatic castration-resistant prostate cancer. Eur Urol 80(1): 82-94, 2021. DOI: 10.1016/j.eururo.2021.03.004

21 von Eyben FE, Bauman G, von Eyben R, Rahbar K, Soydal C, Haug AR, Virgolini I, Kulkarni H, Baum R, Paganelli G: Optimizing PSMA radioligand therapy for patients with metastatic castration-resistant prostate cancer. A systematic review and meta-analysis. Int J Mol Sci 21(23): 9054, 2020. DOI: 10.3390/ijms21239054

22 Satapathy S, Mittal BR, Sood A: Visceral metastases as predictors of response and survival outcomes in patients of castration-resistant prostate cancer treated with 177Lu-labeled prostate-specific membrane antigen radioligand therapy. Clin Nucl Med 45(12): 935-942, 2020. DOI: 10.1097/RLU.0000000000003307

23 Kim YJ, Kim YI: Therapeutic responses and survival effects of ^{177}Lu-PSMA-617 radioligand therapy in metastatic castrate-resistant prostate cancer. Clin Nucl Med 43(10): 728-734, 2018. DOI: 10.1097/RLU.0000000000002210

24 Calopedos RJS, Chalasani V, Asher R, Emmett L, Woo HH: Lutetium-177-labelled anti-prostate-specific membrane antigen antibody and ligands for the treatment of metastatic castrate-resistant prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 20(3): 352-360, 2017. DOI: 10.1038/pcan.2017.23

25 Barrio M, Fendler WP, Czernin J, Herrmann K: Prostate specific membrane antigen (PSMA) ligands for diagnosis and therapy of prostate cancer. Expert Rev Mol Diagn 16(11): 1177-1188, 2016. DOI: 10.1080/14737159.2016.1243057

26 Heitkötter B, Trautmann M, Grünewald I, Bögemann M, Rahbar K, Gevensleben H, Wardelmann E, Hartmann W, Steinestel K, Huss S: Expression of PSMA in tumor neovasculature of high grade sarcomas including synovial sarcoma, rhabdomyosarcoma, undifferentiated sarcoma and MPNST. Oncotarget 8(3): 4268-4276, 2017. DOI: 10.18632/oncotarget.13994

27 Robinson KA, Akinyede O, Dutta T, Sawin VI, Li T, Spencer MR, Turkelson CM, Weston C: Framework for determining research gaps during systematic review: Evaluation. Rockville, MD, Agency for Healthcare Research and Quality (US), 2013 Feb. Report No.: 13-EHC019-EF.

28 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 6(7): e1000100, 2009. DOI: 10.1371/journal.pmed.1000100

29 Howick J, Chalmers I, Glasziou P: Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence (background document). Oxford Centre for Evidence-Based Medicine. Available at: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/levels-of-evidence-introductory-document and https://www.cebm.ox.ac.uk/resources/levels-of-evidence/explanation-of-the-2011-ocebm-levels-of-evidence [Last accessed on April 24, 2024]

30 Common Terminology Criteria for Adverse Events (CTCAE) Version 5, 2017. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf [Last accessed on April 21, 2024]

31 Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH: GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 64(4): 401-406, 2011. DOI: 10.1016/j.jclinepi.2010.07.015

32 Sterne JAC, Hernán MA, McAleenan A, Reeves BC, Higgins JPT: Chapter 25: Assessing risk of bias in a non-randomized study. *In*: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (eds.). Cochrane Handbook for Systematic Reviews of Interventions, version 6.4 (updated August 2023). Cochrane, 2023.

33 Klein Nulent TJW, van Es RJJ, Krijger GC, de Bree R, Willems SM, de Keizer B: Prostate-specific membrane antigen PET imaging and immunohistochemistry in adenoid cystic carcinoma-a preliminary analysis. Eur J Nucl Med Mol Imaging 44(10): 1614-1621, 2017. DOI: 10.1007/s00259-017-3737-x

34 Tolkach Y, Gevensleben H, Bundschuh R, Koyun A, Huber D, Kehrer C, Hecking T, Keyver-Paik M, Kaiser C, Ahmadzadehfar H, Essler M, Kuhn W, Kristiansen G: Prostate-specific membrane antigen in breast cancer: a comprehensive evaluation of expression and a case report of radionuclide therapy. Breast Cancer Res Treat 169(3): 447-455, 2018. DOI: 10.1007/s10549-018-4717-y

35 Has Simsek D, Kuyumcu S, Agaoglu FY, Unal SN: Radionuclide therapy with ^{177}Lu-PSMA in a case of metastatic adenoid cystic carcinoma of the parotid. Clin Nucl Med 44(9): 764-766, 2019. DOI: 10.1097/RLU.0000000000002645

36 Assadi M, Ahmadzadehfar H: (177)Lu-DOTATATE and (177)Lu-prostate-specific membrane antigen therapy in a patient with advanced metastatic radioiodine-refractory differentiated thyroid cancer after failure of tyrosine kinase inhibitors treatment. World J Nucl Med 18(4): 406-408, 2019. DOI: 10.4103/wjnm.WJNM_112_18

37 Kunikowska J, Charzyńska I, Kuliński R, Pawlak D, Maurin M, Królicki L: Tumor uptake in glioblastoma multiforme after IV injection of [(177)Lu]Lu-PSMA-617. Eur J Nucl Med Mol Imaging 47(6): 1605-1606, 2020. DOI: 10.1007/s00259-020-04715-z

38 Kumar A, Ballal S, Yadav MP, ArunRaj ST, Haresh KP, Gupta S, Damle NA, Garg A, Tripathi M, Bal C: ^{177}Lu-/^{68}Ga-PSMA theranostics in recurrent glioblastoma multiforme. Clin Nucl Med 45(12): e512-e513, 2020. DOI: 10.1097/RLU.0000000000003142

39 de Vries LH, Lodewijk L, Braat AJAT, Krijger GC, Valk GD, Lam MGEH, Borel Rinkes IHM, Vriens MR, de Keizer B: (68)Ga-PSMA PET/CT in radioactive iodine-refractory differentiated thyroid cancer and first treatment results with (177)Lu-PSMA-617. EJNMMI Res 10(1): 18, 2020. DOI: 10.1186/s13550-020-0610-x

40 Hirmas N, Leyh C, Sraieb M, Barbato F, Schaarschmidt BM, Umutlu L, Nader M, Wedemeyer H, Ferdinandus J, Rischpler C, Herrmann K, Costa PF, Lange CM, Weber M, Fendler WP: (68)Ga-PSMA-11 PET/CT improves tumor detection and impacts management in patients with hepatocellular carcinoma. J Nucl Med 62(9): 1235-1241, 2021. DOI: 10.2967/jnumed.120.257915

41 Has Simsek D, Civan C, Ekenel M, Kuyumcu S, Sanli Y: ^{177}Lu-PSMA therapy for metastatic testicular mixed germ cell tumor. Clin Nucl Med 46(5): 415-418, 2021. DOI: 10.1097/RLU.0000000000003563

42 Klein Nulent TJW, van Es RJJ, Willems SM, Braat AJAT, Devriese LA, de Bree R, de Keizer B: First experiences with (177)Lu-PSMA-617 therapy for recurrent or metastatic salivary gland cancer. EJNMMI Res 11(1): 126, 2021. DOI: 10.1186/s13550-021-00866-8

43 Truckenmueller P, Graef J, Scheel M, Vajkoczy P, Capper D, Kaul D, Furth C, Amthauer H, Brenner W, Onken JS: [(68)Ga]Ga-PSMA PET/MRI, histological PSMA expression and preliminary experience with [(177)Lu]Lu-PSMA therapy in relapsing high-grade glioma. Front Oncol 12: 980058, 2022. DOI: 10.3389/fonc.2022.980058

44 Zhang J, Schuchardt C, Chen X, Baum RP: Rapid tumor washout of ^{177}Lu-PSMA radioligand in renal cell carcinoma. Clin Nucl Med 48(8): 732-734, 2023. DOI: 10.1097/RLU.0000000000004725

45 Civan C, Kasper S, Berliner C, Fragoso-Costa P, Grünwald V, Pogorzelski M, Schaarschmidt BM, Lang S, Kersting D, Nader M, Lückerath K, Herrmann K, Fendler WP, Weber M: PSMA-directed imaging and therapy of salivary gland tumors: a single-center retrospective study. J Nucl Med 64(3): 372-378, 2023. DOI: 10.2967/jnumed.122.264342

46 Terroir M, Lamesa C, Krim M, Vija L, Texier JS, Cassou-Mounat T, Delord JP, Vallot D, Courbon F: RadioLigand therapy with [(177)Lu]Lu-PSMA-617 for salivary gland cancers: literature review and first compassionate use in France. Pharmaceuticals (Basel) 16(5): 754, 2023. DOI: 10.3390/ph16050754

47 Naeem Z, Zahra UB, Numair Younis M, Khan IU, Shahid A: Lutetium-177 prostate specific membrane antigen therapy in a patient with double malignancy and single functioning kidney: a case report. Cureus 15(3): e36938, 2023. DOI: 10.7759/cureus.36938

48 Graef J, Bluemel S, Brenner W, Amthauer H, Truckenmueller P, Kaul D, Vajkoczy P, Onken JS, Furth C: [^{177}Lu]Lu-PSMA therapy as an individual treatment approach for patients with high-grade glioma: dosimetry results and critical statement. J Nucl Med 64(6): 892-895, 2023. DOI: 10.2967/jnumed.122.264850

49 Kratochwil C, Fendler WP, Eiber M, Baum R, Bozkurt MF, Czernin J, Delgado Bolton RC, Ezziddin S, Forrer F, Hicks RJ, Hope TA, Kabasakal L, Konijnenberg M, Kopka K, Lassmann M, Mottaghy FM, Oyen W, Rahbar K, Schöder H, Virgolini I, Wester HJ, Bodei L, Fanti S, Haberkorn U, Herrmann K: EANM procedure guidelines for radionuclide therapy with ^{177}Lu-labelled PSMA-ligands (^{177}Lu-PSMA-RLT). Eur J Nucl Med Mol Imaging 46(12): 2536-2544, 2019. DOI: 10.1007/s00259-019-04485-3

50 Gafita A, Calais J, Grogan TR, Hadaschik B, Wang H, Weber M, Sandhu S, Kratochwil C, Esfandiari R, Tauber R, Zeldin A, Rathke H, Armstrong WR, Robertson A, Thin P, D'Alessandria C, Rettig MB, Delpassand ES, Haberkorn U, Elashoff D, Herrmann K, Czernin J, Hofman MS, Fendler WP, Eiber M: Nomograms to predict outcomes after ^{177}Lu-PSMA therapy in men with metastatic castration-resistant prostate cancer: an international, multicentre, retrospective study. Lancet Oncol 22(8): 1115-1125, 2021. DOI: 10.1016/S1470-2045(21)00274-6

51 Kratochwil C, Fendler WP, Eiber M, Hofman MS, Emmett L, Calais J, Osborne JR, Iravani A, Koo P, Lindenberg L, Baum RP, Bozkurt MF, Delgado Bolton RC, Ezziddin S, Forrer F, Hicks RJ, Hope TA, Kabasakal L, Konijnenberg M, Kopka K, Lassmann M, Mottaghy FM, Oyen WJG, Rahbar K, Schoder H, Virgolini I, Bodei L, Fanti S, Haberkorn U, Hermann K: Joint EANM/SNMMI procedure guideline for the use of (177)Lu-labeled PSMA-targeted radioligand-therapy ((177)Lu-PSMA-RLT). Eur J Nucl Med Mol Imaging 50(9): 2830-2845, 2023. DOI: 10.1007/s00259-023-06255-8

52 Can C, Gündoğan C, Kömek H: Is 68Ga-prostate-specific membrane antigen PET/CT superior than 18F-FDG PET/CT for evaluation of metastatic osteosarcoma? Clin Nucl Med 46(4): e233-e235, 2021. DOI: 10.1097/RLU.0000000000003320

53 Nadiminty N, Lou W, Lee SO, Mehraein-Ghomi F, Kirk JS, Conroy JM, Zhang H, Gao AC: Prostate-specific antigen modulates genes involved in bone remodeling and induces osteoblast differentiation of human osteosarcoma cell line SaOS-2. Clin Cancer Res 12(5): 1420-1430, 2006. DOI: 10.1158/1078-0432.CCR-05-1849

54 Bonk S, Kluth M, Hube-Magg C, Polonski A, Soekeland G, Makropidi-Fraune G, Möller-Koop C, Witt M, Luebke AM, Hinsch A, Burandt E, Steurer S, Clauditz TS, Schlomm T, Perez D, Graefen M, Heinzer H, Huland H, Izbicki JR, Wilczak W, Minner S, Sauter G, Simon R: Prognostic and diagnostic role of PSA immunohistochemistry: A tissue microarray study on 21,000 normal and cancerous tissues. Oncotarget 10(52): 5439-5453, 2019. DOI: 10.18632/oncotarget.27145

55 Gygi CM, Leibovitch IY, Adlington R, Baldwin JE, Chen B, Mccoull W, Pritchard GJ, Becker GW, Dixon EP, Little SP, Sutkowski DM, Teater C, Neubauer BL: Prostate-specific antigen (PSA)-mediated proliferation, androgenic regulation and inhibitory effects of LY312340 in HOS-TE85 (TE85) human osteosarcoma cells. Anticancer Res 22(5): 2725-2732, 2002.

56 Miyaji Y, Nakanishi K, Yamamoto A, Yoden E, Tokiya R, Okawaki M, Inubushi M, Katsui K: Spinal instability as a prognostic factor in patients with spinal metastasis of castration-resistant prostate cancer. Cancer Diagn Progn 3(4): 449-456, 2023. DOI: 10.21873/cdp.10238

57 Kim DY, Lee WW, Song YS, Hong SK, Byun SS, Kim JS: Detection of recurrence sites using (18)F-fluorocholine PET/CT in prostate cancer patients with PSA failure. Prostate Int 11(2): 69-75, 2023. DOI: 10.1016/j.prnil.2022.11.001

Received March 27, 2024
Revised April 21, 2024
Accepted April 25, 2024