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Review

The Potential of Ga-68 PSMA-PET/CT as a Main Diagnostic Tool in Prostate Cancer Staging

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Abstract: Gallium-68 prostate-specific membrane antigen positron emission tomography/computed tomography (Ga-68 PSMA-PET/CT) is a diagnostic tool used in urology to detect oligometastatic disease in patients with prostate cancer (PC). Although increasingly popular and extensively studied, it is not considered a standard diagnostic tool for primary PC staging, because it lacks validation when compared to mpMRI. Numerous studies have suggested its promising role in PC diagnostics. Our objective was to comprehensively review and summarize the existing literature on the potential and feasibility of utilizing Ga-68 PSMA-PET/CT as the sole method for primary PC staging and to compare it with currently employed diagnostic tools (mainly mpMRI). The main goal of the study was to consolidate the data on the sensitivity and specificity of PSMA-PET for PCa staging when compared with other diagnostic tools. The use of PSMA-PET/CT as the only diagnostic tool of primary PC in the future might potentially reduce diagnostic time and costs. In addition, we examined the limitations of its use. Ga-68 PSMA-PET/CT demonstrates encouraging outcomes during the initial assessment of PC, potentially leading to a transformative leap in PC diagnosis and treatment, due to the utilization of Ga-68 PSMA, with high affinity to prostate cells.

Keywords: prostate cancer; PSMA PET/CT; staging

1. Introduction

Prostate cancer (PC) is the second-most prevalent malignancy globally and the fifth leading cause of cancer-related deaths among males [1]. The American Cancer Society predicted approximately 288,300 new cases of PC and 34,700 deaths attributed to the disease in 2023 [2].

For accurate local tumor staging, seminal vesicle (SV) invasion (SVI) and extracapsular extension (ECE) are critical parameters, and prostate magnetic resonance imaging (MRI) is the worldwide standard imaging technique [3]. Traditional methods for evaluating locoregional lymph node metastases (LNMs) and remote metastatic spread typically involve computed tomography (CT) and bone scintigraphy (BS). However, the sensitivities of those modalities remain modest at approximately 42% for CT and 79% for BS [4,5]. Consequently, patients often require multiple imaging procedures before treatment, to precisely evaluate the disease stage.

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From a public health perspective, the rising number of new PC cases and, in turn, patients waiting for rapid radiological imaging, demand optimized staging protocols. Therefore, this study aimed at assessing the feasibility of single-stage examination of primary PCa with the utilization of single, novel diagnostic tool. Investigating gallium-68 prostate-specific membrane antigen positron emission tomography/CT (Ga-68 PSMA-PET/CT) presents an encouraging avenue for addressing this question. Leveraging the advanced imaging capabilities of this diagnostic technique might potentially offer a feasible solution for conducting a single-stage examination to diagnose primary PC. This cutting-edge technology holds the potential to streamline the diagnostic process, providing valuable insights into the feasibility of a more efficient and comprehensive approach to PCa staging.

2. Imaging Technologies in Primary Staging

2.1. T-Staging (MRI)

T2-weighted MRI is the preferred method for local staging, renowned and commonly accepted in international guidelines with standardized protocol. A meta-analysis by Caglic et al. showed that the sensitivity and specificity for extraprostatic extension (EPE) were 0.57 (95% confidence interval [CI]: 0.49–0.64) and 0.91 (95% CI: 0.88–0.93), respectively. For SVI, the sensitivity was 0.58 (95% CI: 0.47–0.68), and the specificity was 0.96 (95% CI: 0.95–0.97)[6].

2.2. N-Staging (MRI and CT)

MRI (T1-T2-weighted) and abdominal CT indirectly evaluate nodal invasion by examining the lymph node (LN) size. Typically, LNs with short axes measuring >8 mm in the pelvic region and >10 mm outside the pelvis are indicative of malignancy. Reducing these threshold values increases the sensitivity but decreases the specificity, making the optimal size threshold uncertain [7,8]. The sensitivities of CT and MRI for detecting LN involvement are <40% [9,10]. Significantly, the sensitivity of identifying microscopic LN invasion through CT scans is <1% in patients with International Society of Urological Pathology (ISUP) grades <4, prostate-specific antigen (PSA) levels <20 ng/mL, or localized disease [11–13] In summary, those methods show limited sensitivity and specificity for N-staging and might not be an optimal option for identifying lymph nodes involvement.

2.3. M-Staging (Bone Scintigraphy)

The 99mTc bone scan (BS) is a widely used conventional imaging technique that exhibits high sensitivity in assessing the pattern of active bone formation across the entire skeleton, aiding in the detection of both malignant and benign diseases. In a meta-analysis [14] assessing its effectiveness, BS demonstrated a sensitivity and specificity of 79% and 82%, respectively. Notably, the diagnostic output of BS is significantly affected by factors such as the clinical stage, PSA level, and ISUP grade of the tumor [15]. A retrospective study of 703 patients with newly diagnosed PC who were referred for BS showed the association between age, PSA level, and Gleason score (GS). The findings revealed a substantial increase in the incidence of bone metastases with higher PSA levels and GS [16]. These factors play crucial roles in determining the likelihood of detecting bone metastasis through BS.

3. PSMA-PET/CT

3.1. Biological Principles and Clinical Applications

PSMA-PET/CT is an advanced imaging modality designed to identify PC cells. This technique utilizes a radioactive substance that specifically targets PSMA, a protein expressed by PC cells. The PSMA PET precision surpasses that of other imaging modalities commonly employed for PC detection. While PSMA expression is evident in both normal prostate epithelium and PC cells, it is also detected in other tissues such as the kidneys, small intestine, and salivary glands. Notably, PSMA expression in PC cells is approximately 1000-fold higher than that in normal tissues [17].

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Elevated PSMA expression has been observed in PCa cells, not only in primary focus but also in lymph nodes, soft tissues, and bone metastases [18]. Additionally, PSMA is expressed during the neovascularization of various tumors and their metastases [19,20]. While PSMA expression has been noted in benign granulomatous and inflammatory diseases, the precise mechanisms governing PSMA uptake have not been fully elucidated. However, tracer accumulation in neovascular processes, reduced vascular permeability, heightened blood flow during inflammation, and other nonspecific factors may be contributing factors. PSMA expression has also been observed in diverse bone-related illnesses and conditions [21–23]. The positive correlation between increased PSMA expression, higher GS, and the development of metastatic disease further underscores the significance of PSMA as a valuable target in PC imaging [24–26].In contemporary PCa treatment, urologists are increasingly integrating PSMA-PET/CT as a standard imaging tool. The evolving body of evidence, encompassing its performance across diverse PCa stages, along with the incorporation of insights from new tracers, has fueled a collective effort among urologists to optimize the application of this technology. While this tool is regularly utilized in metastatic scenarios, where it might outperform traditional imaging methods and potentially guide treatment decisions, interest in extending its utility to localized PC has increased, particularly in high-risk cases [27].

3.2. Prostate Cancer Recurrence Detection

Biochemical recurrence (BCR) in PC, signaling recurrence following curative-intent treatments such as prostatectomy or radiation therapy, is characterized by elevated PSA levels. BCR affects approximately four in every ten patients with PC, with approximately quarter experiencing clinical recurrence after 7–8 years [28]. Despite advancements in MRI technology, pinpointing specific BCR sites through imaging has proven challenging. The clinical significance of disease detection lies in directing effective treatment planning and minimizing the unnecessary treatment and its associated side effects [29].

Conventional imaging methods, such as BS and CT, exhibit limited accuracy in identifying metastases to lymph nodes and bones, particularly among patients with low PSA levels. In this scenario, MRI has emerged as the preferred approach for detecting local recurrence, boasting a sensitivity of approximately 75%. However, even though MRI outperforms conventional imaging, its primary utility lies in identifying local recurrence. For patients with low PSA levels, experiencing BCR, radiation therapy of the prostate bed is the first-line salvage treatment, making the identification of local recurrence a critical but not the sole determinant for treatment adjustments.

In the last 5 years, Ga-68 PSMA-PET/CT has become a revolutionary imaging technique for detecting PC relapse. Numerous studies have consistently illustrated that PSMA exhibits superior sensitivity and specificity compared to traditional approaches or choline PET, particularly in identifying tumor recurrence, especially in patients with low PSA levels (<1.0 ng/mL) [30]. While promising results suggest a significant clinical impact in altering approaches based on PSMA PET evaluations of BCR, demonstrating improvements in long-term outcomes is crucial to validate the clinical utility of this transformative molecular imaging technique [31].

3.3. Lymph Nodes Involvement Detection

In a study by Van Leeuwen et al., the main objective was to scrutinize the precision of 68Ga PSMA-PET/CT for LN staging in patients diagnosed with intermediate- and high-risk PC. Their findings indicate that 68-Ga PSMA-PET/CT is a promising alternative to current imaging techniques for LN staging in patients with PC, undergoing radical prostatectomy (RP) [32].

Cytawa et al. used 68-Ga PSMA-PET/CT for staging in 82 men with PC. They found PSMA-positive disease in 83% of patients, and 80.5% of primary tumors were visualized. PSMA-avid lymph nodes were present in 20.7% of patients, and distant disease was identified in 17.1% of patients. The maximum standardized uptake value (SUVmax) of primary tumors was weakly correlated with PSA levels and GS. LN metastasis detection had a 35.0% sensitivity, 98.4% specificity, 63.6% positive predictive value (PPV), 95.0% negative predictive value (NPV), and 93.0% accuracy [33].

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In another study, patients diagnosed with PC were compared based on whether they underwent Ga-68 PSMA-PET/CT or conventional imaging alone. The analysis focused on predicting clinical regional node-positive disease, metastatic disease, and the treatment received. Of 6,139 patients, 14% received a staging PET scan, 40% had conventional imaging without a PET scan, and 45% had no recorded PET or conventional imaging. Over time, the proportion of patients undergoing staging PET increased, especially in the high-risk group. After adjusting for the grade, patients who underwent PET had a higher proportion of cN1 disease, but not cM1 disease, compared to those who had conventional imaging alone [34]. The results suggest an increasing use of PET imaging, particularly for patients with high-risk PC, and hints at its potential contribution to improved nodal disease detection, possibly optimizing patient selection for definitive PC treatment.

In summary, 68-Ga PSMA-PET/CT has emerged as a valuable staging tool for individuals initially diagnosed with intermediate- to high-risk PC. It demonstrates effectiveness in detecting nodal and distant metastases. Nevertheless, PSMA-PET/CT is constrained in low-risk diseases due to the relatively low occurrence of extraprostatic extension.

4. Could PSMA-PET/CT Guide the Treatment of Prostate Cancer?

Accurate staging is a critical factor through which PSMA-PET/CT can influence treatment strategies. Traditional imaging modalities, such as BS and CT scans, may sometimes miss small metastatic lesions. In contrast, PSMA-PET/CT has shown superior sensitivity, particularly for detecting LN metastases and distant organ involvement. This enhanced sensitivity can lead to a more precise determination of the extent of the disease, influencing decisions regarding the treatment intensity and modality.

Lima et al. focused on PSMA-PET/CT for the initial assessment of intermediate- and high-risk PC. Patients were categorized based on whether additional imaging modalities were used alongside PSMA-PET/CT. The results of 57 patients were gathered, with 77.2% (n=44) having CT scan or bone scan (BS) prior to PSMA-PET/CT. Prostate cancer management strategy was changed in 61.4% (n=27), when PSMA-PET/CT was performed following CT and BS. BS and CT results were consistent with PSMA-PET/CT in 43.2% and 44.8%, respectively. In 30 cases, a curative strategy was used based on PSMA-PET/CT findings. PSMA-PET/CT revealed a negative predictive value of 95.2% in 23 patients submitted to radical prostatectomy with bilateral pelvic lymphadenectomy. Prostate SUV values on preoperative PSMA-PET/CT correlated with initial PSA, ISUP grade, PC risk staging, and presence of extraprostatic lesions [35].

Taking abovementioned data into consideration it may be speculated that indeed PSMA-PET/CT might in fact guide the therapeutic decisions in PC treatment. However, due to the lack of long-term follow-up of the patients treated based on the PSMA-PET/CT findings, it is still too early for the introduction of this diagnostic modality into the diagnostic algorithms and guidelines.

5. PSMA-PET/CT as a Single Diagnostic Tool for Prostate Cancer Staging

5.1. PSMA-PET/CT for T-Staging

Precisely evaluating T-staging is vital to determine the most suitable treatment course, thereby enhancing the likelihood of achieving the longest progression-free survival. Comprehension of the spatial correlation among the suspected leasion and nearby critical structures is crucial for effective surgical and intensity-modulated radiotherapy planning. MRI has been the traditional approach [36]. However, detecting subtle signs depends on the subjective evaluation of neurovascular symmetry and focal low-signal intensity in the SV or periprostatic fat.

CT has a restricted role in primary PC diagnosis, and is primarily employed for distant staging in patients with PC, or for assessing LNM and bone metastases in metastatic PC cases. Despite its common usage in PC management, CT imaging lacks adequate soft tissue contrast and targeted molecular information [37].

Prostate MRI was initially used for staging in males with known PC before treatment. In this setting, prostate MRI provides information on the presence or absence of ECE or the involvement of

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the neurovascular bundles and SV, thus helping to differentiate stage T2 disease from locally advanced disease.

Studies have compared PSMA-PET/CT and MRI. Berger et al. compared both techniques with histopathological analysis of prostatectomy specimens. Their findings revealed that PSMA- PET/CT exhibits supreme sensitivity in PCa lesions detection compared to MRI. All 50 histopathologically confirmed index lesions were identified by PSMA-PET/CT, achieving a detection rate of 100%, while MRI detected 47 (94%) lesions. Moreover, PSMA-PET/CT demonstrated superior sensitivity for localizing index lesions compared to MRI (81.1% vs. 64.8%) [38].

Another study comparing both modalities in patients with intermediate- and high-risk PC found that Ga-68 PSMA-PET/CT, MRI, and a combination of both had similar cancer detection rates. However, MRI outperformed Ga-68 PSMA-PET/CT in detecting EPE and SVI. In the evaluation of T staging, MRI was the reference imaging modality. In summary, those studies indicate that both modalities have similar accuracies in detecting and localizing PC foci. Ga-68 PSMA-PET/CT shows better sensitivity and detection rates, whereas MRI performs better at identifying EPE and SVI. Therefore, MRI is still the reference imaging modality for T-staging evaluation [39].

Yi Yi Li et al. conducted a study involving a consecutive cohort of 115 patients who underwent both tools. They showed that Ga-68 PSMA-PET/CT exhibits superior diagnostic performance, especially in terms of specificity, compared to MRI in individuals suspected of having PC, with PSA levels of 4–20 ng/mL. Additionally, the uptake values of Ga-68 PSMA-PET/CT (SUV max or SUV ratio) were positively correlated with the GS, suggesting the potential use of this imaging modality as a noninvasive tool for predicting PC risk and determining malignancy severity. The findings reveal that Ga-68 PSMA-PET/CT exhibits a superior sensitivity for detecting ECE in comparison to MRI, while there is no significant difference in detecting SVI [40].

While BS plays an essential role in the overall staging of PC, particularly in identifying bone metastases (M-staging), its direct contribution to T-staging is limited. T-staging is typically performed using other imaging modalities, such as MRI [41].

5.2. PSMA-PET/CT for N-Staging

The N staging of PC involves the assessment of LN involvement. Determining whether PC has spread to nearby LN has a crucial role in cancer staging that influences treatment decisions and prognosis.

In a randomized controlled trial comparing Ga-68 PSMA-PET/CT with conventional CT and BS, Ga-68 PSMA-PET/CT was superior to other tools in LNM detection, both in sensitivity and specificity. Additionally, CT and BS identified more equivocal lesions compared to Ga-68 PSMA-PET/CT, and CT and BS resulted in superior radiation exposure than Ga-68 PSMA-PET/CT [42].

In a recent meta-analysis that evaluated LNM identification using MRI and Ga-68 PSMA-PET/CT, the PSMA-PET/CT exhibited superior sensitivity and comparable specificity. Moreover, Ga-68 PSMA-PET/CT has more positive outcomes in detecting smaller LN than MRI [43].

Summarizing, there is a growing body of evidence justifying the sole use of PSMA-PET/CT in N-staging of prostate cancer.

5.3. PSMA-PET/CT for M-Staging

Conventional imaging techniques are valuable for detection of distant metastases, and CT can identify sclerotic bone lesions and metastases in internal organs. Nonetheless, CT has produced positive results in only 14% of cases [44].

Accurately diagnosing bone metastasis in PC is becoming increasingly important for guiding both local and systemic treatments. Globally, both tools are being utilized for assessing bone metastases in PC. In a meta-analysis of a high-volume series conducted by Liu et al. [45], the effectiveness of Ga-68 PSMA-PET/CT with various radioligands was compared to that of MRI with different parameters. This comprehensive review and network meta-analysis of diagnostic tests, involving 45 studies with 2,843 patients and 4,263 lesions, recommended the use of 68Ga PSMA-PET/CT for diagnosing bone metastasis in patients with PC.

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Ga-68 PSMA-PET/CT surpasses planar BS in detecting affected bone regions and assessing the overall involvement of the bones in patients with PC.

In a comparative study by Pyka et al., bone metastasis were diagnosed in 60% of patients. Ga-68 PSMA-PET/CT demonstrated sensitivities and specificities ranging from 98.7% to 100% and 88.2% to 100% respectively, for overall bone involvement. In contrast, for BS, the values were 86.7–89.3% for sensitivity and 60.8–96.1% for specificity ($p < 0.001$), considering "optimistic" or "pessimistic" classifications of equivocal lesions. A region-based analysis of 1,115 bone regions with 410 metastases showed a PSMA-PET/CT sensitivity and specificity of 98.8–99.0% and 98.9–100%, respectively, while BS demonstrated a sensitivity of 82.4–86.6% , and specificity of 91.6–97.9%. Ga-68 PSMA PET/CT exhibited superior performance in all subgroups, except for the patient-based analysis of mCRPC [46].

5.3.1. PSMA-PET/CT and Other Diagnostic Modalities in High-Risk PC

Hirmas et al. compared the diagnostic efficacy of 68-Ga PSMA-PET/CT with that of CT, MRI, and BS for the primary staging of 21 patients with high-risk PC. Ga-68 PSMA-PET/CT demonstrated a markedly increased concordance rate with BS, MRI, and CT (90%, 75%, and 73%, respectively. It exhibited similar precision to that of MRI in identifying prostate lesions but superior accuracy in detecting suspicious pelvic LNs. It outperformed CT in detecting suspicious pelvic LNs, extra-pelvic LNs and outperformed BS in detecting bone lesions. Utilization of Ga-68 PSMA-PET/CT resulted in management changes for 11 patients. Those findings suggest potential advantages of using Ga-68 PSMA-PET/CT over other modalities in PC diagnosis and staging, particularly in terms of specificity, accuracy in detecting LNs, and impact on patient management. However, further research and larger populations are needed for confirmation.

6. Economic Aspects

Several studies have explored the cost implications of utilizing PSMA-PET/CT in different healthcare settings. Holzgreve et al. found that in Europe and the US, PSMA-PET/CT is generally associated with increased costs. Notably, the scan duration plays a significant role in determining the cost-effectiveness. Despite the higher upfront costs, the expenses related to achieving an accurate diagnosis through Ga-68 PSMA-PET/CT appear to be reasonable when compared to the potential downstream costs associated with inaccurate diagnosis [47].

7. Limitations of PSMA-PET/CT

Although it is a rapid and noninvasive imaging modality, it has limitations and potential side effects. The efficacy of Ga-68 PSMA-PET/CT can be influenced by various factors, such as dual-time-point acquisition, androgen deprivation therapy, forced diuresis, and hydration. Although patients undergoing Ga-68 PSMA-PET/CT are subjected to radiation, the dose is relatively low [48]. Notably, the risk of cancer mortality due to serial radiation exposure through CT, estimated at approximately 2% over 30 consecutive years of annual exposure, is considered negligible for most patients who undergo several Ga-68 PSMA-PET/CT scans during their lifetime [49].

Difficulties in interpreting Ga-68 PSMA-PET/CT images may occur for patients who have trouble remaining still during the scan, possibly necessitating repeat imaging or sedation to improve the image quality. Additionally, variations in the timing of tracer administration and SUV measurements can introduce interdepartmental and international differences [50,51].

Clinically, the effectiveness of Ga-68 PSMA-PET/CT for detecting PC has been extensively documented, with positive scans observed in the majority of patients with suspected cancer (approximately 83%), demonstrating high specificity.

Despite its high accuracy compared to that of cross-sectional imaging, Ga-68 PSMA-PET/CT has limitations, such as occurrence of false-negative results, especially in detecting small nodal metastases below the spatial resolution of PET[51] . Mannweiler et al. found that 5% of primary PC and 15% of PC metastases show negativity for PSMA on immunohistochemistry [52]. Moreover, the

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concept of stage migration, impacted by the precision of Ga-68 PSMA-PET/CT, has become a topic of interest. Patients who experience upstaging may now represent a more favorable disease state than others in the updated stage classification. While survival rates have improved, no impact on individual patient outcomes is evident—a phenomenon commonly referred to as the "Will Rogers phenomenon."

8. Conclusion

The advent of PSMA-PET/CT imaging for the primary staging of PC presents transformative potential for refining diagnostic accuracy and treatment planning. Traditional methods, including MRI, CT, and BS have sensitivity limitations which leads to the necessity of multiple imaging procedures to comprehensively assess the disease stage, and therefore prolonging the time-to-treat which may potentially exacerbate oncological outcomes. Integrating PSMA-PET/CT, with its high specificity for prostate-specific membrane antigens, with traditional methods holds promise for a more efficient and precise staging examination.

The question posed regarding the feasibility of a single-stage examination for primary PC before RP determines the potential of PET/PSMA imaging. This technology offers a comprehensive and efficient approach for T-, N-, and M-staging, potentially streamlining the diagnostic pathway. However, ongoing research and economic evaluations are essential to determine the feasibility of its widespread clinical application, and optimal integration of PSMA-PET/CT into the evolving landscape of PC staging protocols.

Economic evaluations underline the possible cost-effectiveness of Ga-68 PSMA-PET/CT, especially when considering its impact on treatment outcomes and avoidance of futile approaches. The demonstrated accuracy of PSMA-PET/CT in guiding treatment decisions, as reflected in its superior sensitivity and specificity compared to those of traditional methods, supports its role in optimizing patient selection for definitive treatment.

Retrospective studies offer compelling evidence that integrating Ga-68 PSMA-PET/CT into the diagnostic pathway can potentially change tactics for managing patients diagnosed with PC. The ability to identify lesions that may be missed by other imaging modalities, coupled with their impact on treatment decisions, positions PSMA-PET/CT as a transformative tool in the clinical landscape of PC.

In essence, PSMA has emerged not only as a diagnostic powerhouse but also as a driver of change in treatment strategies. As research continues to validate its long-term impact on patient outcomes, PSMA-PET/CT remains a pivotal player in the pursuit of precision medicine for PC management. Whilst PSMA-PET/CT has significant advantages in detecting PC, its limitations include technical challenges, radiation exposure, and potential clinical implications, such as false-negative results and stage migration. The overall effects of those limitations on patient outcomes and survival rates require careful consideration.

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