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Changes in Treatment After Gallium-68 Prostate-Specific Membrane Antigen-11 Positron Emission Tomography/Computed Tomography in Patients With Prostate Cancer: A Retrospective Case Series Study

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Purpose: The use of gallium-68 prostate-specific membrane antigen-11 positron emission tomography/computed tomography (Ga-68 PSMA-11 PET/CT) is becoming increasingly common among men with prostate cancer (PCa). However, it remains uncertain which patients will derive the most benefit, and there is a scarcity of real-world data regarding its impact on altering treatment plans. This study investigated which patients would most benefit from Ga-68 PSMA-11 PET/CT, focusing on detection rates and changes in treatment strategies, drawing from a single-center experience.

Materials and Methods: In total, 230 men with PCa who underwent Ga-68 PSMA-11 PET/CT between November 2021 and August 2022 were included in this retrospective study. The patients were classified into 5 groups based on their disease status: group 1, further work-up for high-risk localized PCa; group 2, *de novo* metastatic PCa; group 3, biochemical recurrence after definitive treatment; group 4, castration-resistant PCa; group 5, others. The positivity rate, positive lesions, predictive value of lymph node metastases, comparison with conventional images, and treatment changes after Ga-68 PSMA-11 PET/CT were analyzed in each group.

Results: Of the 230 patients, 40 (17.4%), 20 (8.7%), 77 (33.5%), 76 (33.0%), and 17 (7.4%) were classified into groups 1–5, respectively. Ga-68 PSMA-11 PET/CT showed lesions in 74.8% of patients, and the optimal cutoff value for PSA was 1.99 ng/mL. Lesions not observed on conventional imaging were found in 62 patients (33.2%). In 38 patients (13.5%), treatment was changed due to Ga-68 PSMA-11 PET/CT.

Conclusions: These real-world data suggest that Ga-68 PSMA-11 PET/CT may be clinically useful for various disease conditions, as substantial stage migration and subsequent treatment changes occur in men with PCa. However, the prognostic impact of this modality remains unclear; thus, a well-designed prospective study is needed to address this issue.

Key Words: Positron emission tomography, Computed tomography, Gallium-68 prostate-specific membrane antigen -11, Prostatic neoplasms, Lymph node, Cancer staging

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INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in men in the United States (US) [1], and its incidence is steadily increasing in Korea. In 2017, it was the fourth most common male cancer in Korea, and its incidence is increasing every year due to advancements in diagnostic methods [2]. Although it is the second leading cause of cancer-related deaths in men in the US, the 5-year survival rate for those diagnosed with localized prostate cancer exceeds 90%. There are more cases of localized or metastatic prostate cancer with a high degree of malignancy in Korea than in other countries [3]. Therefore, accurate staging and appropriate treatment are crucial.

Conventional diagnostic imaging tools for prostate cancer include magnetic resonance imaging (MRI), computed tomography (CT), and bone scans. MRI is particularly useful for local staging, especially in assessing whether there is invasion of the prostate capsule and seminal vesicles [4]. CT scans are effective in identifying metastases in intra-abdominal lymph nodes. Bone scans are commonly used to detect metastatic spread, as bony metastases frequently occur in prostate cancer [5-7]. However, these methods face difficulties in identifying metastatic disease outside of the targeted areas, potentially leading to mis-staging and initial treatment failure. This issue is particularly important in patients with high-grade tumors and elevated prostate-specific antigen (PSA) levels, who may have undetected metastases and consequently receive only localized treatment. For instance, prostate MRI might overlook metastatic lesions in the upper abdomen or lungs, especially if these lesions are out of the visible range or too small to be detected.

Gallium-68 prostate-specific membrane antigen-11 positron emission tomography/CT (Ga-68 PSMA-11 PET/CT), which was approved by the U.S. Food and Drug Administration in 2020, releases protons by attaching to a protein called PSMA, which is located on the surface of prostate cells. Therefore, protons originating from locations other than the prostate are likely indicative of metastasis. This method demonstrates higher diagnostic accuracy than conventional CT and bone scans, offering clinicians improved information for making treatment decisions [8].

Among patients with localized prostate cancer, Ga-68 PSMA-11 PET/CT is expected to be especially useful in those with high Gleason scores and PSA levels. Although conventional imaging may show these cancers to be localized, metastasis or micrometastasis may still be present. Systemic therapy is more effective than definitive therapy for these patients. Therefore, Ga-68 PSMA-11 PET/CT may contribute to establishing an accurate treatment plan. It can also be used in cases of biochemical recurrence (BCR) or castration-resistant prostate cancer (CRPC). Androgen receptor-targeting agents or chemotherapy are generally preferred. For smaller metastatic lesions, targeted radiation or surgical excision can significantly delay the progression of BCR [9]. Conventional imaging tests are often limited due to their limited ability to guide treatment decisions and their low sensitivity. Ga-68 PSMA-11 PET/CT, in contrast, can provide more precise information to both patients and clinicians, thereby significantly influencing treatment outcomes [10].

Recognized for its superior accuracy in staging compared to traditional imaging tests, Ga-68 PSMA-11 PET/CT was approved for use in Korea in 2021, and an application for national medical insurance reimbursement was submitted in 2022. This study aimed to evaluate the sensitivity, specificity, and accuracy of Ga-68 PSMA-11 PET/CT in patients under specific conditions. Additionally, the diagnostic performances of conventional imaging and Ga-68 PSMA-11 PET/CT were compared, and the impact of Ga-68 PSMA-11 PET/CT on treatment decisions or changes was investigated.

MATERIALS AND METHODS

1. Study Design and Patients' Clinical Data

Patients who underwent Ga-68 PSMA-11 PET/CT for prostate cancer between November 2021 and August 2022 were included. A retrospective review was conducted of the basic and imaging information of the patients included in the study.

The following clinical data were assessed: age, PSA level, pathological prostate biopsy results, surgical status, whole specimen and pathological results, Ga-68 PSMA-11 PET/CT, MRI, CT, bone scan results, and final treatment. A nuclear medicine doctor reviewed the Ga-68 PSMA-11 PET/CT

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results, and 3 experienced radiologists assessed the MRI and CT results. An experienced pathologist confirmed the final pathological results.

The Ga-68 PSMA-11 PET/CT protocol was as follows. After an intravenous injection of Ga-68 PSMA-11 and approximately 60 minutes of rest, whole-body images were acquired from the base of the skull to the femur.

2. Patient Classification According to Disease Status for Ga-68 PSMA-11 PET/CT

Patients were divided into 5 groups according to the disease findings on Ga-68 PSMA-11 PET/CT: group 1, further work-up for high-risk localized prostate cancer; group 2, *de novo* metastatic prostate cancer; group 3, BCR; group 4, CRPC; and group 5, others.

3. Outcomes

The primary outcome was the diagnostic performance of Ga-68 PSMA-11 PET/CT. The positivity rate for PSMA was obtained and categorized according to the disease status and PSA level. Additionally, the most appropriate cutoff value for PSA that would correlate with a positive result on Ga-68 PSMA-11 PET/CT was calculated. The secondary outcomes examined were the accuracy of lymph node diagnosis, comparison with conventional images, and changes in treatment triggered by Ga-68 PSMA-11 PET/CT findings.

4. Statistical Analysis

Baseline characteristics are presented using descriptive statistics, and a subanalysis was conducted for each group. For group comparisons, continuous variables were analyzed using the Kruskal-Wallis test, while ordinal variables were assessed with the Cochran-Mantel-Haenszel test. The positivity rate of Ga-68 PSMA-11 PET/CT was analyzed across different groups and PSA levels. The PSA cutoff value was determined using the receiver operating characteristic (ROC) curve method. Lymph node accuracy was also evaluated through ROC curve analysis. This approach calculates the positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity of a diagnostic test. Additionally, it assesses the test's discriminatory power through the area under the curve (AUC). Finally, the proportion of patients whose treatment was altered in each group was analyzed. Changes in treatment are reported using descriptive statistics. All statistical analyses were conducted using R ver. 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

1. Basic Characteristics

The median age of the patients was 71.8 years, and the median PSA level was 1.77 ng/mL. Patients were categorized into International Society of Urological Pathology (ISUP) grade groups as follows: 14 patients (6.2%) in grade 1, 31 patients (13.8%) in grade 2, 49 patients (21.8%) in grade 3, 70 patients (31.1%) in grade 4, and 61 patients (27.1%) in grade 5 (Table 1). The reasons for undergoing PSMA imaging were classified into 5 categories: 40 patients (17.4%) in group 1, 20 patients (8.7%) in group 2, 77 patients (33.5%) in group 3, 76 patients (33.0%) in group 4, and 17 patients (7.4%) in group 5 (Fig. 1).

The age, PSA level, and ISUP grade of each group are shown in Table 2. There was a statistically significant difference in age between group 1 and the other groups and statistically significant differences in PSA levels and ISUP grades between each group.

Table 1. Baseline characteristics (N=230)

Characteristic	Value
Age (yr)	71.8 (65.9–79.1)
PSA at time of PSMA PET/CT (ng/mL)	1.77 (0.36–10.75)
ISUP grade group	
1	14 (6.2)
2	31 (13.8)
3	49 (21.8)
4	70 (31.1)
5	61 (27.1)

Values are presented as median (interquartile range) or number (%).
PSA, prostate-specific antigen; PSMA PET/CT, gallium-68 prostate-specific membrane antigen-11 positron emission tomography/computed tomography; ISUP, International Society of Urological Pathology.

2. Ga-68 PSMA-11 PET/CT Positivity Rate (per Patient)

The overall positivity rate for Ga-68 PSMA-11 PET/CT was 74.8%. An analysis of Ga-68 PSMA-11 PET/CT uptake lesions revealed negative results in 25.2% of cases. The findings included multiple metastases in 15.2%, bone metastases in 16.1%, extrapelvic nonbone lesions in 8.3%, pelvic lymph nodes in 11.7%, the prostate bed in 2.2%, and the prostate in 21.3% (Fig. 2).

In groups 1 and 2, all patients tested positive. However, in the BCR and CRPC groups, the positivity rates were 46.8% and 89.5%, respectively. The results of the subanalysis for each group are depicted in Fig. 3. Bone metastasis was detected in 11 case (2.5%) in group 1, while only the prostate tested positive in 22 cases (10%) in group 2.

Differences in lesion uptake were confirmed by categorizing them according to the PSA range (Fig. 4). The differences between the groups were statistically significant ($p<0.01$). Subanalyses were conducted separately for BCR and CRPC (Supplementary Fig. 1).

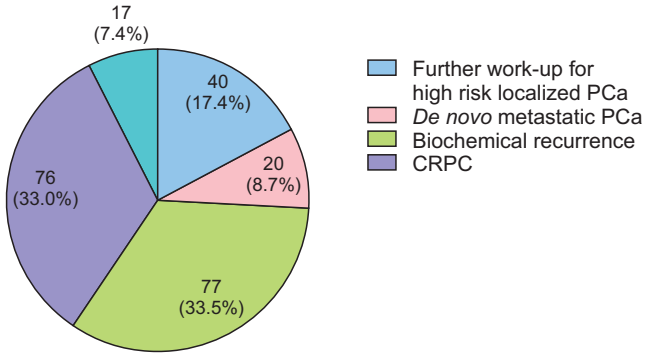

Fig. 1. Disease status of patients who underwent Ga-68 PSMA-11 PET/CT. Ga-68 PSMA-11 PET/CT, gallium-68 prostate-specific membrane antigen-11 positron emission tomography/computed tomography; PCa, prostate cancer; CRPC, castration-resistant prostate cancer.

3. Optimal Cutoff Value of PSA for Ga-68 PSMA-11 PET/CT

The optimal cutoff value of PSA for all patients was determined to be 1.99 ng/mL, exhibiting a sensitivity of 0.62, specificity of 0.93, accuracy of 0.69, PPV of 0.96, NPV of 0.45, and an AUC of 0.84. Additionally, the optimal cutoff value of PSA was identified as 0.22 ng/mL for BCR, demonstrating a sensitivity of 0.94, specificity of 0.25, accuracy of 0.57, PPV of 0.52, NPV of 0.83, and an AUC of 0.58. For CRPC patients, the optimal PSA cutoff value was 3.27 ng/mL, with a sensitivity of 0.47, specificity of 1.0, accuracy of 0.53, PPV of 1.0, NPV of 0.17, and an AUC of 0.72 (Fig. 5).

4. Lymph Node Metastasis Prediction Accuracy (per Patient)

Of the patients who underwent 68-Ga PSMA-11 PET/CT, 23 underwent radical prostatectomy and pelvic lymphadenectomy. The accuracy of lymph node metastasis prediction was confirmed for these patients through a per-patient analysis. An experienced pathologist verified the presence of lymph node invasion. The results are displayed in Table 3 as a 2×2 table, showing a sensitivity of 0.43, specificity of 0.88, accuracy of 0.74, PPV of 0.6, NPV of 0.78, and AUC of 0.65.

Table 2. Subgroup baseline characteristics

Characteristic	Group 1 (N=40)	Group 2 (N=20)	Group 3 (N=77)	Group 4 (N=76)	Group 5 (N=17)	p-value
Age (yr)	67.57 (62.4–74.54)	72.8 (68.46–79.5)	72.26 (66.84–78.54)	72.17 (65.86–80.98)	73.13 (65.35–80.04)	0.07
PSA at time of PSMA PET/CT (ng/mL)	10.69 (4.77–18.3)	48.81 (17.82–216.03)	0.37 (0.25–0.99)	2.27 (0.76–8.22)	0.3 (0–22.3)	<0.01
ISUP grade group						<0.01
1	2 (5.1)	0 (0)	11 (14.5)	1 (1.3)	0 (0)	
2	8 (20.5)	0 (0)	12 (15.8)	5 (6.7)	6 (40.0)	
3	7 (18.0)	2 (10.0)	21 (27.6)	14 (18.7)	5 (33.3)	
4	10 (25.6)	12 (60.0)	23 (30.3)	23 (30.7)	2 (13.3)	
5	12 (30.8)	6 (30.0)	9 (11.8)	32 (42.7)	2 (13.3)	

Values are presented as median (interquartile range) or number (%).
Group 1, further work-up for high-risk localized prostate cancer; group 2, *de novo* metastatic prostate cancer; group 3, biochemical recurrence; group 4, castration-resistant prostate cancer; group 5, others; PSA, prostate-specific antigen; PSMA PET/CT, Gallium-68 prostate-specific membrane antigen-11 positron emission tomography/computed tomography; ISUP, The international society of urological pathology.

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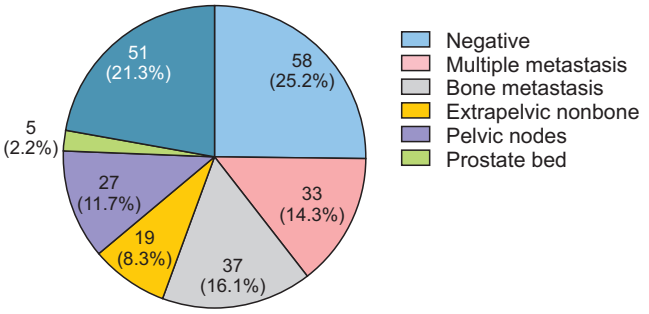


Fig. 2. Ga-68 PSMA-11 PET/CT positive lesion. Ga-68 PSMA-11 PET/CT, gallium-68 prostate-specific membrane antigen-11 positron emission tomography/computed tomography.

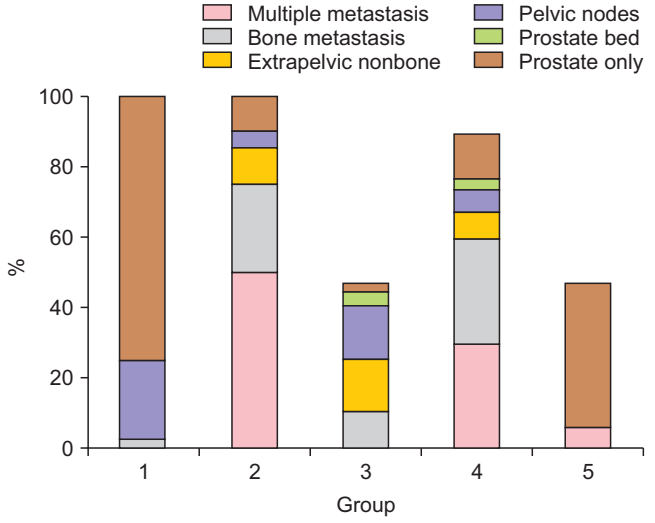


Fig. 3. Ga-68 PSMA-11 PET/CT positive rate. Ga-68 PSMA-11 PET/CT, gallium-68 prostate-specific membrane antigen-11 positron emission tomography/computed tomography; group 1, further work-up for high-risk localized prostate cancer; group 2, *de novo* metastatic prostate cancer; group 3, biochemical recurrence; group 4, castration-resistant prostate cancer; group 5, others.

5. Comparison of Ga-68 PSMA-11 PET/CT and Conventional Images (per Patient)

In 62 patients (33.2%) who underwent Ga-68 PSMA-11 PET/CT, lesions that were not visible on conventional images were detected. Analysis of Ga-68 PSMA-11 PET/CT uptake revealed various types of lesions: multiple metastases (17.7%), bone metastases (24.2%), extrapelvic nonbone lesions (27.4%), pelvic lymph nodes (21.0%), involvement of the prostate bed (3.2%), and involvement of the prostate only (6.5%). The cutoff value for PSA is 1.68 in situations where lesions that cannot be identified on conventional imaging are discovered with a sensitivity of 0.52, specificity of 0.61, accuracy of 0.58, PPV of 0.39, NPV of 0.72, and AUC of 0.52 (Supplementary Fig. 2).

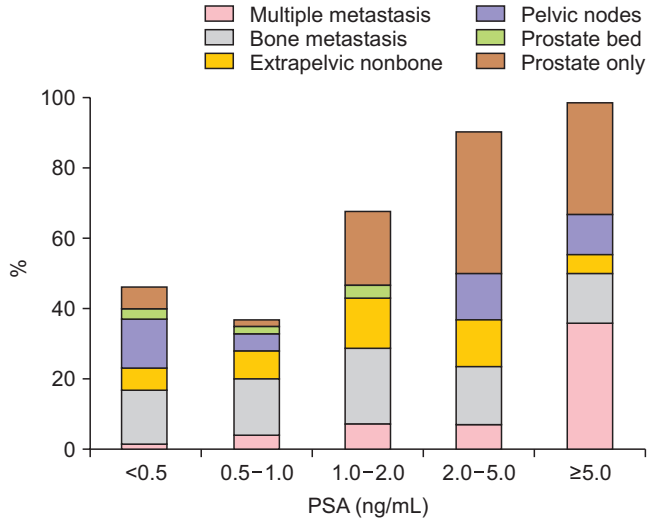


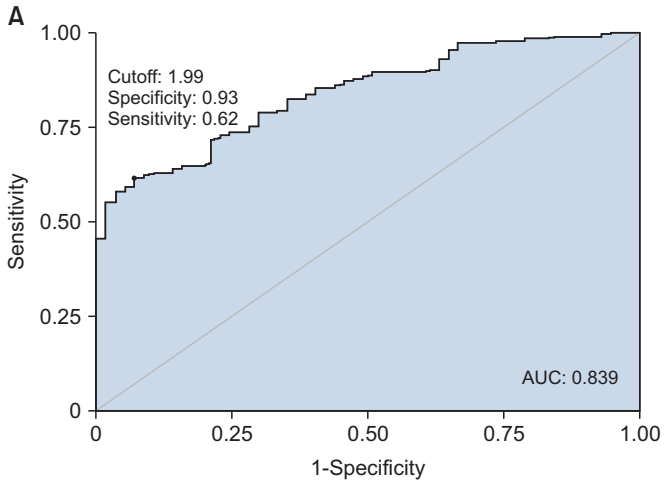
Fig. 4. Ga-68 PSMA-11 PET/CT positive rate by PSA. Ga-68 PSMA-11 PET/CT, gallium-68 prostate-specific membrane antigen-11 positron emission tomography/computed tomography. PSA, prostate specific antigen.

6. Treatment Change due to Ga-68 PSMA-11 PET/CT (per Patient)

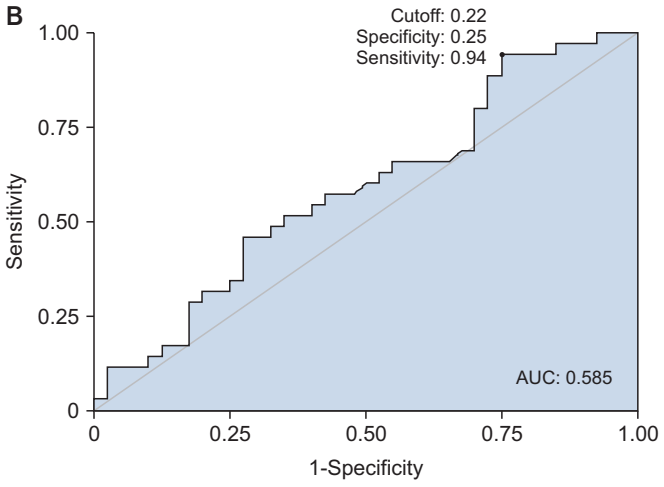
The treatment regimen was changed for 31 patients (13.5%) following Ga-68 PSMA-11 PET/CT imaging. In group 1, treatment changes occurred in 4 patients (10%); one developed metastatic prostate cancer, while three required pelvic lymph node dissection. In group 2, 6 patients (30%) had their treatment plans modified; 2 with localized prostate cancer underwent surgical treatment, and 4 received metastasis-directed radiotherapy for oligometastatic lesions. In group 3, 7 patients (9.1%) experienced changes in their treatment, including one who underwent retroperitoneal lymph node dissection. In group 4, 14 patients (18.4%) had adjustments to their treatment regimen, with radiotherapy being added to the metastatic area. However, these changes did not show statistically significant differences across the groups (p=0.14) (Table 4).

DISCUSSION

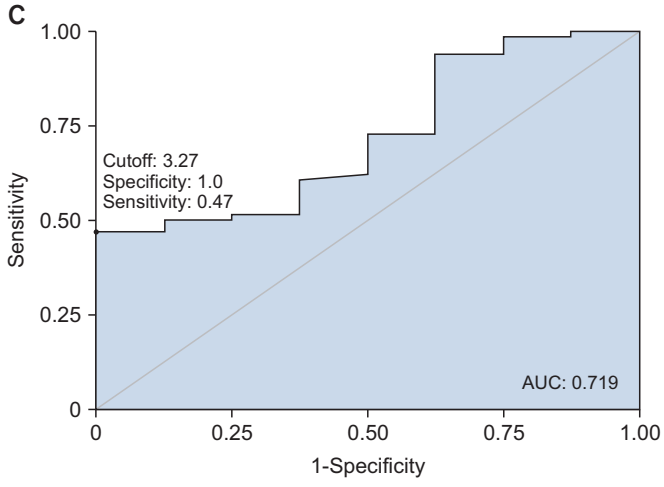
PSMA-PET/CT has received considerable attention for the diagnosis and treatment of prostate cancer [11]. Its ability



	Sensitivity	Specificity	Accuracy	PPV	NPV	AUC
PSMA+	0.62	0.93	0.69	0.96	0.45	0.84



	Sensitivity	Specificity	Accuracy	PPV	NPV	AUC
PSMA+BCR	0.94	0.25	0.57	0.52	0.83	0.58



	Sensitivity	Specificity	Accuracy	PPV	NPV	AUC
PSMA+CRPC	0.47	1.0	0.53	1.0	0.17	0.72

Fig. 5. Ga-68 PSMA-11 PET/CT diagnostic performance. (A) ROC curve, sensitivity, specificity, accuracy, PPV, NPV, AUC for detection of prostate cancer. (B) ROC curve, sensitivity, specificity, accuracy, PPV, NPV, AUC for detection of prostate cancer with BCR, (C) ROC curve, sensitivity, specificity, accuracy, PPV, NPV, AUC for detection of prostate cancer with CRPC. Ga-68 PSMA-11 PET/CT, gallium-68 prostate-specific membrane antigen-11 positron emission tomography/computed tomography; ROC, receiver operating characteristic; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; BCR, biochemical recurrence; CRPC, castration-resistant prostate cancer.

Table 3. Lymph node metastasis prediction accuracy in men who underwent radical prostatectomy and pelvic lymph node dissection

	pN (+)	pN (-)
Ga-68 PSMA-11 (+)	3	5
Ga-68 PSMA-11 (-)	4	11

	Sensitivity	Specificity	Accuracy	PPV	NPV	AUC
LN (+)	0.43	0.88	0.74	0.6	0.78	0.65

pN, pathology lymph node metastasis; Ga-68 PSMA-11, gallium-68 prostate specific membrane antigen-11; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; LN (+), lymph node positive.

to rapidly identify low-volume metastases from prostate cancer is particularly useful, as it can lead to modifications in treatment plans [10]. In this study, metastases were detected using Ga-68 PSMA-11 in patients with high-risk localized prostate cancer. Subsequently, metastasis-directed radiation therapy was administered to patients with BCR

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Table 4. Treatment change by Ga-68 PSMA-11 PET/CT

Category	Treatment change, n (%)	
High risk localized prostate cancer	4/40 (10)	Changed to the metastatic prostate cancer: 1 Change in PLND boundary: 3
De novo metastatic prostate cancer	6/20 (30)	Changed to the localized prostate cancer: 2 Metastasis-directed RTx.: 4
BCR	7/77 (9.1)	Metastasis-directed RTx.: 6 RPLND: 1
CRPC	14/76 (18.4)	Palliative RTx. to Prostate: 4 Metastasis-directed RTx.: 10

Ga-68 PSMA-11 PET/CT, gallium-68 prostate-specific membrane antigen-11 positron emission tomography/computed tomography; PLND, pelvic lymph node dissection; RTx., radiation therapy; BCR, biochemical recurrence; RPLND, retroperitoneal lymph node dissection; CRPC, castration resistance prostate cancer.

and CRPC. As a result, the initial treatment plans, which were based on conventional imaging, were changed. Despite these advancements, the routine use of Ga-68 PSMA-11 PET/CT for diagnostic purposes is still a subject of debate. Additionally, there is a scarcity of research demonstrating that changes in treatment strategy, prompted by early detection, improve overall survival.

Several PSMA ligands exist, such as Ga-68 PSMA-11, F-18 PSMA-1007, and F18-DCFPyL. Ga-68 PSMA-11 is the most widely used because of its high tumor uptake and rapid pharmacokinetics [12]. Other tracers are currently emerging, but are still in clinical trials [13,14]. To date, there have been no direct comparative studies, and future research will need to assess their diagnostic accuracy. Furthermore, CRPC can be treated with another ligand, Lutetium-177 PSMA-617 [15]. Due to these diagnostic and therapeutic capabilities, PSMA-mediated therapy is now widely utilized.

PSA levels and Gleason scores are associated with the results of Ga-68 PSMA-11 PET/CT [16]. In that study, the Gleason score and PSA level showed positive correlations with the maximum standardized uptake value (SUVmax). Patients were divided according to PSA level, and there was a statistically significant difference in the positivity rate of each group. This was used to determine the optimal PSA cutoff value. However, the analysis mixed various cases, such as primary stage, BCR, and CRPC, and the sample size was very small.

The use of Ga-68 PSMA-11 PET/CT to detect lymph node metastases in prostate cancer is receiving substantial interest. A multicenter prospective study was conducted, and a patient-specific analysis was performed [17]. The sensitivity and specificity were reported as 0.4 and 0.95, respectively. These results closely align with those of the per-patient analysis in the current study, which reported a sensitivity of 0.43 and a specificity of 0.88. However, evidence is lacking to support the omission of lymph node dissection in prostate cancer patients at intermediate or higher risk [18]. Ga-68 PSMA-11 PET/CT is more effective than conventional imaging in detecting lymph node metastases, but it may miss small lymph nodes. Consequently, further well-designed studies are necessary to consider replacing conventional lymph node dissection with PSMA PET/CT.

Studies have also explored the use of PSMA in surgical procedures and prostate biopsies. PSMA has been employed during salvage surgery for patients with recurrent prostate cancer [19]. After imaging with Ga-68 PSMA-11 or F-18 DCFPyl PET/CT, the 99m technetium ligand was injected before surgery. During the operation, a specialized probe was utilized to detect the signal. This approach was deemed safe and feasible. Additionally, patients who met the criteria experienced a reduction in PSA levels postsurgery. However, due to the short duration of follow-up, an analysis of survival rates was not conducted. A targeted biopsy study using Ga-68 PSMA-11 PET/CT was also conducted [20]. This randomized controlled trial compared systematic biopsy using transrectal ultrasonography with targeted biopsies. Targeted biopsies were only performed on patients with an SUVmax of 8 or higher. The results showed significantly higher diagnostic accuracy in patients with PSA levels ranging from 4 to 20 ng/dL.

To our knowledge, this is the first case series on Ga-68 PSMA-11 PET/CT in Korea. It provides real-world data on Ga-68 PSMA-11 PET/CT scans, which currently constitutes a gap in the literature.

This study had several limitations. First, the introduction of a new diagnostic method, Ga-68 PSMA-11 PET/CT, led to one patient undergoing this procedure during the follow-up period without a specific reason. Consequently, it was challenging to categorize this patient based on the rationale for imaging. Second, no definitive cutoff value for SUVmax has been established, and the relevance of SUVmax in Ga-68 PSMA-11 PET/CT continues to be a subject of debate [21]. This study assessed PSMA-11 expression levels, considering any abnormal uptake (higher than surrounding tissues or presence in tissues where expression should not occur) as positive. Third, there is a lack of references for patients who did not undergo lymph node dissection due to negative Ga-68 PSMA-11 PET/CT results. Further analysis of lymph nodes per lesion is necessary, and consensus should be developed through additional studies. Fourthly, as a retrospective, single-center study with a limited number of participants, the findings of this study need to be confirmed and validated in a prospective, large-scale, multicenter study. Finally, the short duration of follow-up makes it unclear whether changes in treatment actually lead to improved survival rates. Moreover, upon confirmation of oligometastasis, the appropriate rate of prostate-directed radiotherapy should be determined based on tumor burden. The ratio of low-to-high volume in *de novo* metastatic prostate cancer warrants further investigation. Despite these limitations, this study lays a groundwork for future research and the organization of prospective multicenter studies, offering several potential directions for further exploration of Ga-68 PSMA-11 PET/CT.

CONCLUSIONS

Ga-68 PSMA-11 PET/CT is applicable in various situations and can provide the necessary information for each situation. Compared with conventional imaging, the prostate bed, pelvic nodal metastasis, and distant metastasis can be identified more accurately, and the stage or treatment can be changed based on Ga-68 PSMA-11 PET/CT images. However, the prognosis of treatment changes using Ga-68 PSMA-11 PET/CT requires long-term follow-up data and further evaluation. In particular, for cases of BCR, clinical trials are needed to determine whether it is better to perform early salvage radiation therapy or wait until the lesion becomes clear on Ga-68 PSMA-11 PET/CT to provide optimal treatment.

NOTES

- **Supplementary Materials:** Supplementary Figs. 1 and 2 found via https://doi.org/10.22465/juo.244800380019.
- **Author Contribution:** Conception and design: SHK, CWJ, GJC, CK; Administrative support: SHK, CWJ, SHJ; Provision of study materials and patients: JCW, HDY, JHK, HHK, CK; Collection and assembly of data: SHK, CWJ, JHH; Data analysis and interpretation: SHK, CWJ, MTD; Funding acquisition: GJC; Manuscript writing: SHK, CWJ, MTD, JHH, SHJ, HDY, JHK, HHK, GJC, CK; Final approval of manuscript: SHK, CWJ, MTD, JHH, SHJ, HDY, JHK, HHK, GJC, CK.
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